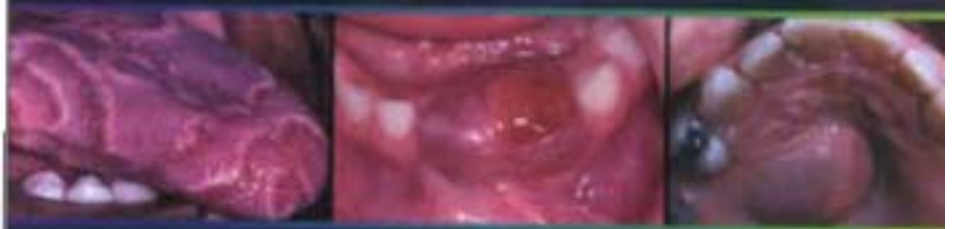
Oral & Maxillofacial PATHOLOGY



SECOND EDITION

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Oral & Maxillofacial
PATHOLOGY

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SECOND EDITION

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This book is *dedicated to three of our mentors:*

Charles A. *\Valdron*
William G. *Shafer*
Robert I. Gor/in

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

Preface

Oral and maxillofacial pathology is the specialty of dentistry and discipline of pathology that deals with the nature. identification. and management of diseases affecting the oral and maxillofacial regions. As such, it occupies a unique position in the health care community for both the dental and medical professions. Naturally. members of the dental profession (including general practitioners. specialists. and dental hygienists) must have a good knowledge of the pathogenesis. clinical features. treatment. and prognosis for oral and paraoral diseases. Likewise. such knowledge is also important for those in the medical profession. especially those who specialize in such areas as otolaryngology. dermatology. and pathology.

The purpose of the second edition of this text remains the same: to provide the reader with a comprehensive discussion of the wide variety of diseases that may affect the oral and maxillofacial region. *Oral & Maxillofacial Pathology* has been organized to serve as a primary teaching text, although it should also be a valuable reference source for the practicing clinician. Chapters have been created that include disease processes of a similar source (e.g. "Bacterial Infections." "Salivary Gland Pathology." "Bone Pathology." "Dermatologic Diseases"), because the basic understanding of pathology is facilitated by discussing diseases of a similar nature at the same time. Only after attaining this basic understanding can the clinician tackle the difficult task of clinical diagnosis and treatment. With this in mind. a comprehensive appendix is included at the end of the book to help the clinician with the differential diagnosis of oral and maxillofacial disease processes.

It is impossible to write a book that perfectly matches the requirements of every reader. Because all the authors are involved in teaching, the subjects selected for inclusion in this text primarily reflect what is taught in courses on oral and maxillofacial pathology. Although dental caries is undeniably a common and important disease affecting the oral cavity. it is usually not taught in an oral and maxillofacial pathology course but elsewhere in most dental schools' curricula. Therefore. we have not included a chapter on dental caries. Likewise, our discussion on common gingivitis and periodontitis is limited in scope, although a more in-depth discussion is provided for other conditions that affect the periodontium. In other areas, the text offers greater detail than necessary for some primary courses in oral and maxillofacial pathology. However, because this book is also intended as a reference source for the practicing clinician, this additional material has been included.

The most obvious difference in the second edition is the change to full-color illustrations throughout the book. Oral and maxillofacial pathology is a highly visual subject. and we are excited to offer what we hope will be a significant improvement to the value of the book. In the short time since the publication of the first edition. many significant advances have occurred in the areas of immunohistochemistry. molecular biology. and genetics. When appropriate, some of this new information has been included for certain diseases. The chapter sequence has not changed; however, a few individual topics have been moved to more appropriate locations in the text.

Obviously, this book could not have been accomplished without the help of many individuals. We wish to thank Dr. Edward Herschaft, who revised his excellent chapter on forensic dentistry. We are indebted to many of our colleagues who shared cases with us, and they have been credited in the legends of the illustrations. Although the list is too numerous to cite here, one person in particular, Dr. George Blozis. deserves special recognition for his generosity in sharing his excellent teaching collection. We have attempted to be as thorough as possible in listing credit for all the cases shared with us. However, if someone's name has been inadvertently omitted. please accept our apologies.

For the first edition of this text, we were fortunate to have Dr. Charles Waldron (one of the persons to whom this book is dedicated) write two outstanding chapters on areas of his special interest and expertise. "Bone Pathology" and "Odontogenic Cysts and Tumors." We and those in the oral pathology community were tremendously saddened by his death in 1995. Chuck's unique expertise has been greatly missed during the revision of these chapters, but their content still reflects much of his basic philosophy. We also mourn the recent death in tune 2000 of Dr. William Shafer. another individual to whom this book is dedicated. Dr. Shafer was the principal author of the well-known and respected book, A Textbook of Oral Pathology. a valuable resource that all of us have used for many years to learn about and teach our specialty.

We also would like to thank the people at Harcourt Health Sciences for their hard work in making this book a success. Kimberly Alvis did an excellent job throughout the publishing process. correcting our mis-

takes and taking care of Innumerable details in order to produce the book that you see before you. Tripp Narup provided invaluable guidance to help us with the digitlzation of the illustrations. Many thanks go to Dana Petck. who was responsible for the primary editing of the manuscript and the excellent design of the book. She worked uncounted hours of "overtime" to ensure that it was published on schedule. Our highest praise goes to Penny Rudolph, who guided us at every step during the production of this book–and always with a smile on her face.

Finally, our deepest thanks must go to our families for their support during the writing of this book. They have had to endure our neglect during the long hours of work, and this project could never have been completed without their love and encouragement.

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Contents

CHAPTER 1

Developmental Defects of the Oral and Maxillofacial Region

CHAPTER OUTLINE

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 cctomesenchyrne 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 mid portion 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. tnitially. 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 nasa] septum. The fusion of the palatal shelves begins in the anterior palate and progresses posteriorly; it is completed around the twelfth week.

Defective fusion of the medial nasal process with the maxiilary process leads to cleft lip (CL). Likewise. failure of the palatal shelves to fuse results in cleft palate (CPl. Frequently. CL and CP occur together. Approximately 45% of cases are CL + CP. with 30% being isolated CP 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 O.e. CL :!: CPl. Isolated CP appears to represent a separate entity from CL :!: CP.

The cause of CL :!: CP and CP is still being debated. First of all. it is important to distinguish isolated clefts from cases associated with specific syndromes. Although most facial clefts are isolated anomalies, more than 250 developmental syndromes have been identified that may be associated with CL :!: CP or CP. Such syndromes are estimated to account for 3% to 8% of orofacial clefts. Some of these syndromes are single-gene conditions that may follow autosomal dominant, autosomal recessive, or X-linked tnhcritancc patterns. Other syndromes are the result of chromosome anomalies or are idiopathic. The cause of nonsyndromic clefts does not follow any Simple rncndcllan 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.

CL :!: CP and CP 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. The lateral facial cleft may occur as an isolated defect or may be associated with other disorders. such as mandibulofacial dysostosis (see page 42). This cleft may be unilateral or bilateral. extending from the commissure toward the ear, resulting in macrostomia.

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 laterally bypass the nose as it extends to the eye. This cleft is rare. representing only I in 1300 facial clefts. Some of these clefts may represent failure of fusion of the lateral nasal process with the maxillary process; others may be caused by amniotic bands.

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 oral-facial-digital syndrome and Ellis-van Creveld syndrome. Most apparent median clefts of the upper lip actually represent agenesis of the primary palate associated with holoprosencephaly.

Median maxillary anterior alveolar clefts also have been reported. Such clefts may cause a bony defect in the midline of the maxilla between the central incisors.

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 I 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 per 1000 births. Native Americans appear to have the highest frequency, around 3.6 per 1000 births. Isolated CP is less common than CL ± CP, with a frequency of 0.4 per 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, isolated CP 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.

About 80% of cases of CL will be unilateral, with 20% bilateral (Figure 1-1). Approximately 70% of unilateral CLs occur on the left side. 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.

A CP shows considerable range in severity (Figure 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 (Figure 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 there is a defect in the underlying musculature of the soft palate (Figure 1-4). Frequently a notch in the bone is present

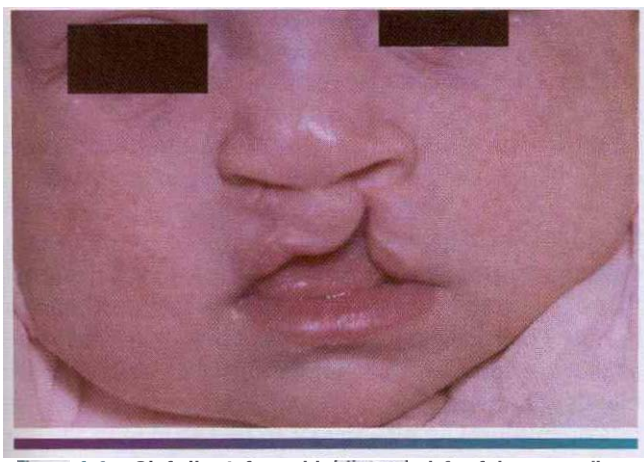

Figure 1-1 • Cleft lip. Infant with bilateral cleft of the upper lip. (Courtesy of Dr. William Bruce.)

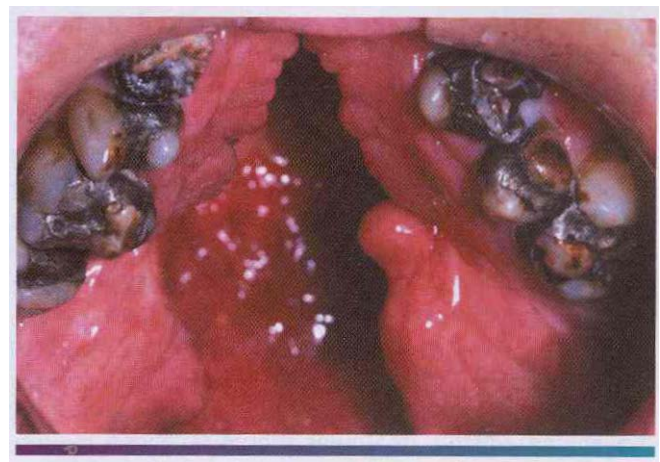

Figure 1-2 • Cleft palate. Palatal defect resulting in communication with the nasal cavity.

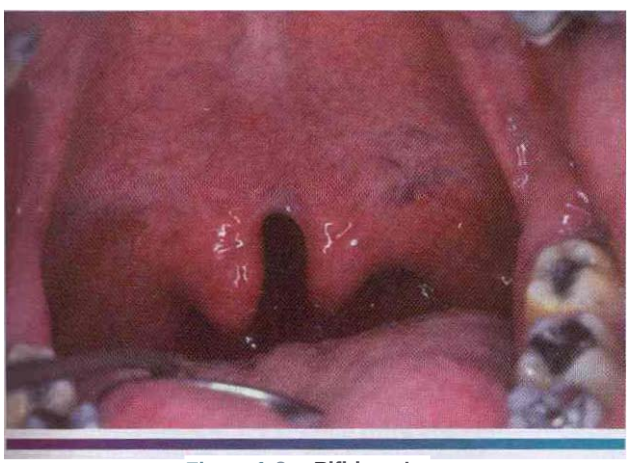

Figure 1-3 • Bifid uvula.

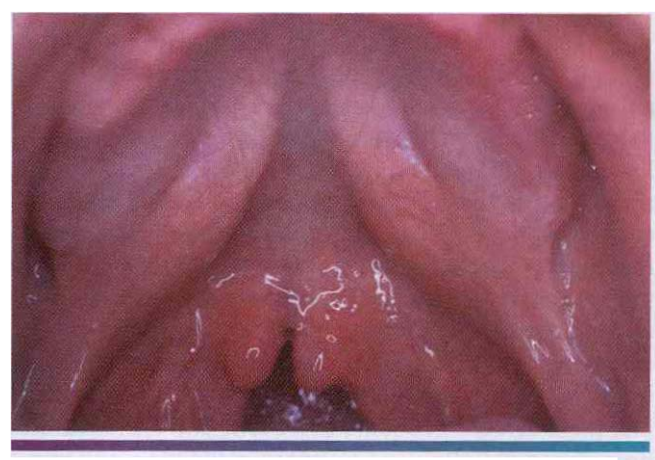

Figure 1-4 • Submucous palatal cleft. There is a cleft of the midline palatal bone, but the overlying mucosa is *intact.* A bifid uvula also is present.

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 is also usually seen.

The Pierre Robin sequence (Pierre Robin anomalad) (Figure 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. It has been 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. is usually noted from birth and can cause asphyxiation. The palatal cleft is often U-shaped and wider than isolated CPo

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 CPoMalocclusion 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 orotacial 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 is usually accomplished during the first few months of lite. 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.

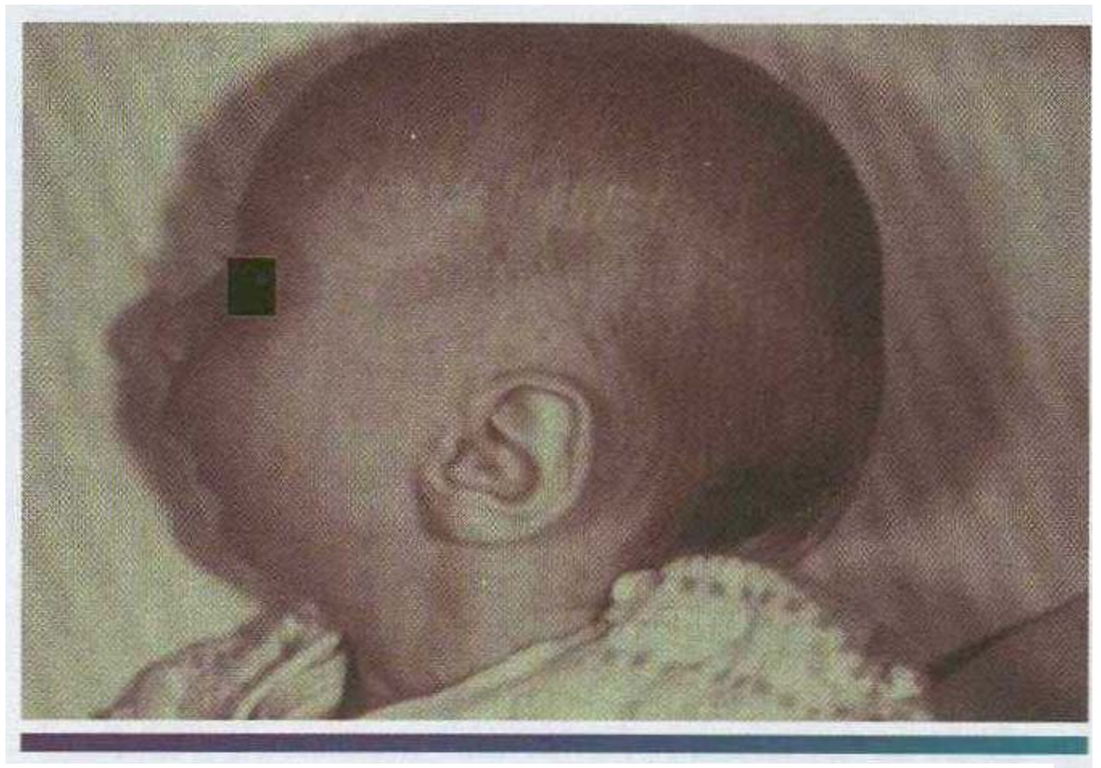

Figure 1-5 • Pierre Robin sequence. Micrognathic mandible in an infant with deft palate. (Courtesy of Dr. Robert Gorlin.)

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

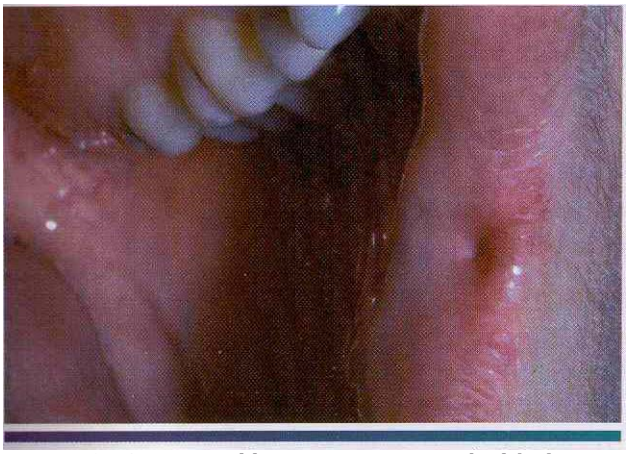

Figure 1-6 • Commissural lip pit. Depression at the labial commissure.

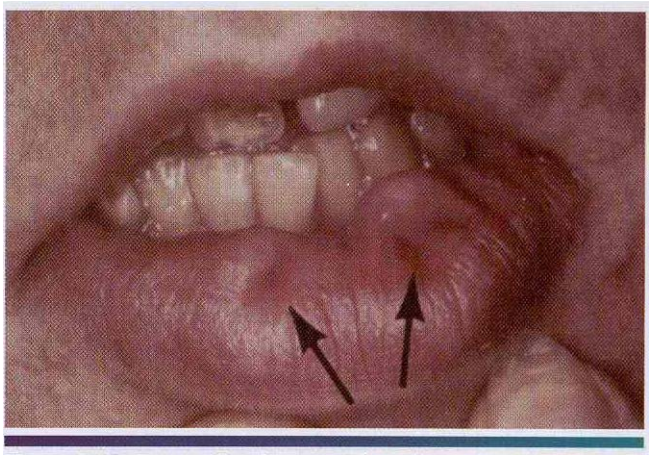

Figure 1-7 • Paramedian lip pits. Bilateral pits *(arrows)* on the lower lip in a patient with van der Woude syndrome.

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.

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 nccessary. 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 present as bilateral and symmetric fistulas on either side of the midline of the vermilion of the lower lip (Figure 1-7). Their appearance can range from subtle depressions to prominent humps. These blind sinuses can extend down to a depth of 1.5 em 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 are usually inherited as an autosomal dominant trait in combination with cleft lip and/or cleft palate (van der Woude syndrome). Recent genetic studies have shown that microdeletions at chromosome bands 1q32-q41 are the cause of van der Woude syndrome in some families. Some people who carry the trait may not demonstrate clefts or may have a submucous cleft palate; however. they may pass the full syndrome on to their offspring. Paramedian lip pits also may be a feature of the popliteal pterygium syndrome. characterized by popliteal webbing (pterygia). cleft lip and/or cleft palate. genital abnormalities. and congenital bands connecting the upper and lower jaws (syngnathla).

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 cleft lip and/or cleft palate. and the potential for transmission of the trait to subsequent generations.

DOUBLE LIP

Double lip is a rare oral anomaly characterized by a redundant fold of tissue on the mucosal side of the lip. It

is most often 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, and 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 (Figure 1-8).

Ascher syndrome is characterized by a triad *at* 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 (Figure 1-9). 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 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 are typically 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 present as multiple yellow or yellowish-white papular lesions that are most common on the buccal mucosa and the lateral portion of the vermilion of the upper lip (Figures 1-10 and 1-11). 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. There may be considerable clinical variation: some patients may have only a few lesions. whereas others may have literally hundreds of these "granules...

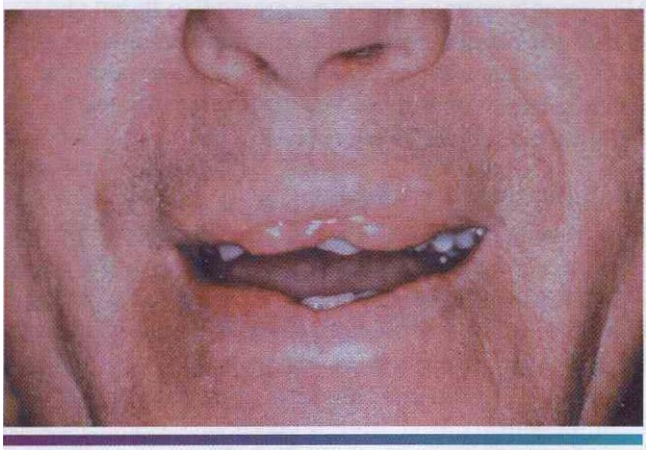

figure 1-8 • Double lip. Redundant fold of tissue on the upper lip in a patient with Ascher syndrome. (Courtesy of Dr. R,C. Zeigler.)

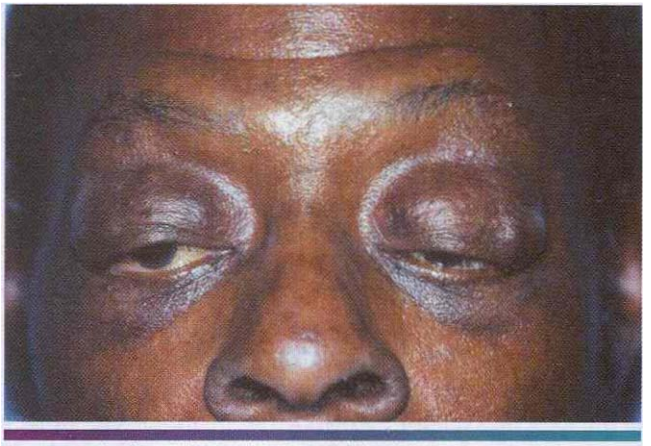

figure 1-9 • Ascher syndrome. Edema of the upper eyelids (blepharochalasis).

Histopathologic Features

Except for the absence of associated hair follicles. Fordycegranules areclosely similar to 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 (Figure 1-12). The sebaceous cells in these lobules are polygonal in shape. containing centrally located nuclei and abundant foamy cytopiasm.

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.

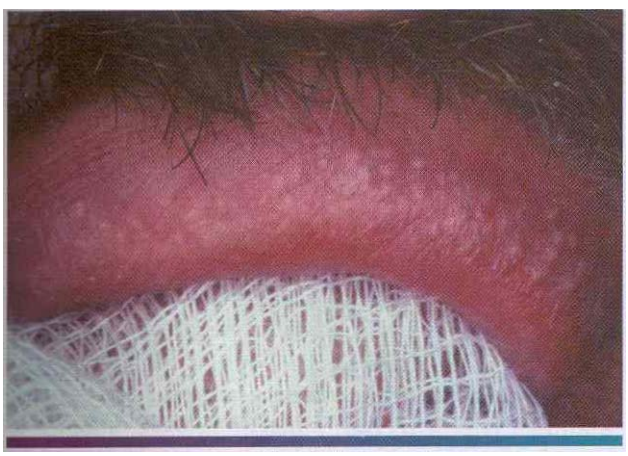

Figure 1-10. fordyce granules. Yellow papules on the vermilion of the upper lip.

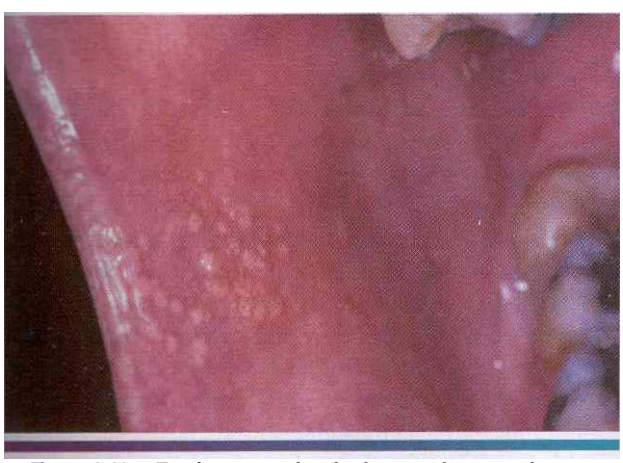

Figure 1-11 • Fordyce granules. lesions at the commissure.

IEUKOEDEMA

Icukocdema 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. Icukocderna shows a much milder presentation in whites. and often it 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." This argument can be further supported by the finding of similar edematous mucosa in the vagina and larynx. Although leukoedcrna appears to be developmental in nature. some studies have indi**cated 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. grayish-white. milky. opalescent appearance of the mucosa (Figure 1-13). 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 can also involve the floor of the

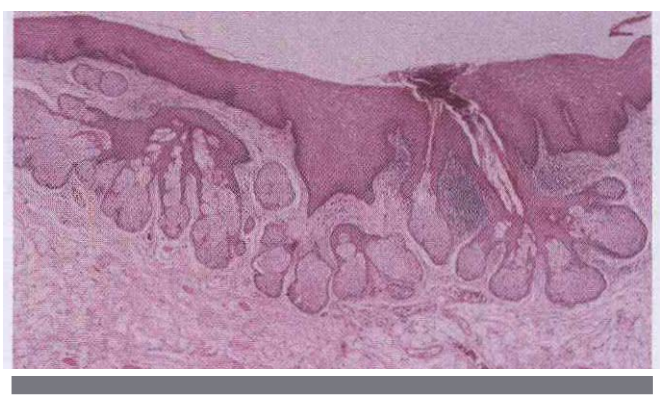

figure 1-12 • fordyce granules. Multiple sebaceous glands below the surface epithelium.

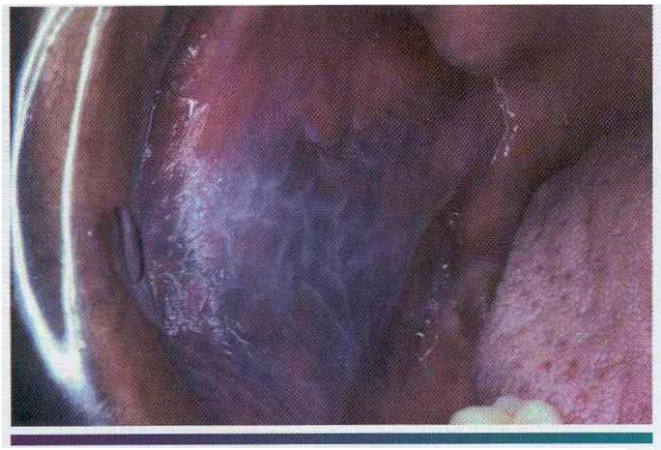

Figure 1-13 • Leukoedema. White. wrinkled appearance of the buccal mucosa.

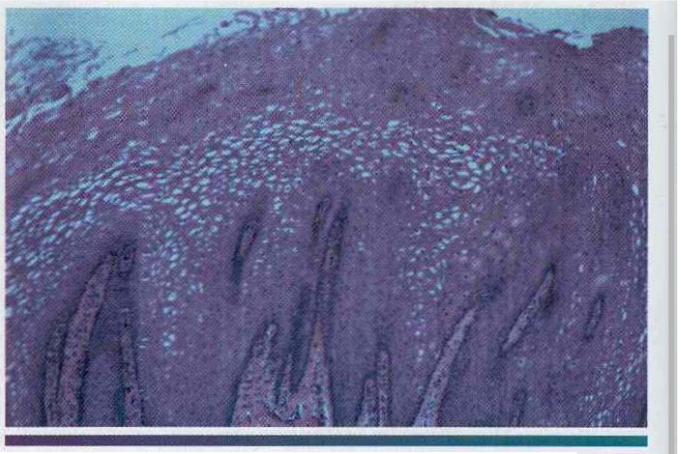

Figure 1-15 • Leukoedema. Parakeratosis and intracellular edema of the spinous layer.

A

B

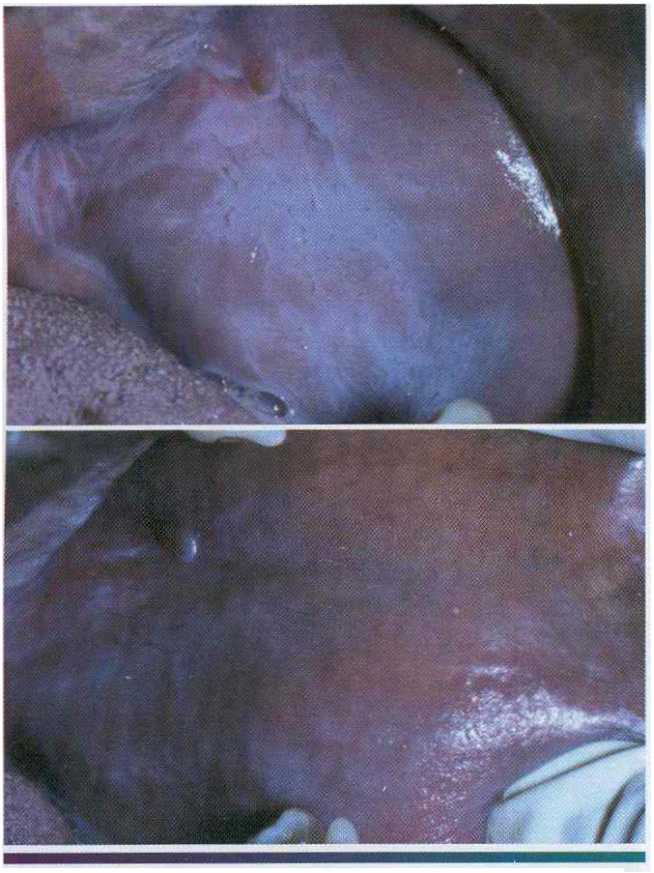

Figure 1-14 . Leukoedema, A. Diffuse white appearance of the buccal mucosa. B. Whiteness disappears when the cheek is stretched.

mouth and palatopharyngeal tissues. Leukcedcrna can be easily diagnosed clinically because the white appearance greatly diminishes or disappears when the cheek is everted and stretched (Figure 1-14).

Histopathologic Features

Biopsy specimens of leukoederna demonstrate an increase in thickness of the epithelium, with striking intracellular edema of the spinous layer (Figure 1-15). These vacuolated cells appear large and have pyknotic nuciei. The epithelial surface Is frequently parakcratInlzed. 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 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 microgiossia 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 (l.e.. absence of digits) and hypomelia (l.e.• hypoplasia of part or all of a limb). **Other patients have had coexisting anomalies. such as** cleft palate, intraoral bands, and situs inversus.

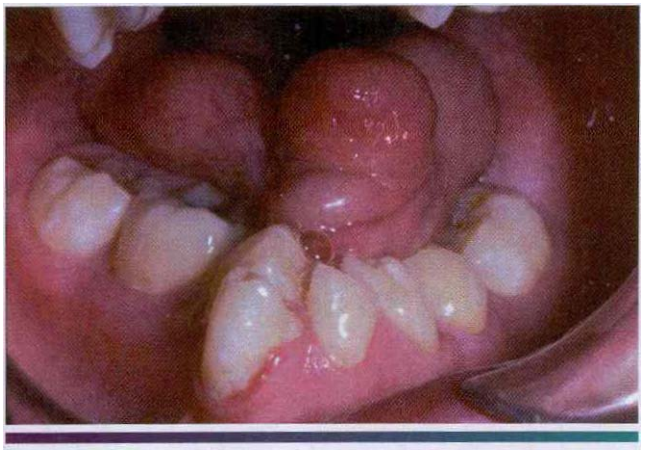

Figure 1-16 • Microglossia. Abnormally small tongue associated with constricted mandibular arch.

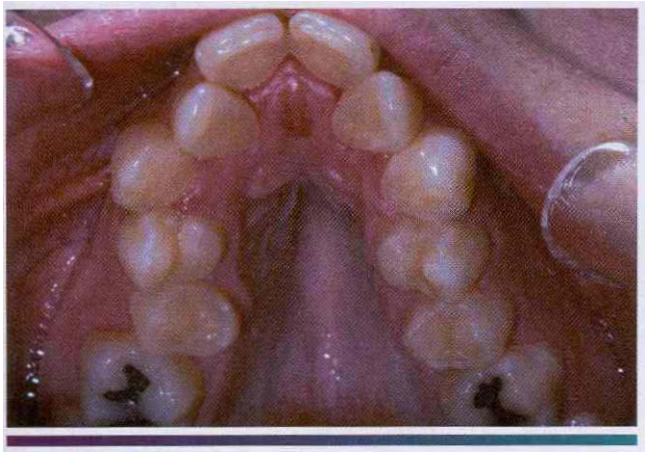

Figure 1-17 • Microglossia. Associated constriction of the maxillary arch in the same patient shown in Figure 1-16.

Microglossia frequently is associated with hypoplasia of themandible. and the lower incisors may be missing (Figures 1-16and I-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 both congenital malformations and acquired diseases. The most frequent causes are vascular malformations and muscular hypertrophy. Box I-I lists the most common and important causes of macroglossia. Many of these diseases are discussed in greater detail in subsequent chapters of this book.

Box 1-1 *Causes of Macroglossia*

CONGENITAL AND HEREDITARY

- Vascular malformations
  - Lymphangioma
  - Hemangioma
- Hemihyperplasia
- Cretinism
- Beckwith-Wiedemann syndrome
- Down syndrome
- Mucopolysaccharidoses
- Neurofibromatosis
- Multiple endocrine neoplasia. type 2B

ACQUIRED

- Edentulous patients
- Amyloidosis
- Myxedema
- Acromegaly
- Angioedema
- Carcinoma and other tumors

Clinical Features

Macroglossia most commonly occurs in children and can range frprn mild to severe in degree (Figure 1-18). In in/ants. 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. 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:

- 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. and

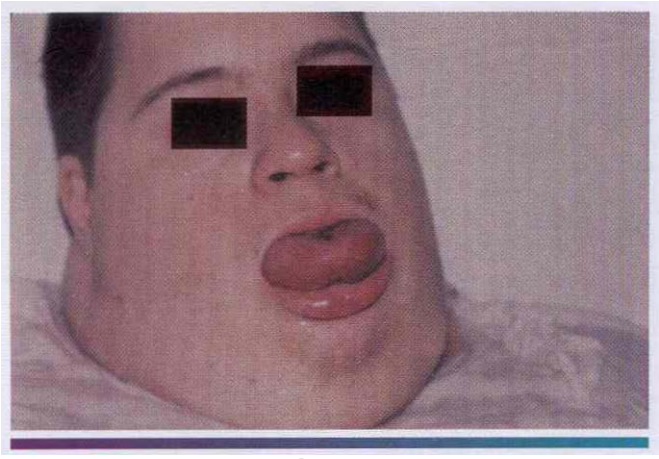

Figure 1-18 • Macroglossia. large tongue in a patient with Down syndrome. (Courtesy of Dr. Sanford Fenton.)

hcpatoblastorna . Facial features may include nevus flam-rneus of the forehead and eyelids, linear indentations of the earlobes. and maxillary hypoplasia (resulting in relative mandibular prognathism). The mode of inheritance of Bcckwith-Wle dcmann syndrome is uncertain, but autosomal dominant transmission has been suggested, with variable expressivity and incomplete pcnctrancc.

In patients with hypothyroidism (see page 720) or Beckwith-Wiedemann syndrome, 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 710) and neoplastic conditions. such as neurofibromatosis (see page 45S1 and multiple endocrine neoplasia. type 2B (see page 461).

In patients with lymphangiomas (see page 475l. the tongue surface is characteristically pebbly and exhibits multiple vesiclelike 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 37l. 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 in Down syndrome or 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 hcmlhypcrplasla and Beckwith-Wiedemann syndrome. In thc 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 limitation of tongue movement. It has been reported to occur in 1.7% to 4.4% of neonates and is four times 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 2 to 3 of every 10.000 people.

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 (Figure 1-19). Sometimes the frenum extends forward and attaches to the tip of the tongue. and there may be slight c1efting of the tip.

Some investigators have speculated that ankyloglossia may contribute 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 rnucogtngival attachment of the lingual frenum may lead to periodontal problems.

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. Recent reports from lapan have theorized that some ankyloglossia cases can be associated with an upward and forward displacement of the epiglottis and larynx. resulting in various degrees of dyspnea.

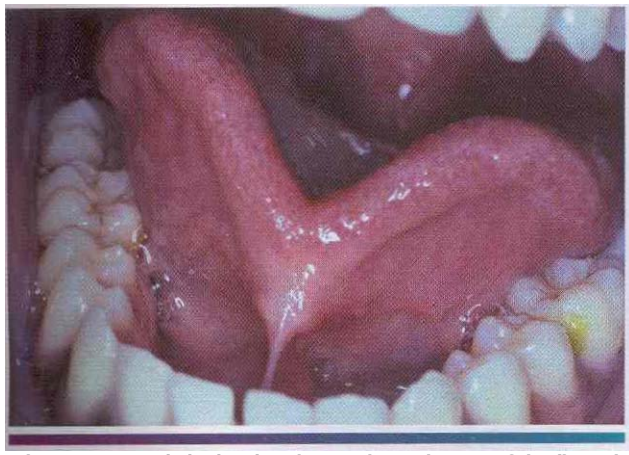

Figure 1-19 • Ankyloglossia. Abnormal attachment of the lingual frenum, limiting tongue mobility.

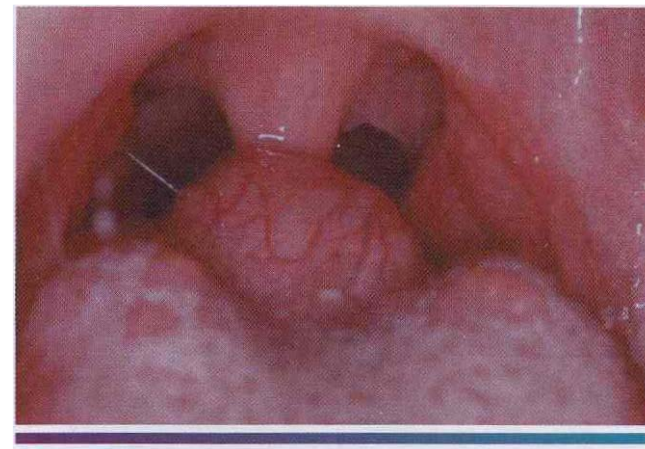

Figure 1-20 • lingual thyroid. Nodular mass of the posterior dorsal midline of the tongue in a a-year-old girl.

Treatment and Prognosis

Because most cases of ankyloglossia result in few or no clinical problems. treatment is often unnecessary. If there are functional or periodontal difficulties. a frenectomy 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. it is difficult in the infant's early life to assess the degree of tongue limitation caused by ankyloglossia. 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 (Figure 1-20). 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 (Figure 1-21). Computed tomography (CT) and magnetic resonance imaging (MRI) can be helpful in delineating the size and extent 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 surgically excised. autotransplantation to another body

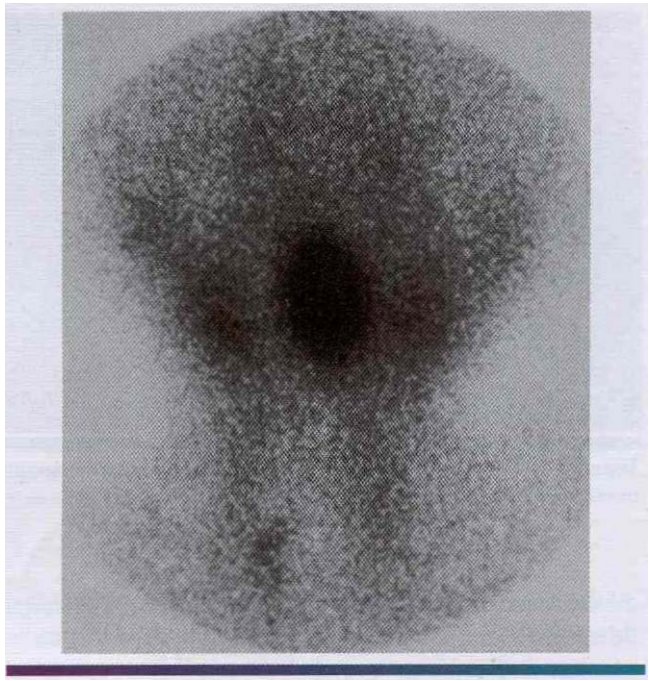

Figure 1-21 • lingual thyroid. Thyroid scan of the same patient as in Figure 1-20. The scan shows localization *(central dark zone)* of iodine isotope in the tongue mass and minimal uptake in the neck.

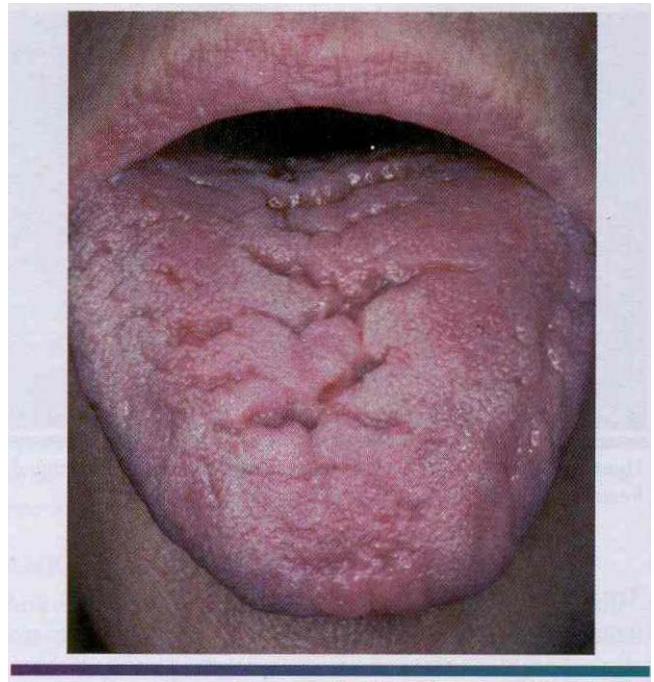

Figure 1-22 • Fissured tongue. Moderate fissuring of the dorsal tongue. (From Allen eM, Camisa C: Diseases of the mouth and lips. In Sams WM. lynch P. editors: *Principles of dermatology.* New York, 1990, Churchill livingstone.}

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.

FISSURED TONGUE (SCROTAL TONGUE)

Fissured tongue is relatively common. Numerous grooves. or fissures. are present on the dorsal tongue surface. The cause is uncertain, but heredity appears to play a significant role. There is evidence that the condition may be either a polygenic trait or an autosomal dominant trait with incomplete pcnetrance. 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 (Figures 1-22 and 1-23). 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 arc 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 is usually 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. In some Investigations, a male predilection has been noted.

A strong association has been found between fissured tongue and geographic tongue (see page 677l. 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 295).

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 arc 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.

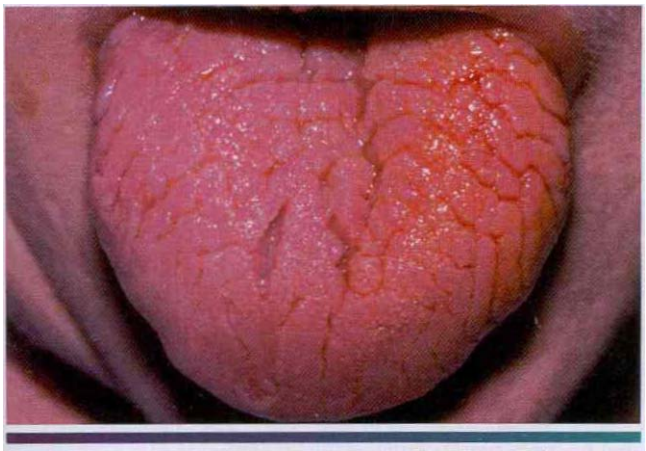

figure 1-23 • **fissured tongue.** Extensive fissuring involving the entire dorsal tongue surface.

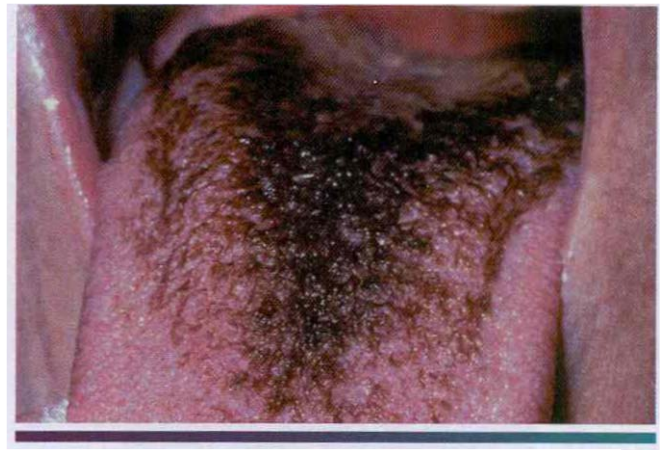

figure 1-24 • **Hairy tongue.** Elongated, black-staining filiform papillae on the posterior dorsal tongue.

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)

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 the following:

- Antibiotic therapy
- Poor oral hygiene
- General debilitation
- Radiation therapy
- Use of oxidizing mouthwashes or antacids
- Overgrowth of fungal or bacterial organisms

Clinical Features

Hairy tongue most commonly affects the midline just anterior to the circumvallate papillae, sparing the lateral and anterior borders (Figure 1-24). 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, mailed appearance (Figure 1-25). Multiple individual elongated filiform papillae may be elevated by using gauze or a dental instrument. The condition is typically asymptomatic, although occasional 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.

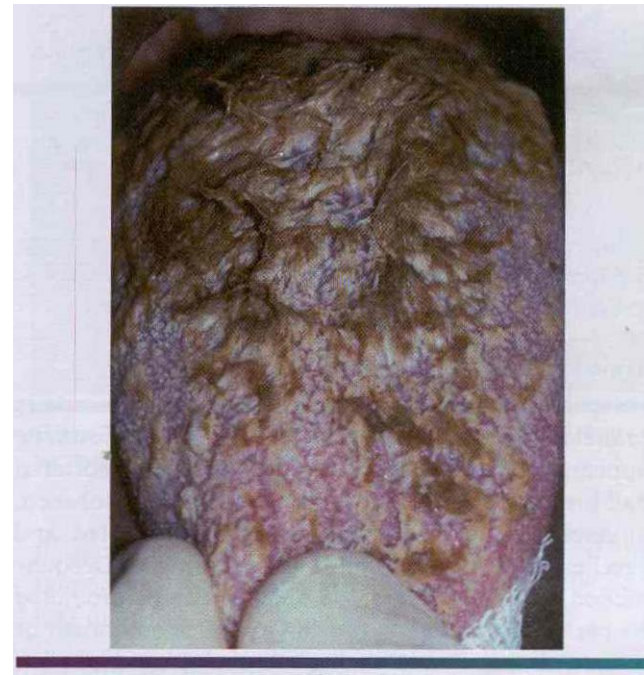

figure 1-25 • **Hairy tongue.** Marked elongation and brown staining of the filiform papillae, resulting in a hairlike appearance. (Courtesy of Dr. Robert Strohaver.)

Because of the similarity in names, care should be taken to avoid confusing hairy tongue with hairy leukoplakia (see page 24i). which typically occurs on the lateral border of the tongue. Hairy leukoplakia is caused by the Epstein-Barr *virus* and is usually associated with human immunodeficiency *virus* (HIV) infection or other immunosuppressive conditions.

Histopathologic Features

On histopathologic examination, hairy tongue is characterized by marked elongation and hyperpara-

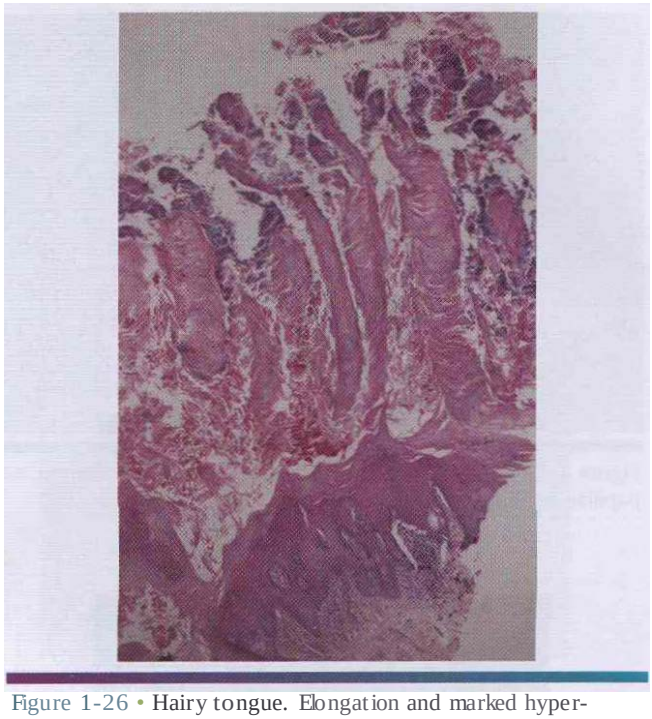

Figure 1-26 • Hairy tongue. Elongation and marked hyperkeratosis of the filiform papillae, with bacterial accumulation on the surface.

keratosis of the filiform papillae (Figure 1-26). Usually, numerous bacteria can be seen growing on the epithelial surface.

Treatment and Prognosis

Hairy 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, antibiotics, or mouthwashes, should be eliminated, and excellent oral hygiene should be encouraged. Desquamation of the hyperkeratotic papillae can be promoted by periodic scraping or brushing with a toothbrush or tongue scraper. Keratolytic agents, such as podophyllin, also have been tried with success, but for safety reasons their use probably should not be encouraged.

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 there is a loss of connective tissue tone supporting the vessels. Oral varices have not been associated with systemic hypertension or other cardiopulmonary diseases, although one study did find that people with varicose veins of the legs were more likely to have varicosities of the tongue.

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 bluish-purple, elevated or papular blebs on the ventral and lateral border of the tongue (Figure 1-27). The lesions are usually 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 (Figure 1-28). Clinically, a thrombosed varix presents as a firm, nontender, bluish-purple nodule that may feel like a piece of buckshot 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, 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 are typically asymptomatic, and no treatment is indicated. Solitary varicosities of the lips and buccal mucosa may need to be surgically removed to confirm the diagnosis, because of secondary thrombus formation, or for aesthetic purposes.

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 (Figure 1-29). Stretching the lip usually causes the artery to become inconspicuous. The unique

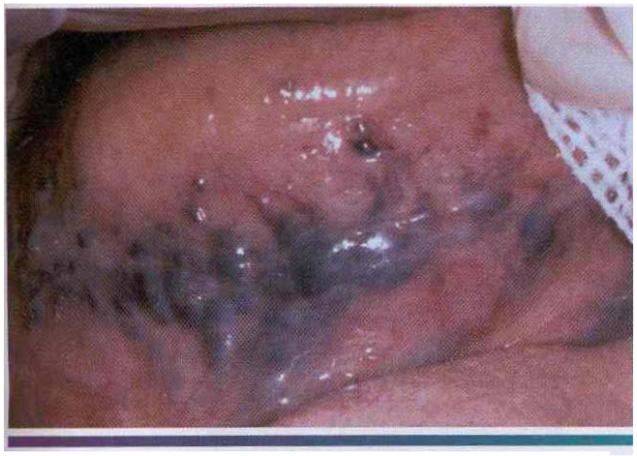

Figure 1-27 • Varicosities. Multiple purple dilated veins on the ventral and lateral surface of the tongue.

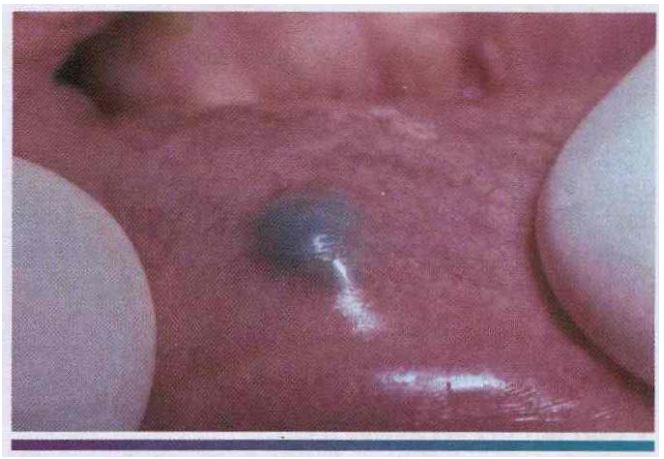

Figure 1-28 • Varicosity. firm. thrombosed varix on the lower lip.

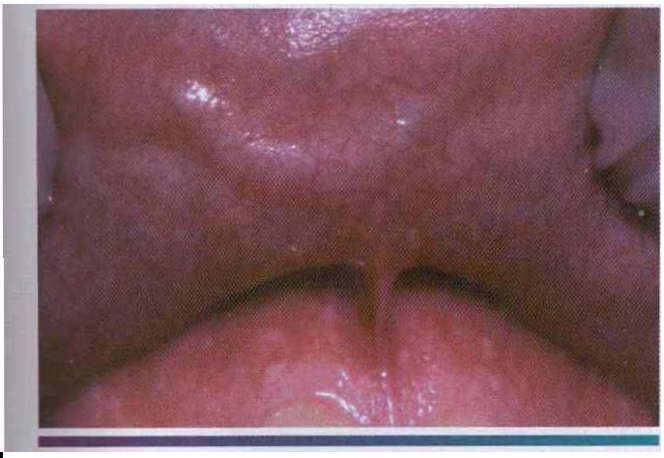

Figure 1-29 • Caliber-persistent artery. linear. arcuate lesion on the upper labial mucosa. (Courtesy of Dr. John Lovas.]

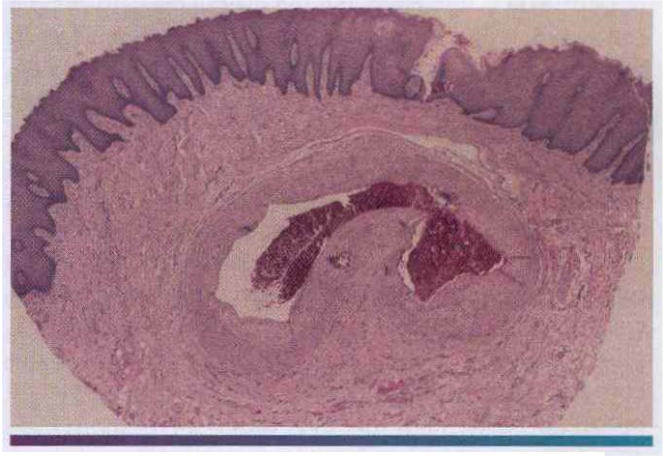

Figure 1-30 • Caliber-persistent artery. Thick-walled artery located just beneath the mucosal surface.

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.

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 (Figure 1-30). The ratio of the diameter of the artery (measured from the media to the external elastic laminal to the depth of the artery (measured from the epithelial and connective tissue junction to the most superficial aspect of the junction of the media and external elastic laminal should be less than 1.6.

Treatment and Prognosis

If the true nature of the callbcr-pcrslstcnt 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 is typically encountered if the lesion is removed.

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 are usually bilateral, but they may occur only on one side. They are more common on the anterior tonsillar pillar (Figure 1-31), but they also may involve the posterior pillar, The perforations are typically asymptomatic, ranging from a few millimeters to more than I em. 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 overall male-to-female ratio is 5:1. Because most cases have been seen in pubertal males. an endocrine influence has been suggested. Heredity also may playa role. because cases have been noted in siblings.

Coronoid hyperplasia may be unilateral or bilateral, although bilateral cases are nearly five 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, 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 is often superimposed on the zygoma on conventional radiographs, tomograms or 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 is usually accomplished via an intraoral approach. Although initial improvement in oral opening can be effected, the long-term results sometimes 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 37); however, in the latter condition the associated soft tissues and teeth also may be enlarged.

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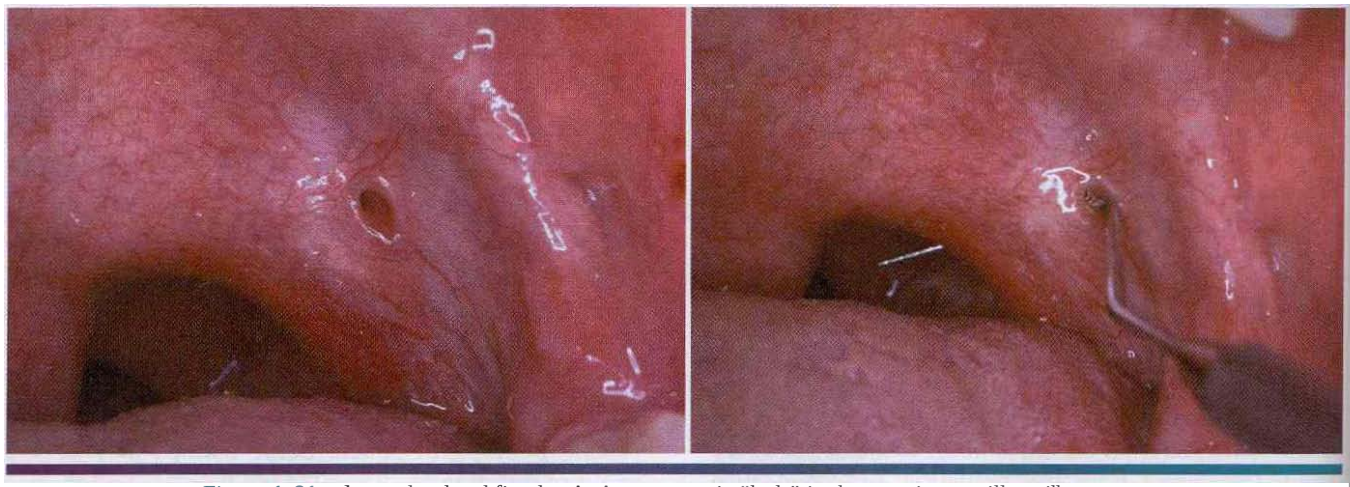


Figure 1-31 • lateral palatal fistula. A. Asymptomatic "hole" in the anterior tonsillar pillar. B. Periodontal probe has been used to demonstrate the communication of the lesion with the tonsillar fossa.

Clinical and Radiographic Features

Condylar hyperplasia may manifest itself in a variety of ways, including facial asymmetry, prognathism, crossbite, and open bite (Figure 1-32). Sometimes there is compensatory maxillary growth and tilting of the occlusal plane. The condition most commonly is discovered in adolescents and young adults.

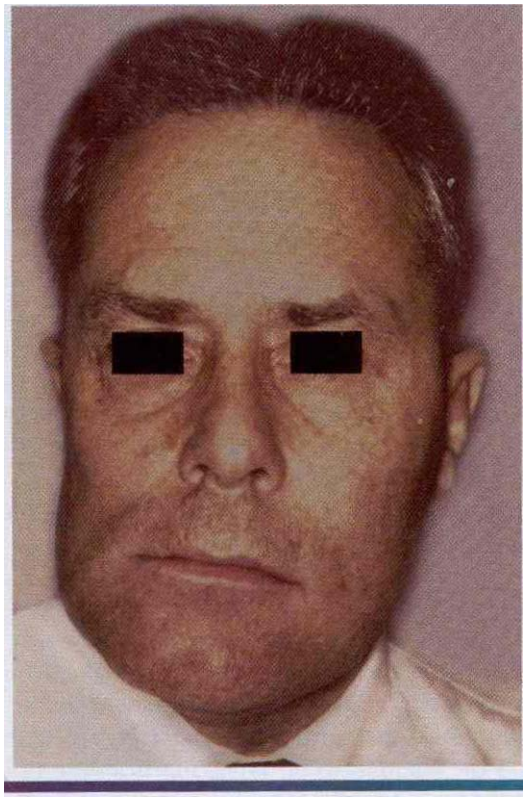


Figure 1-32 • **Condylar hyperplasia. Enlargement of the patient's left condyle has displaced the mandible to the right and resulted in facial asymmetry.**

The radiographic features are quite variable. Some patients have an irregular enlargement of the condylar head (Figure 1-33); others show elongation of the condylar neck. Many cases also demonstrate hyperplasia of the entire ramus, suggesting that the condition sometimes affects more than just the condyle. Scintigraphy using ^{99m}Tc-MDP has been advocated as a useful method for assessing the degree of bone activity in condylar hyperplasia.

Histopathologic Fealures

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 difficuily 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 42), oculoauriculovertebral syndrome (Goidenhar syndrome), and **hemifacial microsomia. In the most severe cases there is complete** agenesis of the condyle or ramus (**condylar aplasia).**

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

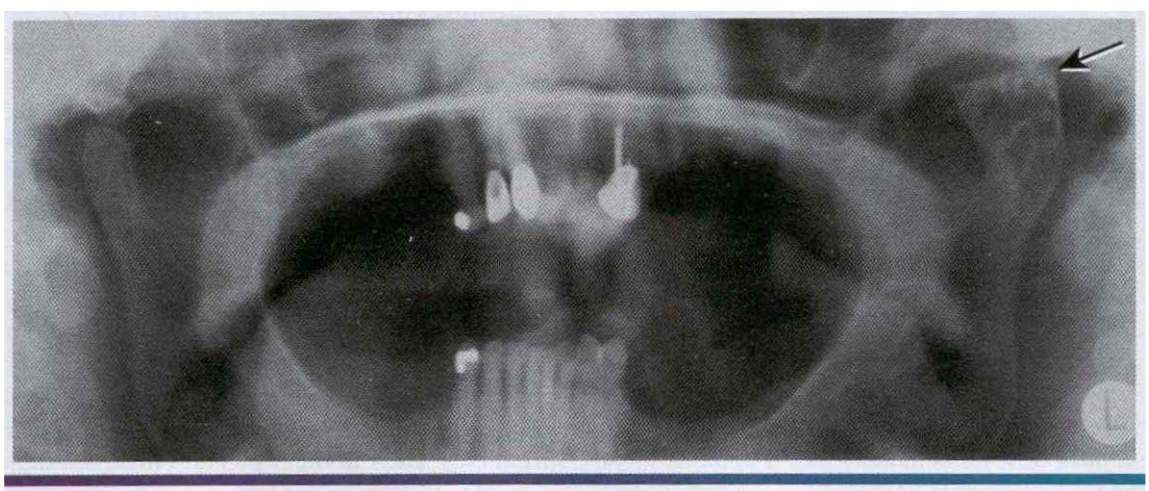


Figure 1-33. Condylar hyperplasia. Enlargement of the left mandibular condyle *(arrow)*. **(Courtesy of Dr. Gary** Reinhart.)

most frequent cause is trauma to thocondylar 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 rnandlbular midline shifts to the involved side when the mouth is opened, accentuattng the deformily. Ankylosis of the temporomandibular joint (TMlJ 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, a costochondral rib graft can be placed to help establish an active growth center. Osteotomies sometimes provide a cosmetically acceptable result.

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 is usually unilateral, but occasionally both sides may be affected. The malformation is often asymptornatlc and rnav be discovered on routine radiographs, although some patients may have a "pop" or "click" of the TM) when opening their mouths. Rarely does the patient complain of TMI. Radiographs demonstrate a bilobed appearance of the condylar head (Figure I-34).

Treatment and Prognosis

Because a bifid condyle is usually asvrnptornatlc. most of the time no treatment is necessary. If the patient has joint complaints, the appropriate temporomandibular therapy may be required.

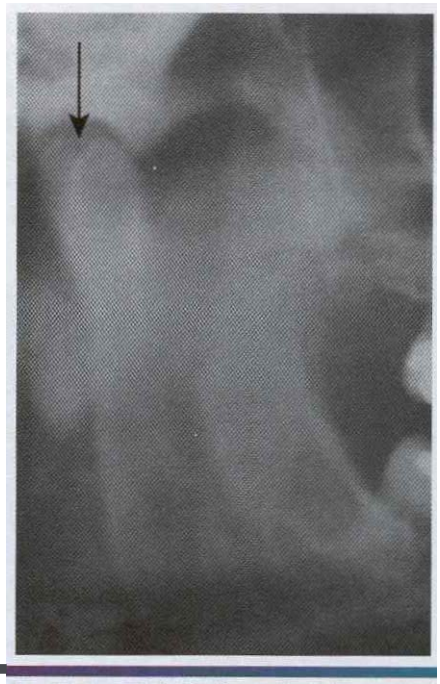


Figure 1-34 • Bifid condyle. Radiograph of the mandibular condyle showing a double head *(arrow)*. (Courtesy of Dr. Ed McGaha.)

EXOSTOSES

Exostoses are localized bony protuberances that arlse from the cortical plate, These benign growths frequently affect the jaws. The best-known oral exostoses. the torus palatinus and the torus mandibularis. are described later in the chapter. Other types of exostoses also may affect the [aws 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 (Figure 1-35). They are usually asyrnpromarie. unless the thin overlying mucosa becomes ulcerated from traurna. One study reported that buccal exostoses were found in 1 of every 1000 adults, although the prevalence could be even higher, They occur equally in males and females.

Palatal exostoses (palatal tubercles) are similar bony protuberances that develop from the lingual aspect of the maxillary tuberosities. These lesions are usually bilateral but may affect only one side (Figure 1-36). They arc more common in males and have been reported in as many as 30% to 69% of various populations. Some patients with buccal or palatal exostoses also may have palatal or mandibular tori.

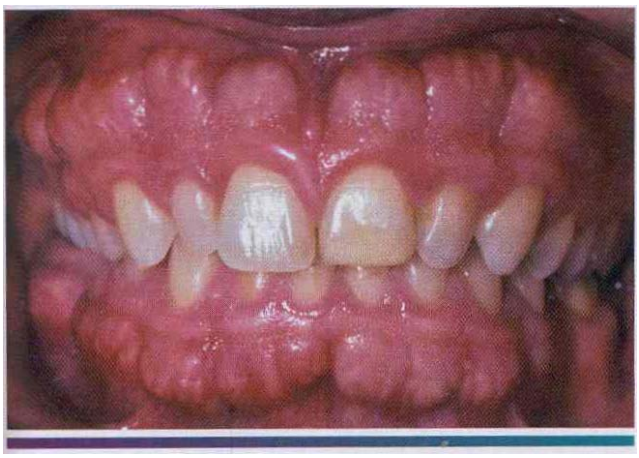


Figure 1-35 • Exostoses. Multiple buccal exostoses of the maxillary and mandibular alveolar ridges.

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 (Figure 1-37).

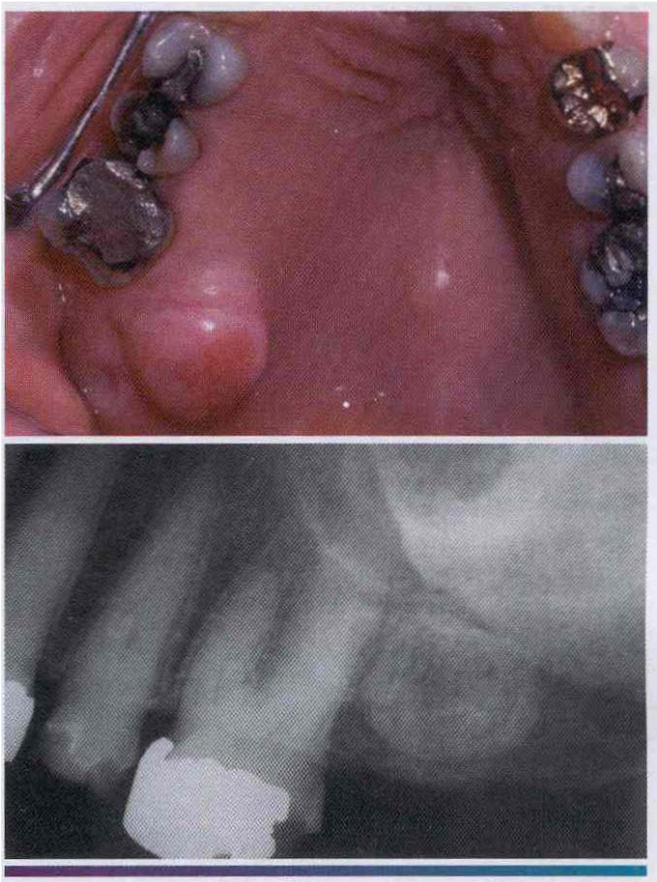
If enough excess bone is present, exostoses may exhibit a relative radiopacity on dental radiographs (see Figure 1-36, B). In rare instances an exostosis may become so large that it is difficult to distinguish from a tumor, such as an osteoma (see page 566).

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 so that biopsy is 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 subpontinc exostoses may need to be *removed* if they interfere with oral hygiene or are associated with adjacent periodontal disease.



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B

Figure 1-36. Exostosis. A. Secondarily ulcerated palatal exostosis. B. Radiograph shows an ovoid radiopacity distal to the molar.

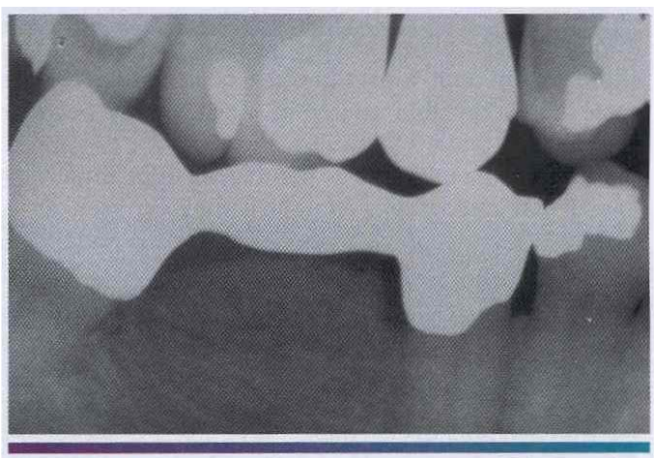

Figure 1-37 • Reactive subpontine exostosis. Nodular growth of bone beneath the pontic of a posterior mandibular bridge.

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, a "threshold" is surpassed and the trait (torus palatinus) will be expressed.

Clinical and Radiographic Features

The torus palatinus presents as a bony hard mass that arises along the midline suture of the hard palate (Figures 1-38 to 1-40). Tori sometimes are classified according to their morphology:

- 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 lobulated 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 does not usually 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 do appear to be significant racial differences, however, with a higher prevalence in Asian and Inuit (i.e., Eskimo) populations. In the United States, most studies have shown a prevalence of 20% to 35%, with little difference between whites and blacks. 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.

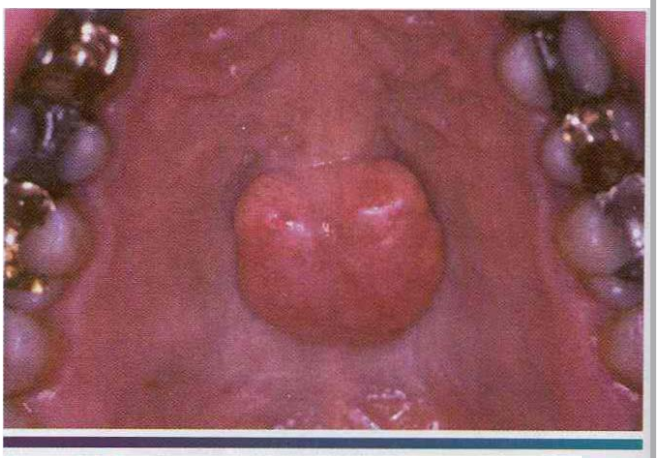

figure 1-38. Torus palatinus. Midline bony nodule of the palatal vault.

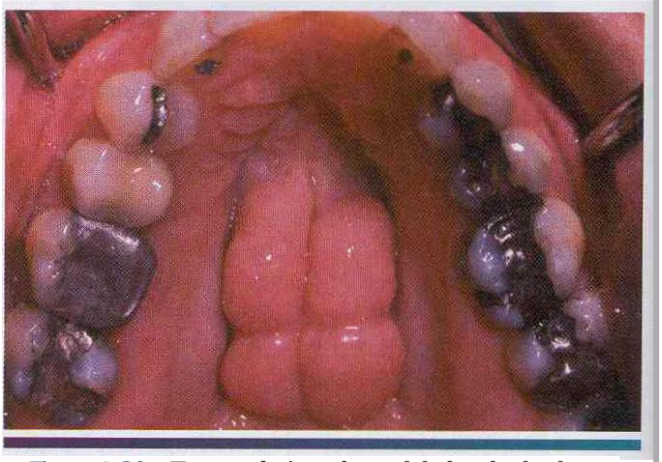

Figure 1-39 • Torus palatinus. Large, lobulated palatal mass.

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 may also be indicated for palatal tori that become repeatedly ulcerated or that interfere with oral function.

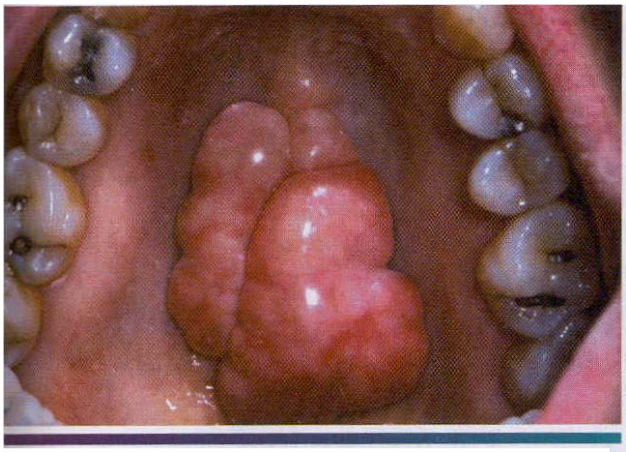

figure 1-40 • **Torus palatinus. Asymmetric, lobulated bony mass.**

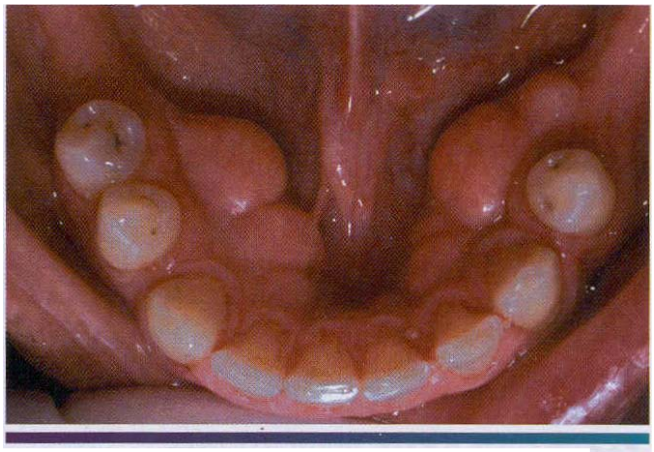

Figure 1-41 • Torus mandibularis. Bilateral lobulated **bony protuberances of the mandibular lingual alveolar ridge.**

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 is** probably multifactorial, including both genetic and environ**mental influences.**

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 (Figure 1-41). **Bilateral *involvement* occurs in more than 900/0 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 (Figure 1-42). A large mandibular torus may appear on periapical radiographs as a radiopacity superimposed on the roots of the teeth (Figure 1-43), especially on anterior films. **Mandibular tori arc easily visualized on occlusal radi**ographs (Figure 1-44).

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 Inuits. The prevalence in the United States ranges from 7% to 10%, 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 mandlbularis is multifactorial in development and responds to functional stresses.

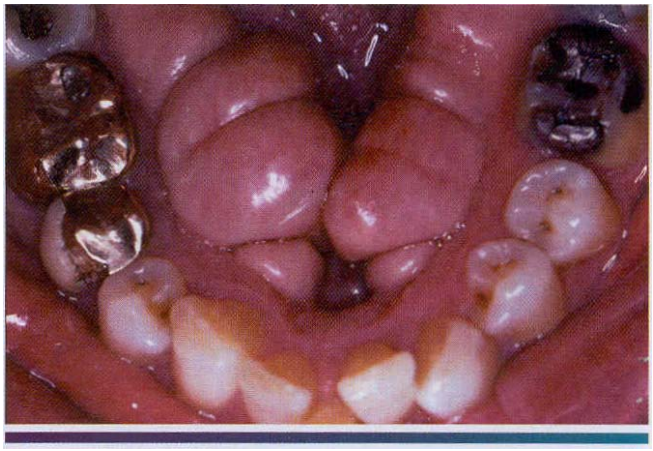

Figure 1-42 • Torus mandibularis. Massive "ktssing" **tori meet in the midline.**

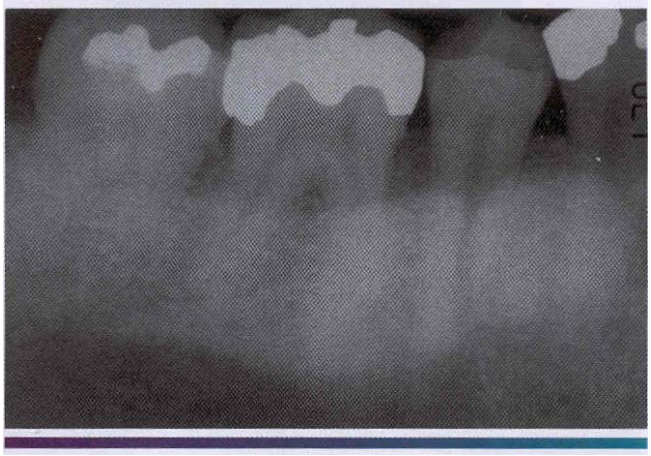

Figure 1-43 • Torus mandibularis. Torus is causing a radiopacity that is superimposed over the roots of the mandibular teeth.

Histopathologic Features

The histopathology of the torus mandibularis is similar to that of other exostoses. consisting primarily of a nodular mass of dense. cortical lamellar bone (Figure 1-45). 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.**

EAGLE SYNDROME (STYLOHYOID SYNDROME; CAROTID ARTERY SYNDROME)

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 40% of the population in some radiographic reviews. 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. 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, and transient syncope.

Elongation of the styloid process or mineralization of the stylohyoid ligament complex can be seen on panoramic or lateral-jaw radiographs (Figure 1-46). 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 cervicopharyngcal 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.

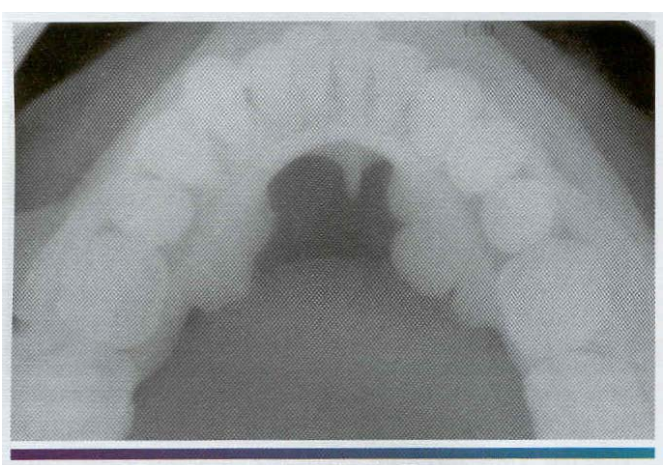

Figure 1-44 • Torus mandibularis. Occlusal radiograph showing bilateral mandibular tori.

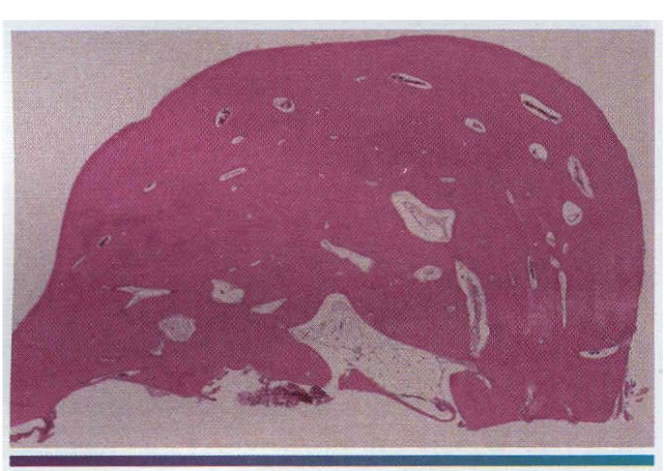

Figure 1-45 • Torus mandibularis. Nodular mass of dense. cortical bone. Some fatty marrow is visible at the base of the specimen.

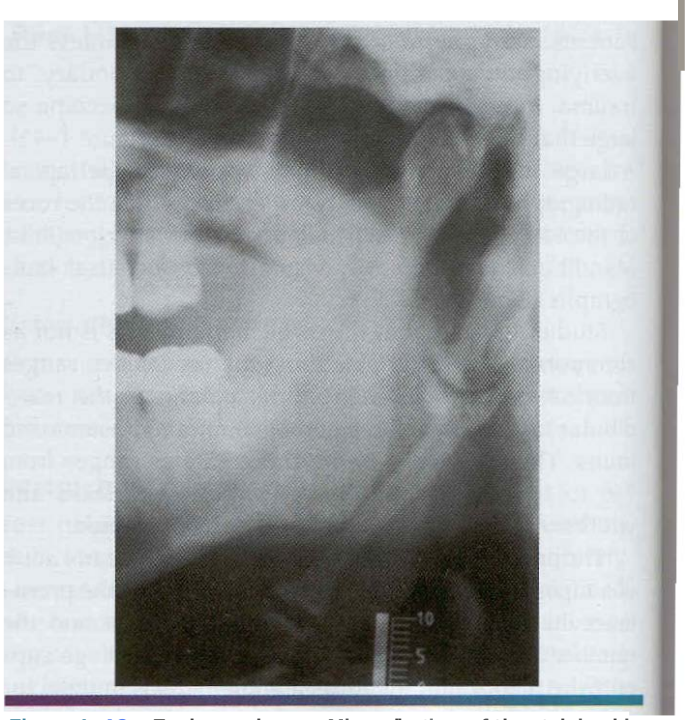

Figure 1-46 • Eagle syndrome. Mineralization of the stylohyoid ligament is visible posterior to the mandibular ramus.

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; UNGUAL 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. 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. tn addition, one report has implicated the parotid gland as the cause of an apparent cortical defect 1o the upper mandibular ramus. Therefore all of the major salivary glands appear to be capable of causing such cortical concavities.

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 (Figure 1-47). 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 (Figures 1-48 and 1-49).

Posterior Stafne defects are not rare, having been reported in 0.3% of panoramic radiographs. A striking male predilection is observed, with 80% to 90% of all cases seen in men.

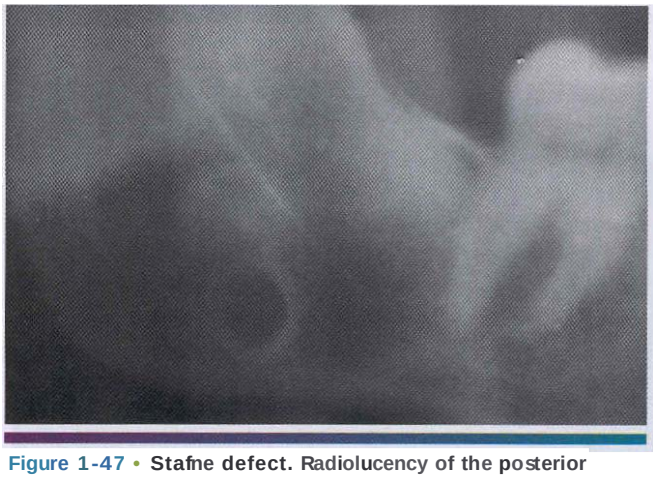

Figure 1-47 • Stafne defect. Radiolucency of the posterior mandible below the mandibular canal.

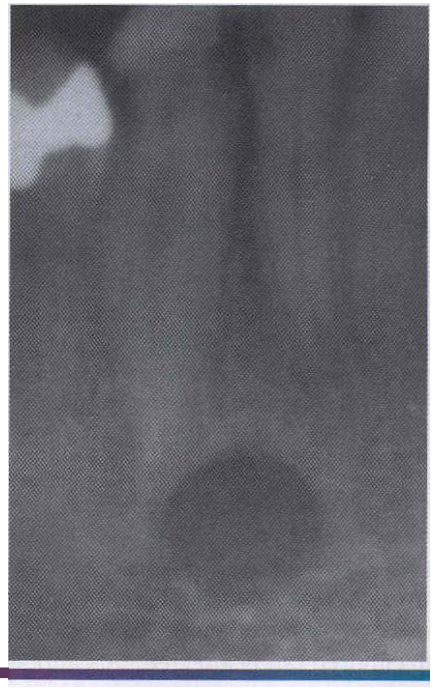

Figure 1-48 • Stafne defect. Anterior radiolucent lesion of the body of the mandible associated with the sublingual gland.

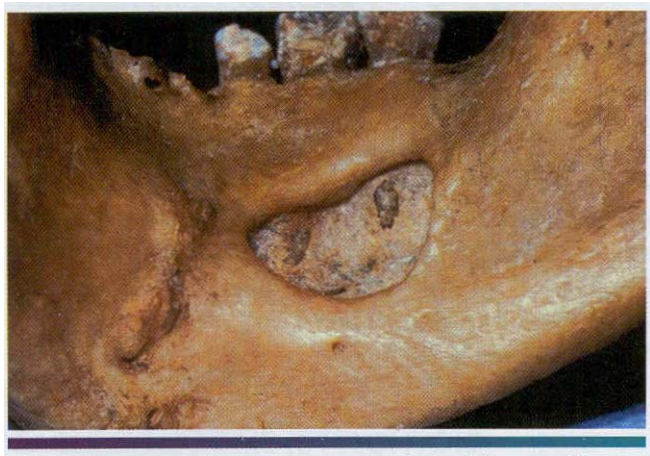

Figure 1-49 • Stafne defect. Lingual surface of the mandible showing an anterior cortical defect caused by the sublingual gland.

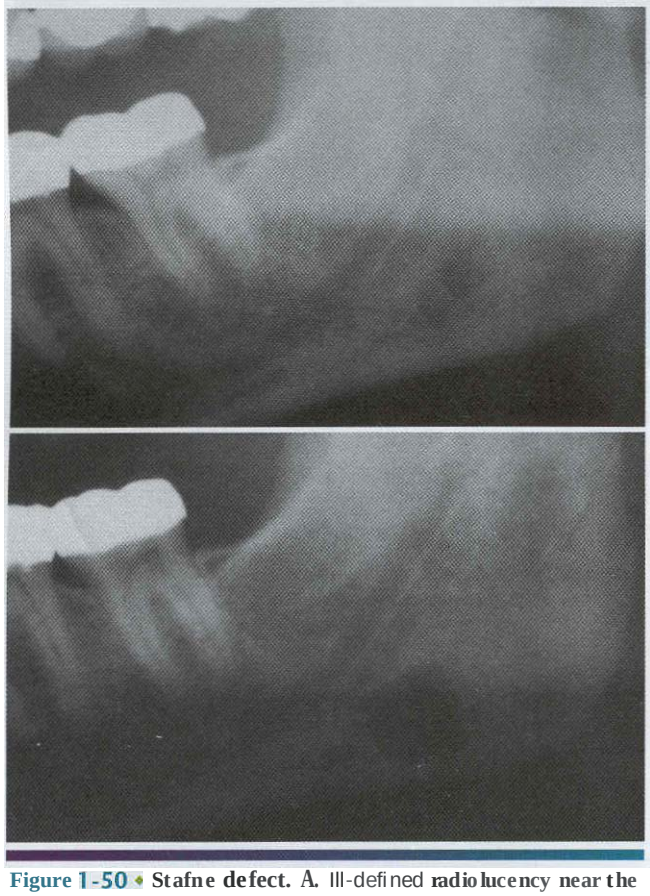

Figure 1-50 • Stafne defect. A. Ill-defined radiolucency near the angle of the mandible. **B.** Appearance of the same defect several years later showing enlargement of the lesion. (Courtesy of Dr. Carroll Gallagher.)

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 (Figure I-SOL This also indicates that these lesions are not congenital.

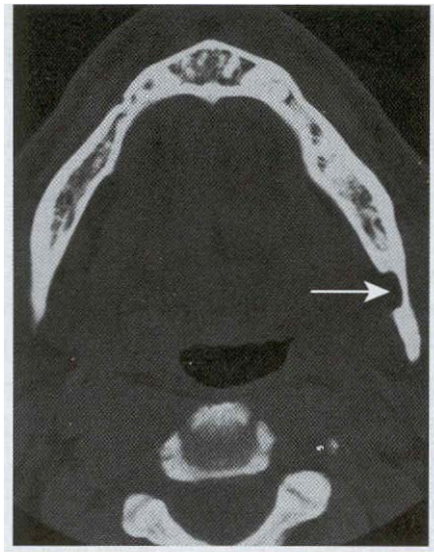

Figure 1-51 • Stafne defect. CT image of the same lesion in Figure 1-50, showing a left lingual cortical defect *(arrow).* (Courtesy of Dr Carroll Gallagher.)

The diagnosis can usually be made on a clinical basis by the typical radiographic location and lack of symptoms. If the clinical diagnosis is in doubt, it can be confirmed by CT scans, MRI, or sialography. CT scans and MRls show a well-defined concavity on the lingual surface of the mandible (Figure I-51). 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 is usually not necessary to establish the diagnosis of Staine defects of the posterior mandible. If biopsy is performed, normal submandibular gland tissue is usually 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 of the posterior mandible, and the prognosis is excellent. Because anterior lingual salivary defects may be difficult to recognize, biopsy may be necessary 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. It has been 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 tram 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 oithe newborn (see page 601), 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 65% to 85% of neonates. The cysts are small, 1- to 3-mm white or yellowish-white papules that appear most often along the midline near the junction of the hard and soft palates (Figure I-52), 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.

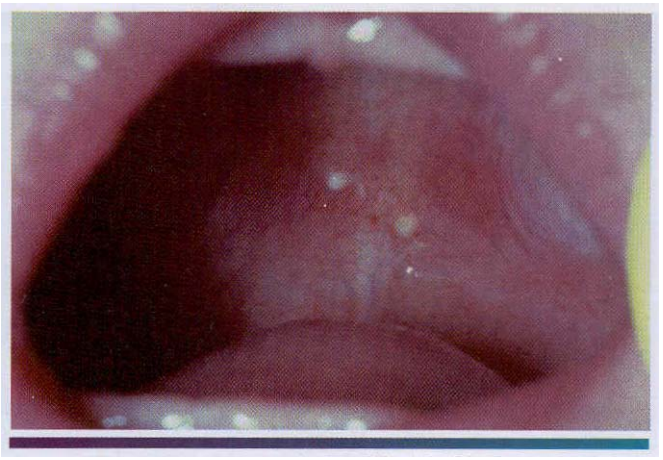

Figure 1-52 • Epstein's pearls. Small keratin-filled cysts at the junction of the hard and soft palates. (From Neville BW, Damm DO, White OK: *Color atlas of clinical oral pathology*, ed 2, Philadelphia, 1999, Williams & Wilkins.)

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)

The nasolabial cyst is a rare developmental cyst that occurs in the upper lip lateral to the midline. Its 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 histology.

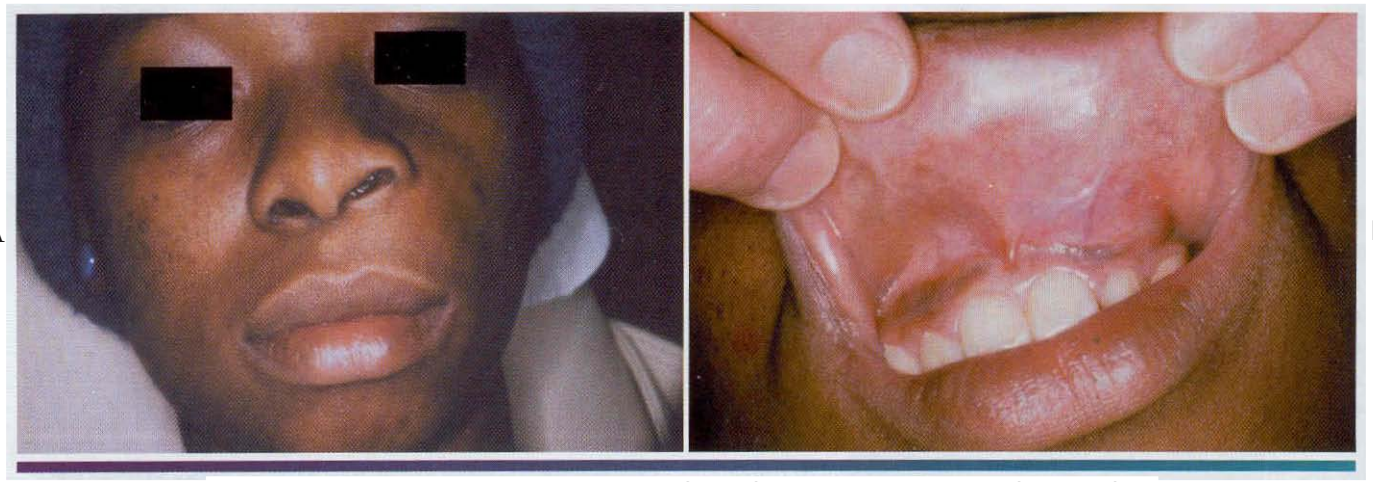

Figure 1-53 • Nasolabial cyst. A. Enlargement of the left upper lip with elevation of the ala of the nose. B. Intraoral swelling fills the maxillary labial fold. (Courtesy of Dr. Jim Weir.)

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 the nose. The enlargement often elevates the mucosa of the nasal vestibule and obliterates the maxillary mucolabial fold (Figure I-53). 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 a 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 there are no radiographic changes. 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 (Figure I-54). 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 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. Recurrence is rare. Recently an alternative transnasal approach has been suggested that allows endoscopic marsupialization of the cystic cavity.

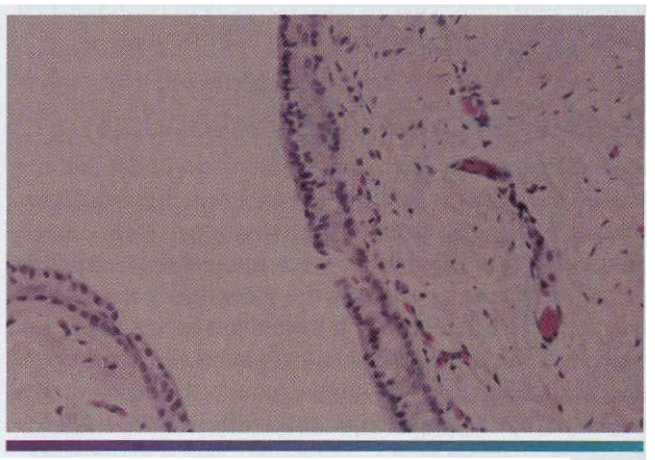

Figure 1-54 • Nasolabial cyst. Pseudostratified columnar epithelial lining.

"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. Current theory holds that most (if not all) cysts that develop in the globulomaxillary area are actually of odontogenic origin.

Clinical and Radiographic Features

The "globulomaxillary cyst" classically develops between the maxillary lateral incisor and cuspid teeth, although occasional globulomaxillary lesions have been reported between the central and lateral incisors. Radiographs typically demonstrate a well-circumscribed unilocular radiolucency between and apical to the teeth (Figure

1-55). Because this radiolucency often is constricted as it extends down between the teeth, it may resemble an inverted pear. As the lesion expands, tipping of the tooth roots may occur.

Histopathologic Features

Virtually all cysts in the globulomaxillary region can be explained on an odontogenic basis. Many are lined by inflamed stratified squamous epithelium and are consistent with periapical cysts (see page 116). Some exhibit specific histopathologic features of an odontogenic keratocyst (see page 594) or developmental lateral periodontal cyst (see page 602). It also has been theorized that some of these lesions may arise from inflammation of the reduced enamel epithelium at the time of eruption of the teeth.

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.

Treatment and Prognosis

Treatment of cysts in the globulomaxillary area usually consists of surgical enucleation. If the lesion can be related to an adjacent nonvital tooth, then endodontic therapy may be appropriate. Prognosis depends on the specific histopathologic type of cyst. Except for the odontogenic keratocyst, the recurrence potential should be low.

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.

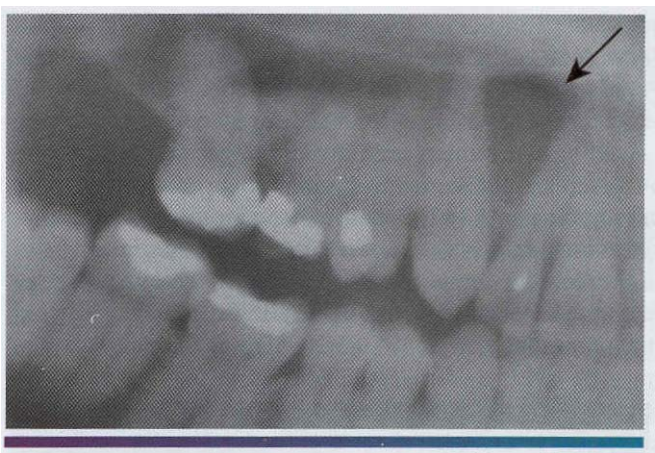

Figure 1-55 • "Globulomaxillary cyst." Inverted pear-shaped radiolucency *(arrow)* between the maxillary right cuspid and the lateral incisor. Biopsy revealed a periapical cyst.

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 vomeronasal organs of Jacobson, acting as an accessory olfactory organ. However, in humans, Jacobson's organ usually recedes in uterine life to become a vestigial structure.

It has been 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 (Figure I-56). 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.

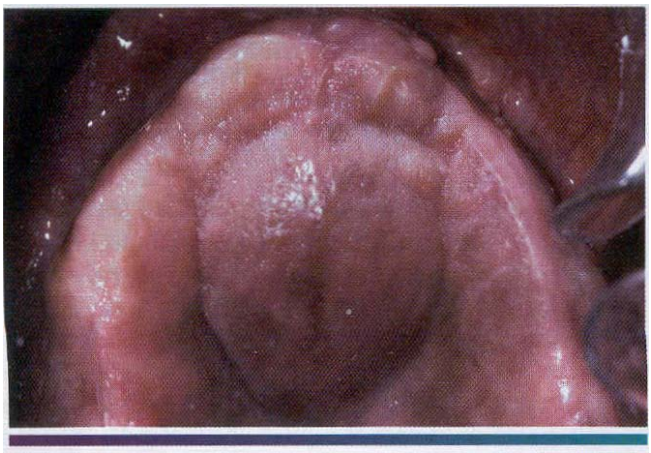

Figure 1-56 • Nasopalatine duct cyst. Fluctuant swelling of the anterior hard palate.

Radiographs usually demonstrate a well-circumscribed **radiolucency in or near the midline of the anterior maxilla**, between and apical to the central incisor teeth (Figures I-57 and I-58). Root resorption is rarely 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** mrn, **to destructive lesions as large as 6 cm. However, most cysts are in** the range of 1.0 to 2.5 em, with an average diameter of 1.5 to 1.7 em. 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 is usu**ally 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 (Figure I-59).

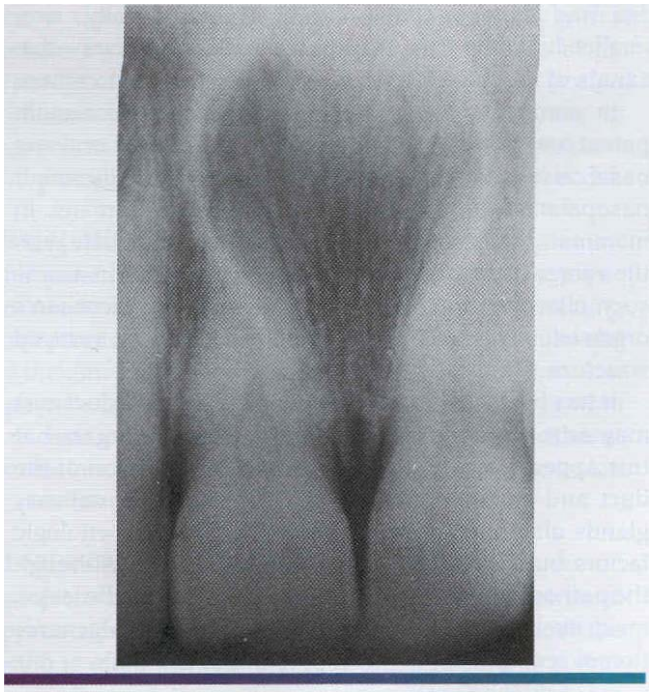

Figure 1-57 • Nasopalatine duct cyst. Well-circumscribed radiolucency between and apical to the roots of the maxillary central incisors.

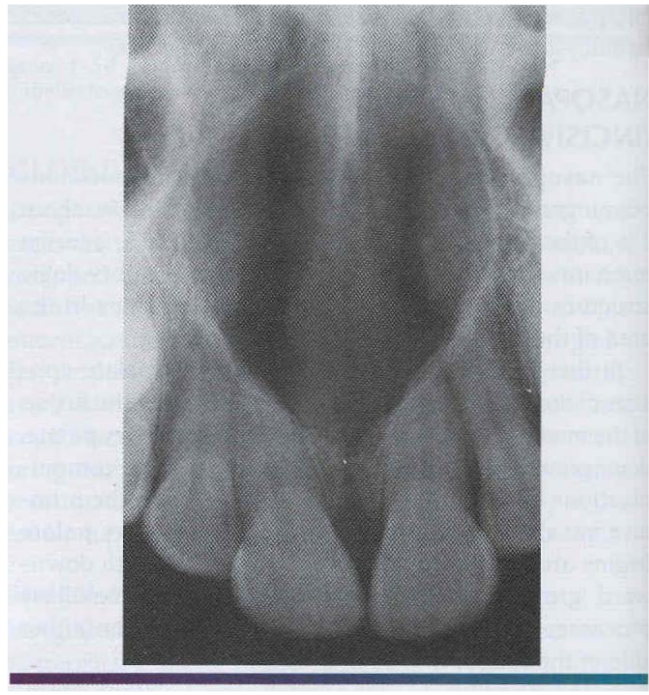

Figure 1-58 • Nasopalatine duct cyst. large destructive cyst of the palate.

Histopathologic Features

The epithelial lining of nasopalatine duct cysts is highly variable (Figures 1-60 and 1-61I. It may be composed of:

- Stratified squamous epitheliu m
- 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 about three fourths of all cysts. Pseudostratified columnar epithelium has been reported in approximately one third of all cases. Simple columnar and cuboidal epithelium are discovered less frequently.

Cilia and goblet cells may be found in association with columnar linings. The type of epithelium may be related 10 the vertical position of the cyst within the incisive canal. 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 squa**mous 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 are usually found in the wall of the cyst (Figure 1-62). 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 is usually chronic in nature and is composed of lymphocytes. plasma cells. and hlstlocytes, Associated acute inflammatory cells (neutrophils) sometimes may be seen.

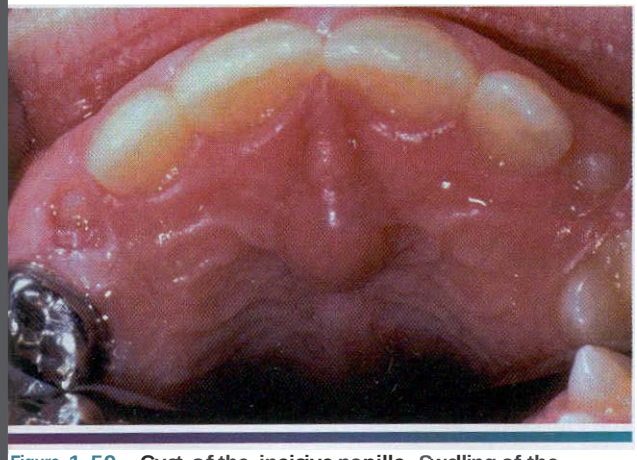

Figure 1-59 • **Cyst of the incisive papilla.** Swelling of the incisive papilla.

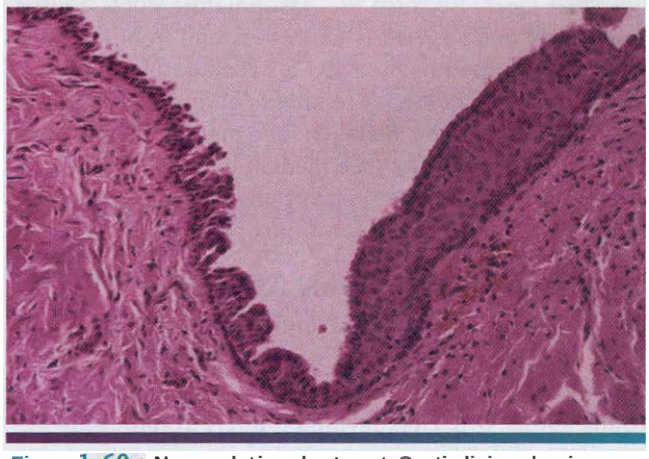

Figure 1-60 • **Nasopalatine duct cyst.** Cystic lining showing transition from pseudostratified columnar to stratified squamous epithelium.

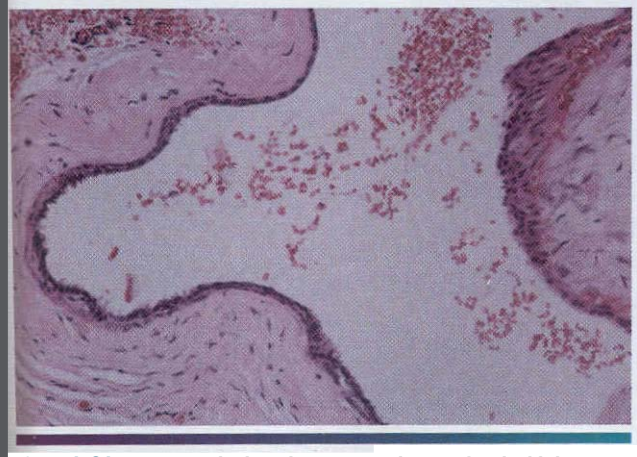

Figure 1-61 • **Nasopalatine duct cyst.** Flattened cuboidal epithelial lining.

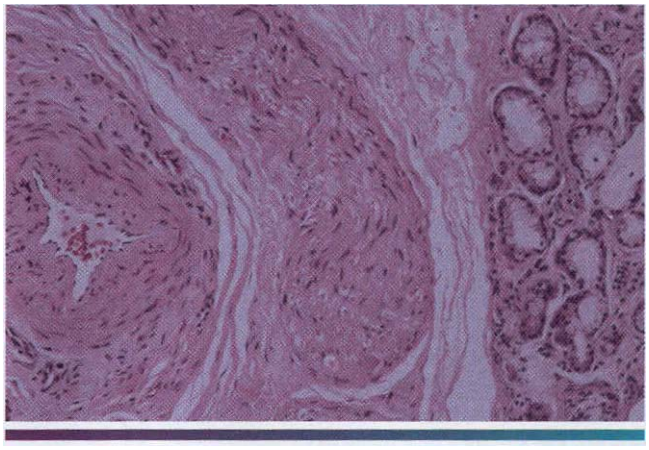

Figure 1-62 • **Nasopalatine duct cyst.** Cyst wall showing blood vessels, nerve bundles, and minor salivary glands.

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 ncar 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, 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. 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 X 2 ern, but sometimes it can become quite large. Occlusal radiographs demonstrate a well-circumscribed radiolucency in the midline of the hard palate (Figure 1-63). 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.

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 is usually lined by stratified squamous epithelium. Areas of ciliated pseudostratified columnar epithelium have been reported in some cases. Chronic inflammation may be present in the cyst wall.

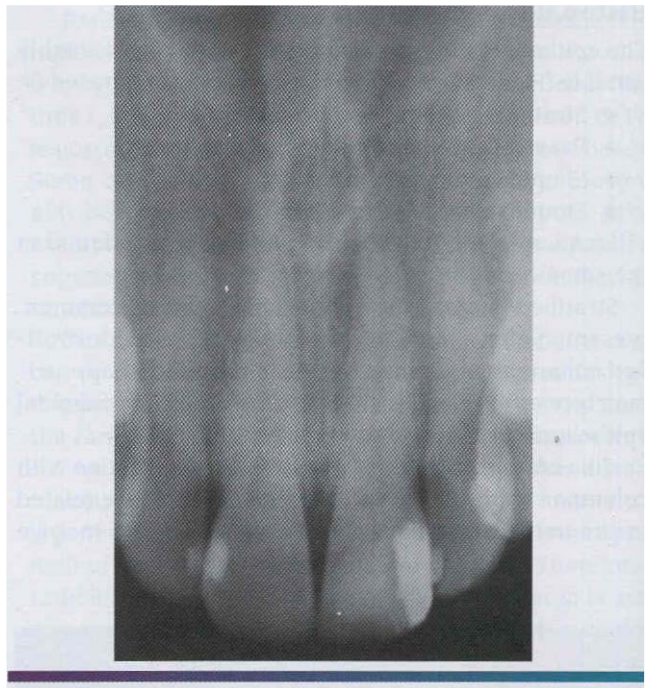

Figure 1-63 • Median palatal cyst. Well-circumscribed radiolucency apical to the maxillary incisors in the midline. At surgery the lesion was unrelated to the incisive canal. (Courtesy of Dr. Timothy Armanini.)

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 bllobcd proliferation of mesenchyme with a central isthmus in the midline. As the mandible develops, this isthmus is eliminated. Therefore because no fusion of epithelium-lined processes occurs, entrapment of epithelium should not be possible. For this reason it appears likely that most (if not all) of these midline cysts are of odontogenic origin.

Clinical and Radiographic Features

Reported cases of "median mandibular cyst" have presented as a midline radiolucency found between or apical to the mandibular central incisor teeth. Cortical expansion may be noted. A couple of purported cases have been partially within bone and partially within soft tissue.

Histopathologic Features

The type of epithelial lining *varies* in reported cases of "median mandibular cyst." The most common lining is composed of stratified squamous epithelium, and most of these cases may actually *have* been periapical or residual cysts, Some cysts in this location may be classified as odontogenic keratocysts or developmental lateral periodontal cysts.

A few reported cysts *have* been lined with pseudostratified, ciliated columnar epithelium. These findings raise the greatest possibility of the existence of an actual fissural cyst in this location. However, periapical cysts exhibit respiratory epithelium in rare instances. In addition. these cases now may fit into the category of glandular odontogenic cyst (see page 607), a more recently recognized developmental cyst of odontogenic origin.

Treatment and Prognosis

The treatrnent of choice for cysts in the median mandibular area **is surgical enucleation. Recurrence is not expected in most cases.**

EPIDERMOID CYST OF THE SKIN

The epidermoid cyst is a common cyst of the skin that is lined by epidermis-like epithelium. Most epidermoid cysts are derived from the follicular infundibulum and also are called infundibular cysts. 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, tricholemmal, 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*.

Epidermoid cysts of the skin may occasionally arise after traumatic implantation of epithelium. Rarely, such epidermal inclusion cysts also can develop in the mouth. These small inclusion cysts probably should be dlstlngulshcd 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 32).

Clinical Features

Epidermoid cysts of the skin 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 567). Young adults are more likely to *have* cysts on the face, whereas older adults are 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 (Figures 1-64 and 1-65). If a noninflamed lesion presents in an area of thin skin, such as the earlobe, it may be white or yellow.

Histopathologic Features

Microscopic examination reveals a cavity that is lined by stratified squamous epithelium resembling epidermis (Figure 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 inflam**matory reaction. including multinucleated giant cells, can be present in the cyst wall because the exposed ker**atin is recognized as a foreign material.**

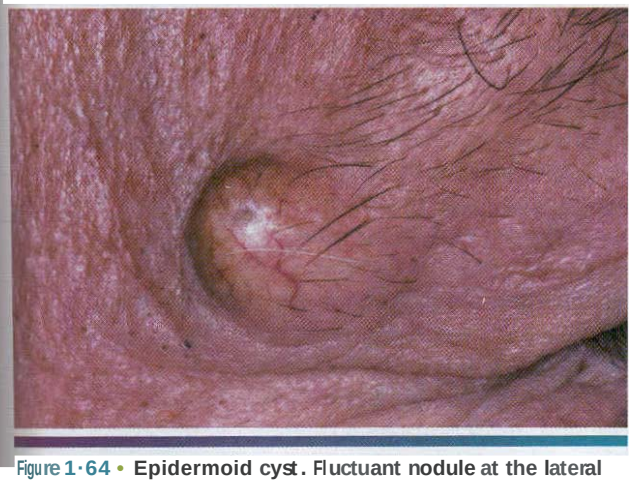

Figure 1-64 • **Epidermoid cyst. Fluctuant nodule at the lateral** edge of the eyebrow.

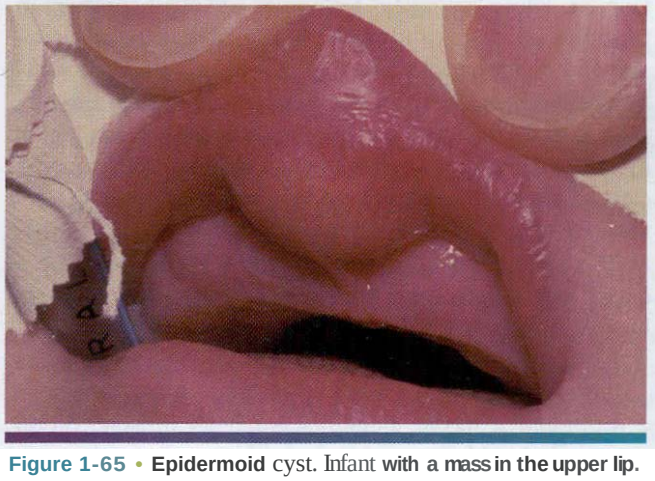

Figure 1-65 • **Epidermoid** cyst. Infant **with a mass in the upper lip.**

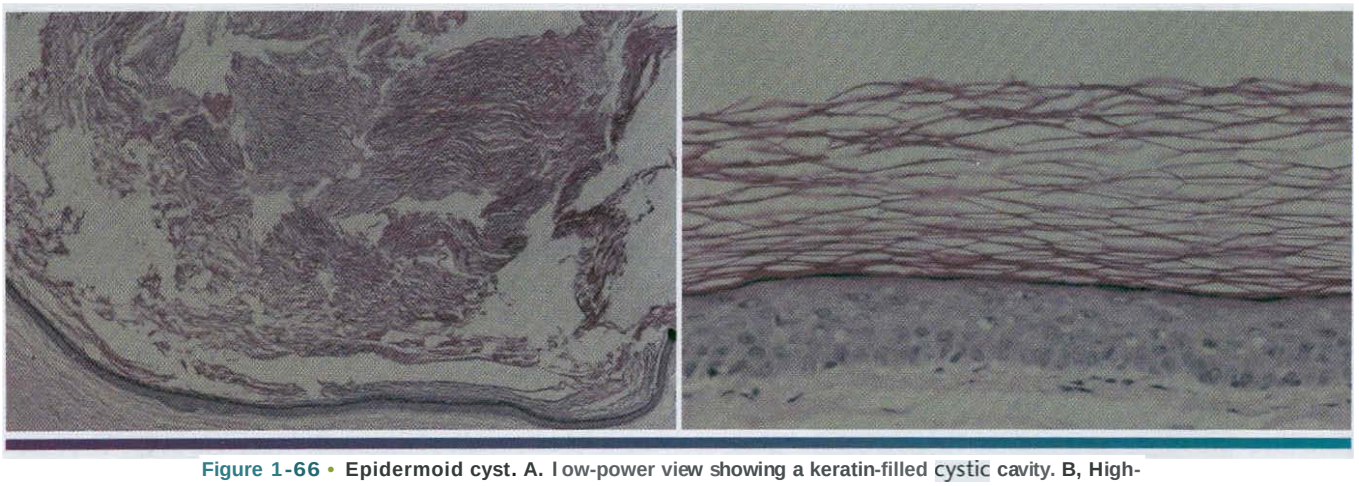

Figure 1-66 • **Epidermoid cyst. A.** low-power view showing a keratin-filled cystic cavity. **B,** High-powered view showing stratified squamous epithelial lining with orthokeratin production.

Treatment and Prognosis

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

DERMOID 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 true teratoma is a developmental tumor composed of tissue from all three germ layers: ectoderm. mesoderm, and 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 **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 are usually congenital in nature. When they occur. they usually extend through a cleft palate from the pituitary area via Rathke's pouch. Cer**vical teratomas also have been reported.**

The term teratoid cysl 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** (cnterocystomas: **enteric duplication cysts) are** usually 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 are occasionally found in combination with dermoid cysts.

Dermoid cysts are simpler in structure than complex ter-atomas 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 31). a nonteratomatous lesion that arises from the hair follicle.

Clinical and Radiographic Features

Dermoid cysts most commonly occur in the midline of the floor of the mouth (Figure 1-67), although occasionally they arc displaced laterally or develop in other locations. If the cyst develops above the geniohyoid muscle, 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 mil**limeters 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.

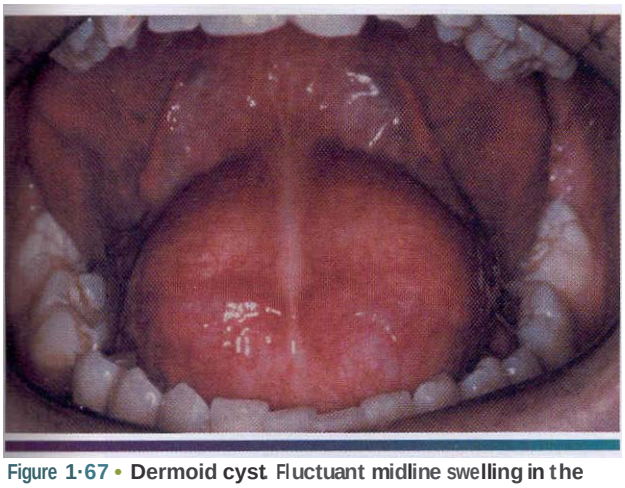

Figure 1-67 • **Dermoid cyst.** Fluctuant midline swelling in the floor of the mouth. (From Budnick SO: *Handbook of pediatric oral pathology,* Chicago, 1981, Year Book Medical.)

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 (Figure 1-68).

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 at the end of the third 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.

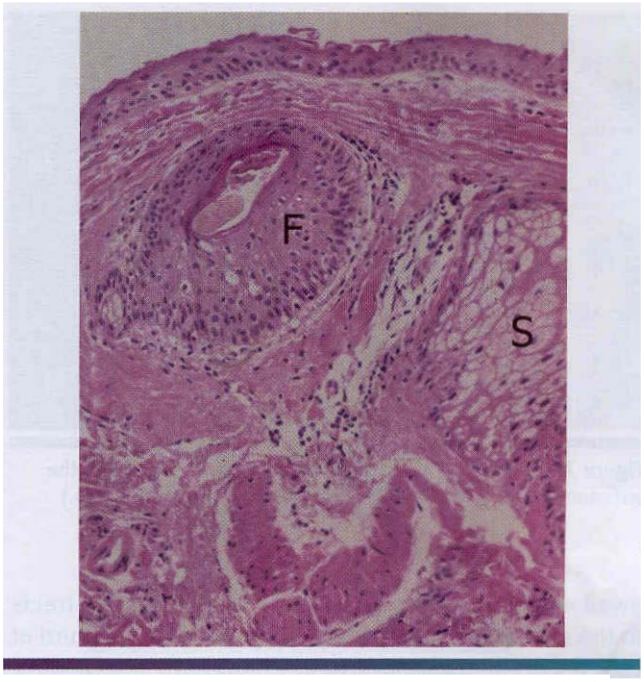

Figure 1-68 • **Dermoid cyst.** Squamous epithelial lining *(top)*, with hair follicle *(F)* and sebaceous glands (5) in the cyst wall.

The thyroglossal duct epithelium normally undergoes atrophy and is obliterated. However, remnants of this epithelium may persist and 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. Suprahyoid cysts may be submental in location. In 60% to 80% of cases, the cyst develops below the hyoid bone. Intralingual cysts are rare. 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.

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 (Figure 1-69). 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 maintains an attachment to the hyoid bone or tongue, it will move vertically during

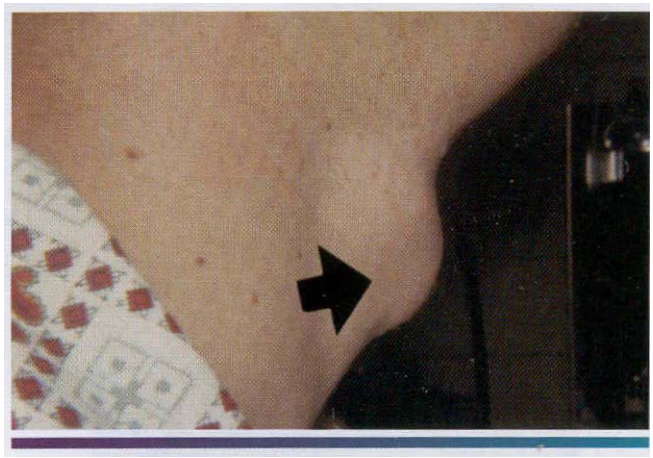

Figure 1-69 • Thyroglossal duct cyst. Swelling *(arrow)* of the anterior midline of the neck. (Courtesy of Dr. Philip Sprinkle.)

swallowing or protrusion of the tongue. Fistulous 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 are usually lined by columnar or stratified squamous epithelium, although occasionally, cuboidal or even small intestine epithelium may be documented (Figure 1-70). Sometimes a mixture of epithelial types is present. 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 less than 1% 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, a developmental cyst of the lateral neck, has a disputed pathogenesis. The classic theory holds that the cyst develops from remnants of the branchial clefts because it occurs in the area of the embryonic gill arch apparatus. A second theory considers that it arises from cystic changes in parotid gland epithelium that becomes entrapped in the upper cervical lymph nodes during embryonic life.

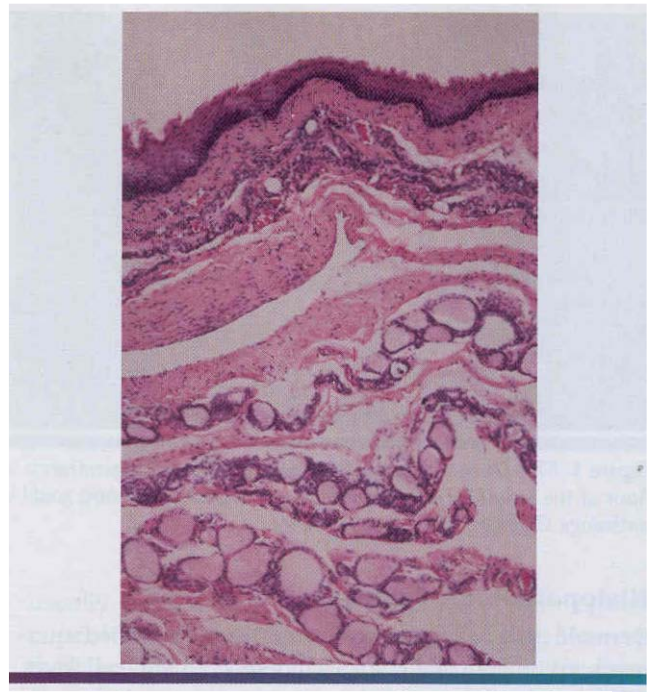

Figure 1-70 • Thyroglossal duct cyst. Cyst *(top)* lined by stratified squamous epithelium. Thyroid follicles can be seen in the cyst wall *(bottom)*.

Recent immunohistochemical evidence has supported the classic branchial cleft theory of pathogenesis for this lesion. About 95% of these cysts are believed to arise from the second branchial arch, with the remaining 5% originating from the first, third, and fourth branchial arches.

Clinical Features

The branchial cleft cyst most commonly occurs in the upper lateral neck along the anterior border of the sternocleidomastoid muscle (Figures 1-71 and 1-72). It most frequently affects young adults between the ages of 20 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 lesions appear as sinuses or fistulae that may produce a mucoid discharge onto the skin. Two thirds of branchial cleft cysts occur on the left side of the neck, and one third are found on the right side. In rare instances bilateral cysts may develop.

Although one theory suggests that these cysts are derived from parotid epithelium that becomes entrapped within lymph node tissue, lymphoepithelial cysts are uncommon within the parotid gland itself. In recent years, however, increased numbers of parotid lymphoepithelial cysts have been reported in patients with human immunodeficiency virus (HIV) infection. These are probably related to intraparotid lymphadenopathy associated with HIV infection.

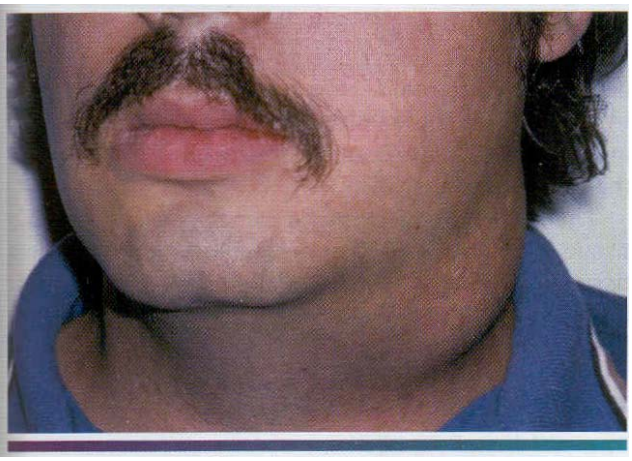

Figure 1·71 • Cervical lymphoepithelial cyst. Fluctuant swelling of the lateral neck.

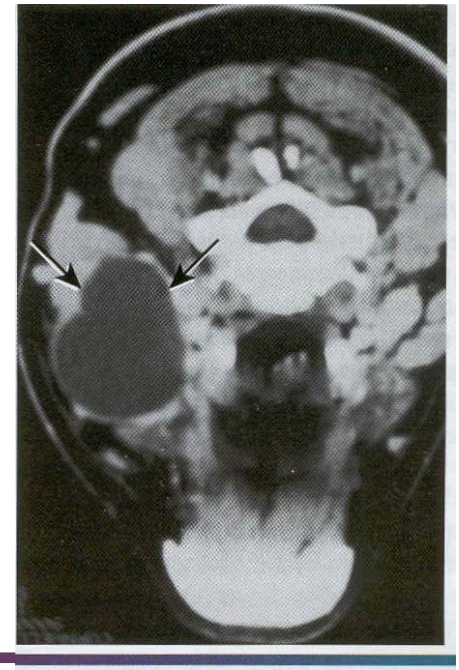

Figure 1-72 • Cervicallymphoepithelial cyst. Imaging study of the same cyst depicted in Figure 1-71. showing a well-circumscribed lesion of the lateral neck *(arrows)*.

Histopathologk Features

More than 90% of branchial cleft cysts are lined by stratified squamous epithelium that mayor may not be keratinized (Figure 1-73). Some cysts demonstrate 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 of these cases probably represent cystic metastases from previously undetected carcinomas of the head and neck region. especially the nasopharynx.

ORAIIYMPHOEPITHELIAL CYST

The oral lymphoepithelial cyst is an uncommon lesion Olthe mouth that develops within oral lymphoid tissue. It is microscopically similar to the branchial cleft cyst lcervical lymphoepithelial cystl but much smaller in size.

lymphold tissue is normally found in the oral cavity and pharynx. principally consisting of Waldeyer's 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 ol'erlying mucosal epithelium. This epithelium demonstrates invaginations into the tonsillar tissue. resulting in blindpouches 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 sartace. jt also is possible that oral lymphoepithelial cysts

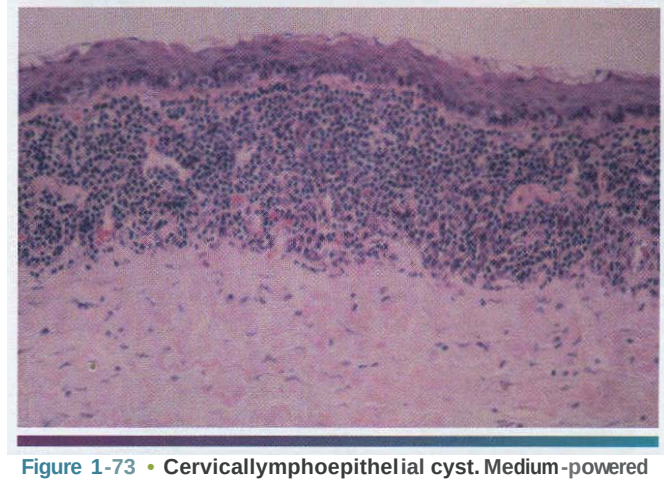

Figure 1-73 • Cervicallymphoepithelial cyst. Medium-powered view showing a cyst lined by stratified squamous epithelium. Note the lymphoid tissue in the cyst wall.

may develop from salivary or surface mucosal epitheliu m 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 I cm in diameter; rarely will the lesion be greater than t.Scm (Figures 1-74 and i-75). 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.**

Oral lymphoepithelial cysts may develop in people of almost any age, but they are most common in young adults. The most frequent location is the floor of the mouth, with at least half of all cases found there. The ventral surface and posterior lateral border of the tongue are the next most common sites. These cysts also may develop in the area of the palatine tonsil or 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 (Figure 1-76). This epithelium is typically parakeratinized, with desquamated epitheiial cells seen filling the cyst lumen. In rare instances the epitheliai 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 is usually 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.

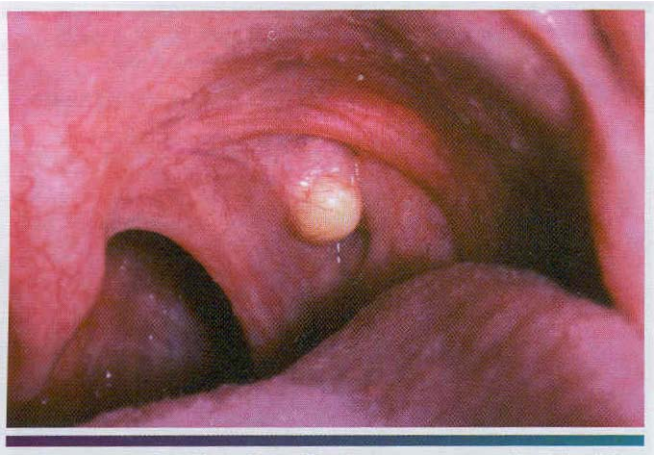

Figure 1-74 . Oral lymphoepithelial cyst. Small yellowish-white nodule of the tonsillar fossa.

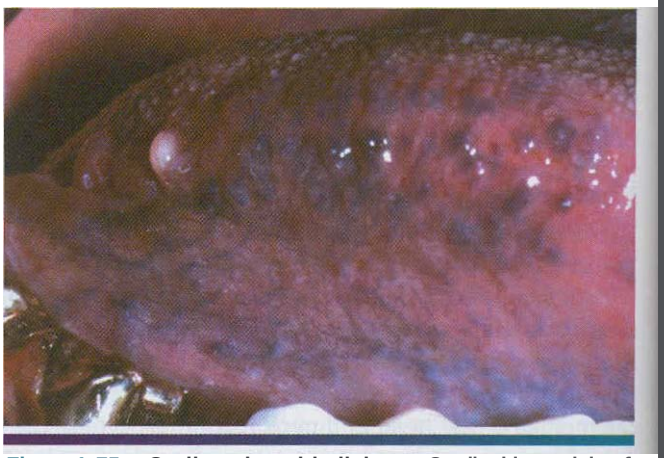

Figure 1-75 • Orallymphoepithelial cyst. Small white nodule of the posterior lateral border of the tongue.

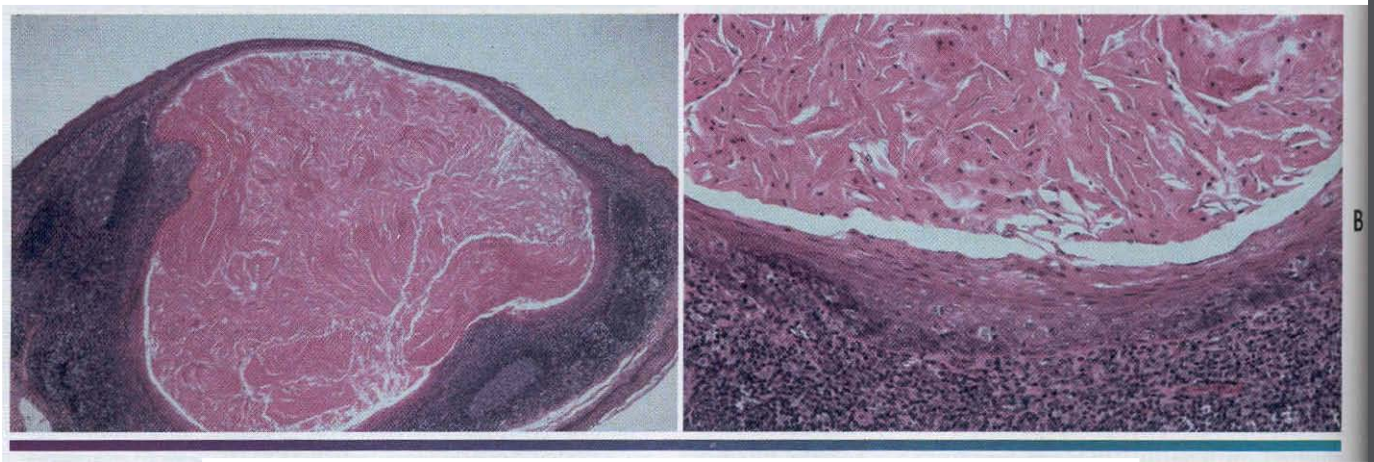

Figure 1-76 . Orallymphoepithelial cyst. A. low-power view showing a keratin-filled cyst below the mucosal surface. lymphoid tissue is present in the cyst wall. B. High-power view showing lymphoid tissue adjacent to the cystic lining.

Other Rare Developmental Anomalies

HEMIHYPERPLASIA (HEMIHYPERTROPHY)

Hemihypcrplasia is a rare developmental anomaly **characterized by asymmetric overgrowth of one or more** body parts. Although the condition is known more commonly 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 1-21.

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

Clinical and Radiographic Features

In a person with hemihyperplasia. one whole side of the body (complex hemihyperpla sia) 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 (or hemifacial hypertrophy) may apply. The condition can occasionally be crossed, involving different areas on both sides of the body, Hemihypcrplasia shows a 2: I 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 (Figure 1-77). 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.** About 20% of those affected are mentally retarded. One **of the most significant features is an increased preva**lence of abdominal tumors. especially Wilms turnor., adrenal cortical carcinoma. and hepatoblastorna. 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 (Figure 1-78). Enlargement of other oral soft tissues and bone can occur (Figure 1-79). The **mandibular canal may be increased in size on radio**graphs. The crowns of the teeth on the affected side.

Box 1-2 *Maltor",a,;o" Syndromes* ***Associated with Hemihyperplasia***

- **Beckwith-Wiedemann syndrome**
- **Neurofibromatosis**
- lippel-Trenaunay-Weber syndrome
- **Proteus syndrome**
- McCune-Albright syndrome
- **Epidermal nevus syndrome**
- Triploid/diploid mixoploidy
- **Langer-Giedion syndrome**
- **Multiple exostoses syndrome**
- **Maffucci's syndrome**
- **Oilier syndrome**
- Segmental odontomaxillary dysplasia

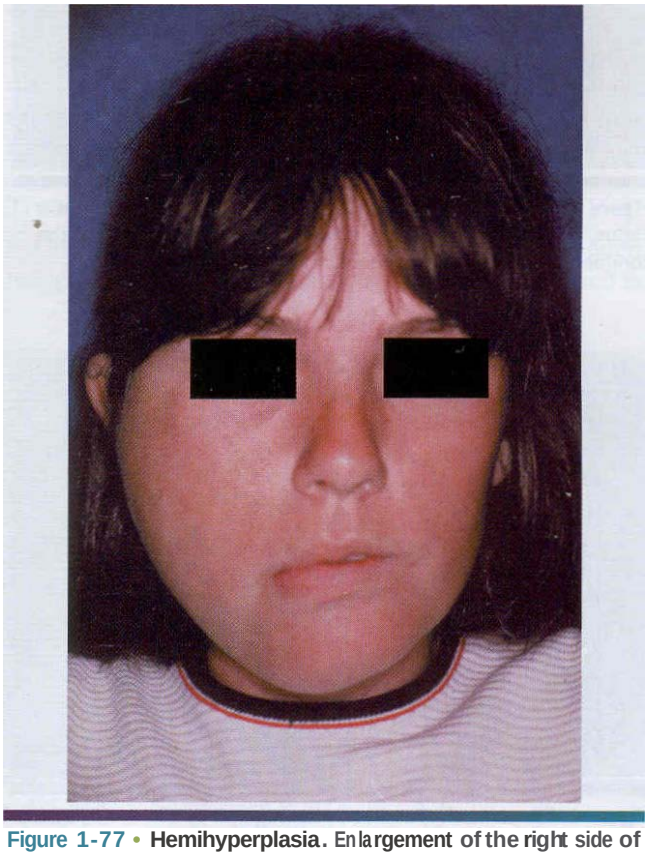

Figure 1-77 • Hemihyperplasia. Enlargement of the right side of the face. (Courtesy of Dr. George Blozis.)

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 and neurofibromatosis (see page 458), 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 is also frequently needed.

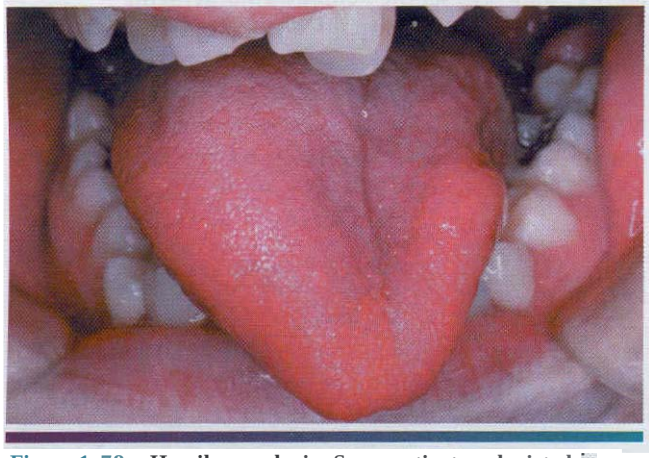

Figure 1-78 • Hemihyperplasia. Same patient as depicted in Figure 1-77. with associated enlargement of the right half of the tongue. (Courtesy of Dr. George Blozis.)

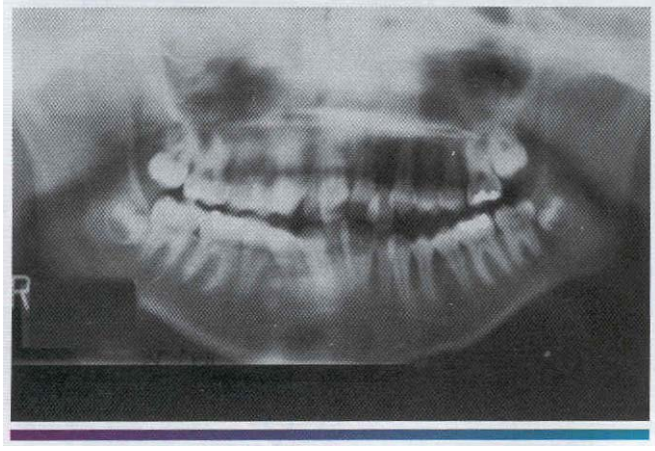

Figure 1-79 • Hemihyperplasia. Radiograph of the same patient in Figures 1-77 and 1-78. Mandible and teeth on the right side are enlarged. (Courtesy of Dr. George Blozis.)

PROGRESSIVE HEMIFACIAL ATROPHY (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 prior trauma has been documented in some cases. although other **reports have considered a viral or *Borrelia* infection.** Usually. the condition is sporadic, but a few familial cases have been reported. suggesting a possible hereditary influence. Many investigators believe that hemifacial atrophy represents a localized form of scleroderma (see page 692).

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 (Figure 1-80). This atrophy progresses at a vari-

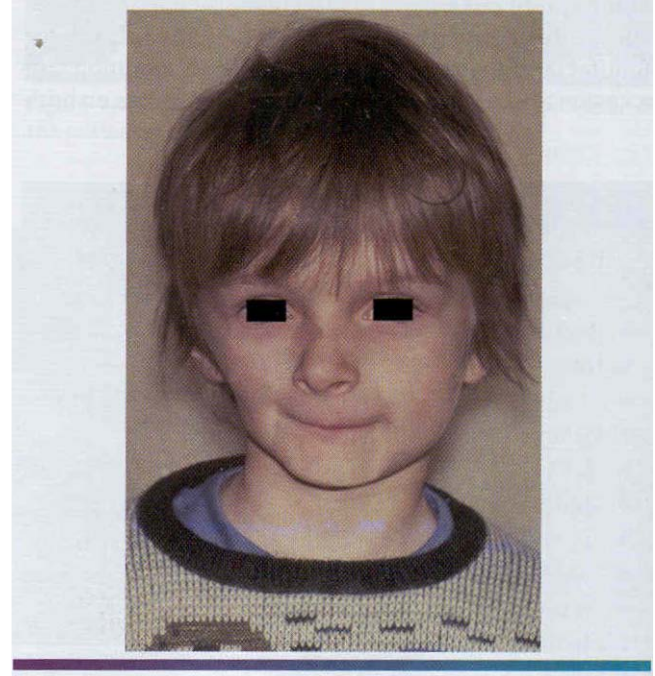

Figure 1-80 • Progressive hemifacial atrophy. Young girl with right-sided facial atrophy.

able 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.

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 *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 contralateral jacksonian epilepsy may develop.

The mouth and nose are deviated toward the defective 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. Degenerative changes in the vascular endothelium can be identified with electron microscopy.

Treatment and Prognosis

The atrophy typically progresses slowly for several 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 is usually discovered during childhood and is characterized by painless, unilateral enlargement of the maxillary bone, along with fibrous hyperplasia of the overlying gingival soft tissues (Figure 1-81). 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 been associated with hypertrichosis of the overlying facial skin. One patient was described with a Becker's 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.

Treatment and Prognosis

Because segmental odontomaxillary dysplasia has been recognized only recently as a distinct entity, not much is

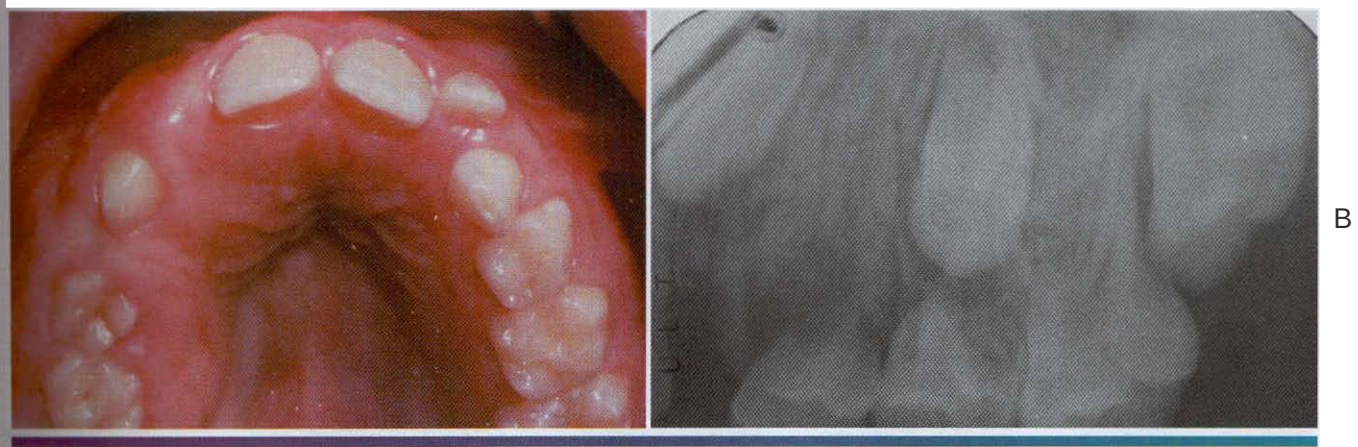

Figure 1-81 • Segmental odontomaxillary dysplasia. A. Unilateral enlargement of the maxilla and overlying gingival soft tissues. B. Periapical radiograph showing coarse trabecular pattern with absence of the first premolar.

known about its natural evolution. Once diagnosed, the condition seems to remain stable and may not require surgical intervention. However, orthodontic therapy and orthognathic surgery may be considered in some cases.

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 a mutation of the fibroblast growth factor receptor 2 (FGFR2) gene on chromosome 10q. 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 *(kleebfattschadei* deformity). The orbits are shallow, resulting in characteristic ocular proptosis (Figure 1-82). 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 ("beaten-metal" pattern).

The maxilla is underdeveloped, resulting in midface hypoplasia. Often the maxillary teeth are crowded, and there is usually occlusal disharmony. 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 intracranial pressure. Frontoorbital advancement can be performed to correct the ocular defects, with midfacial advancement used to correct the maxillary hypoplasia.

APERT SYNDROME (ACROCEPHALOSYNDACTYIY)

Like Crouzon syndrome, Apert syndrome is a rare condition that is characterized by craniosynostosis. It occurs in about 1 of every 65,000 to 160,000 births and is caused by a mutation in the fibroblast growth factor receptor 2 (FGFR2) gene. Although it Is inherited as an autosomal dominant trait, most cases represent sporadic new mutations, often associated with increased paternal age.

Clinical and Radiographic Features

Craniosynostosis typically produces acrobrachycephaly (tower skull); severe cases may demonstrate the *klee-*

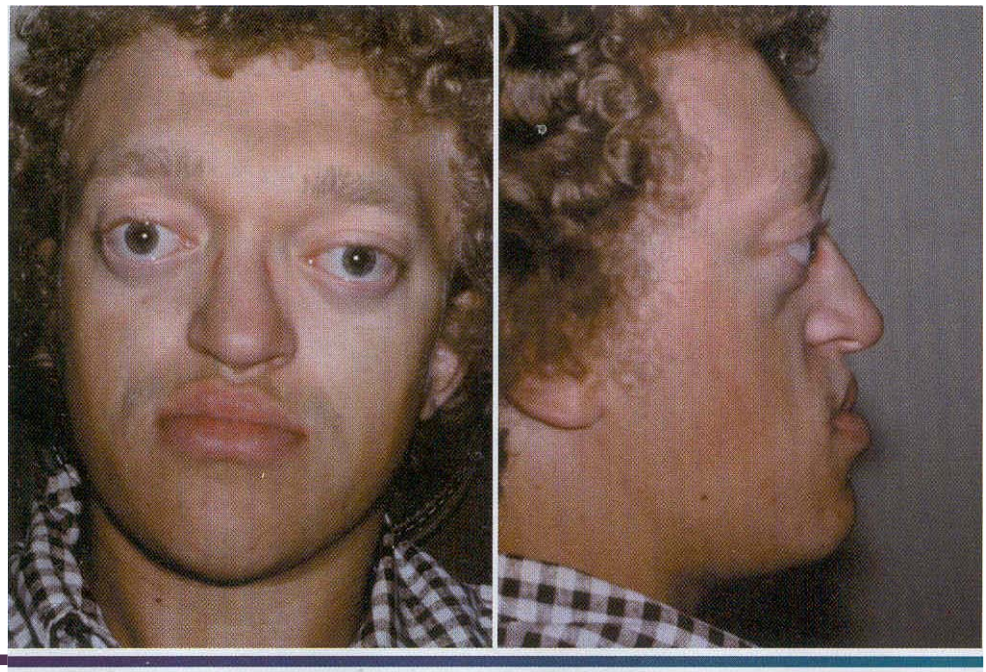

Figure 1-82 • Crouzon syndrome. Ocular proptosis and midface hypoplasia. (Courtesy of Dr. Robert Gorlin.)

blattschädel deformity ("cloverleaf" skull). The occiput is flattened, and there is a tall appearance to the forehead. Ocular proptosis is a characteristic finding, along with hypertelorism and downward slanting lateral palpebral fissures (Figure 1-83). *Visual* loss can result from:

- 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 (Figure 1-84).

The middle third of the face is markedly 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 to distinguish Apert syndrome from other craniosynostosis syndromes. Syndactyly of the second, third, and fourth digits of the hands and feet always is observed (Figure 1-85). Associated synonychia also may occur. The first and fifth digits may be separate or be 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.

Mental retardation is common 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. Three fourths of all 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

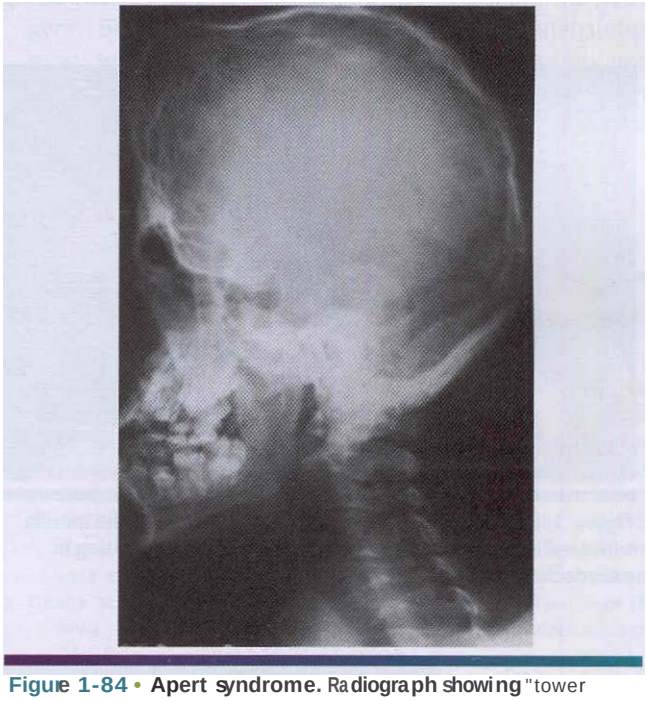

Figure 1-84 • Apert syndrome. Radiograph showing "tower skull," midface hypoplasia, and digital markings. Similar digital impressions are apparent in people with Crouzon syndrome. (Courtesy of Dr. Robert Gorlin.)

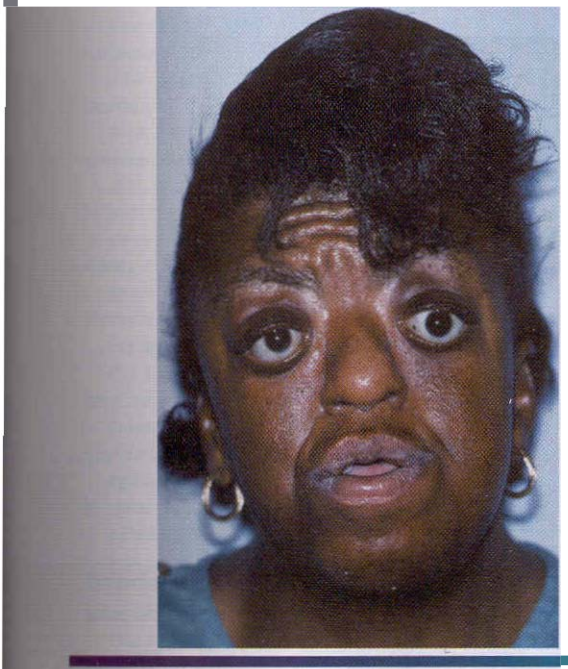

Figure 1-83 • Apert syndrome. Midface hypoplasia and ocular proptosis.

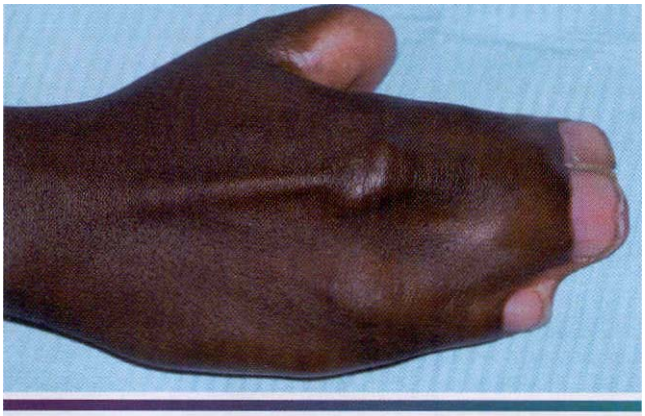

Figure 1-85 • Apert syndrome. Syndactyly of the hand.

and posterior cross bite. Swellings are observed along the lateral hard palate from the accumulation of glycosaminoglycans, especially hyaluronic acid (Figure 1-86). 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. *Shovel*-shaped incisors have been reported in one third of patients.

Treatment and Prognosis

The cosmetic and functional defects of Apert syndrome can be treated by an interdisciplinary approach using multiple surgical procedures. 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.

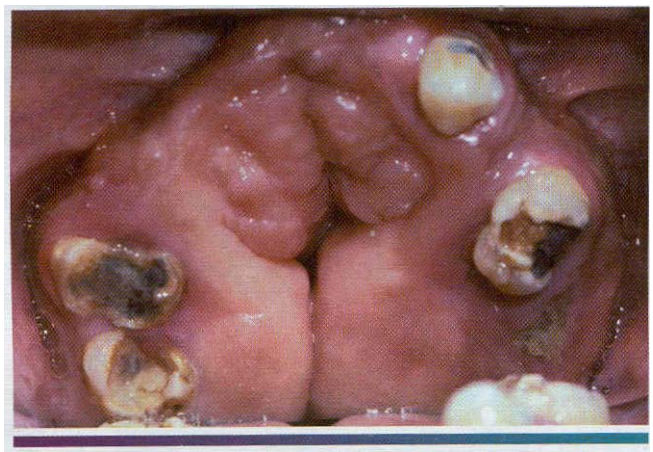

Figure 1-86 • Apert syndrome. Abnormal shape of the maxilla, with swellings of the posterior lateral hard palate, resulting in pseudocleft formation.

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 in around 1 of every 25,000 to 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. Approximately 60% of cases represent new mutations. and these often are associated with increased paternal age. The gene for mandibulofacial dysostosis has been mapped to chromosome 5q31.3-32.

Clinical and Radiographic Features

Individuals with mandibulofacial dysostosis exhibit a characteristic facies (Figure 1-87). The zygomas are hypoplastic, resulting in a narrow face with depressed

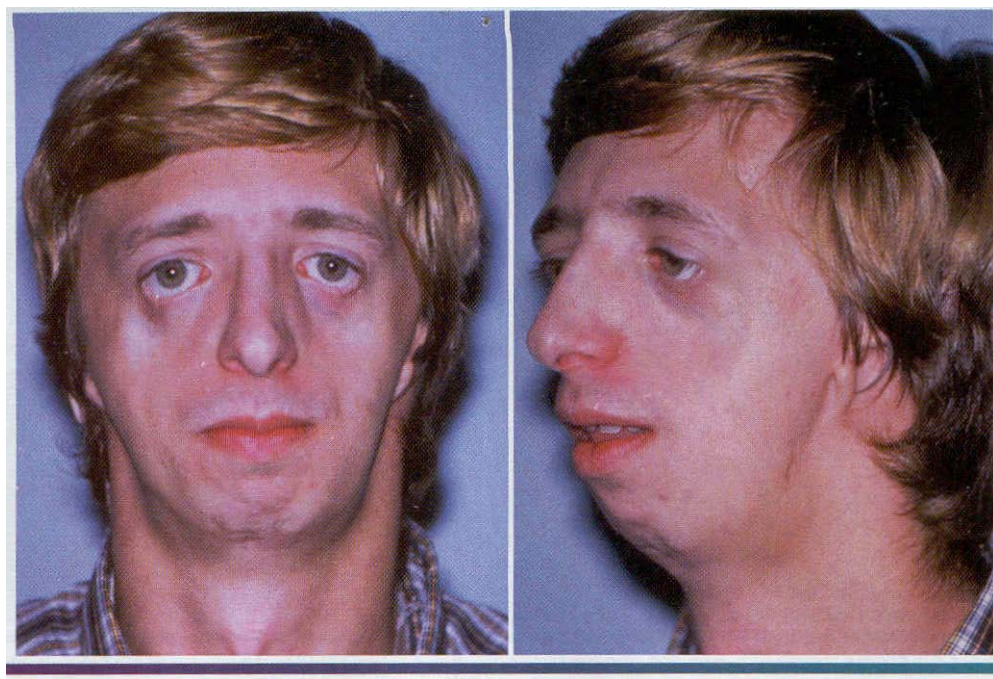

figure 1-87 • Mandibulofacial dysostosis. Patient exhibits a hypoplastic mandible, downward-slanting palpebral fissures, and ear deformities. (Courtesy of Dr: Tom Brock.)

cheeks and downward-slanting palpebral fissures. In 75% of patients, a coloboma, or notch, occurs on the outer portion of the lower eyelid. About 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 often are deformed or misplaced, and extra ear tags may be seen. Ossicle defects or absence of the external auditory canal can cause 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.

A number of infants may experience respiratory and feeding difficulties because of hypoplasia of the nasopharynx, oropharynx, and hypopharynx. Choanal atresia is a common finding, 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 mandibulotacial 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 are usually 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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CHAPTER 2

Abnormalities of Teeth

CHAPTER OUTLINE

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 or appear hereditary in nature. Later parts of this chapter delineate the idiopathic or 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). The primary hereditary abnormalities of the enamel that are unrelated to other disorders are termed amelogenesis imperfecta (see page 89).

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 impact 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 provide a rough estl-

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

1. Birth-related trauma: breech presentations, hypoxia, multiple births, premature birth, prolonged labor
2. Chemicals: antineoplastic chemotherapy, fluoride, lead, tetracycline, thalidomide, vitamin D
3. Chromosomal abnormalities: trisomy 21
4. Infections: chicken pox, cytomegalovirus (CMV), gastrointestinal infections, measles, pneumonia, respiratory infections, rubella, syphilis, tetanus
5. Inherited diseases: amelo-cerebro-hypohidrotic syndrome, amelo-onycho-hypohidrotic syndrome, epidermolysis bullose, galactosemia, mucopolysaccharidosis IV, Nance-Horan syndrome, oculo-dento-osseous dysplasia, phenylketonuria, pseudohypoparathyroidism, tricho-dento-osseous syndrome, tuberous sclerosis, vitamin D-dependent rickets
6. Malnutrition: generalized malnutrition, vitamin D deficiency, vitamin A deficiency
7. Metabolic disorders: cardiac disease, celiac disease, gastrointestinal malabsorption, gastrointestinal lymphangiectasia, hepatobiliary disease, hyperbilirubinemia, hypocalcemia, hypothyroidism, hypoparathyroidism, maternal diabetes, renal disease, toxemia of pregnancy
8. Neurologic disorders: cerebral palsy, mental retardation, sensorineural hearing defects

LOCAL

1. Local acute mechanical trauma: falls, gunshots, neonatal mechanical ventilation, ritual mutilation, surgery, vehicular accidents
2. Electric burn
3. Irradiation
4. local infection: acute neonatal maxillitis, periapical inflammatory disease

mate of the time of damage; but 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 occurs in the form of pits, grooves, or larger **areas of missing enamel. Diffuse opacities of enamel appear as variations in the translucency of the enamel.** The affected enamel is of normal thickness; however, it has 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 enamel is of normal thickness, and the affected opacity may be white, cream, yellow, or brown.

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

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 arc present on the anterior teeth and first molars (Figures 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 (Figure 2-3).

Turner's 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's tooth (after the dental clinician whose publications allowed this problem to be widely recognized). The appearance of the affected area varies according to the timing and severity *at* the insult. The enamel defects vary from focal

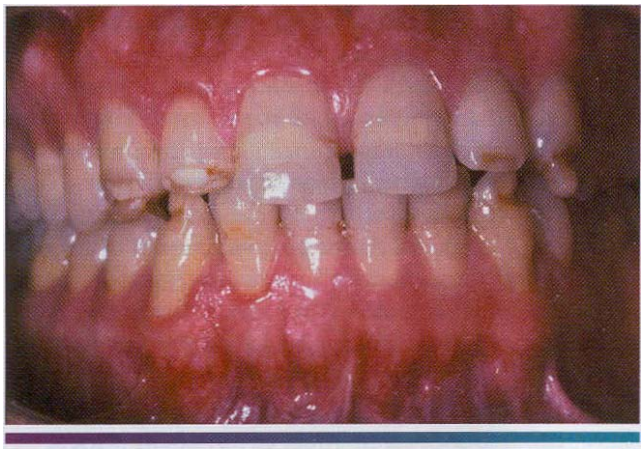

Figure 2-1 • Environmental enamel hypoplasia. Bilaterally symmetric pattern of horizontal enamel hypoplasia of the anterior dentition. Maxillary central incisors have been restored previously (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Baltimore, 1999. Williams & Wilkins.)

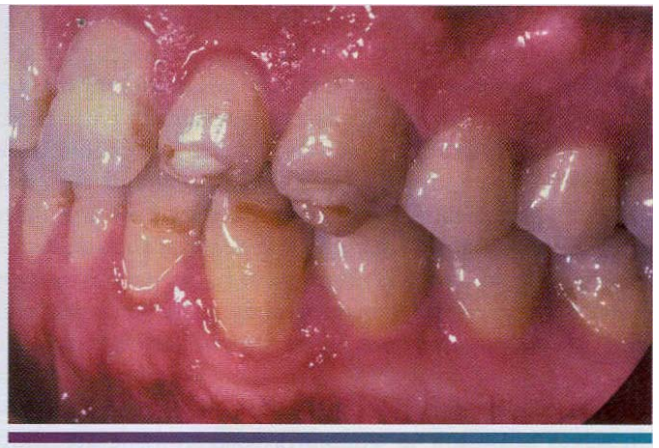

Figure 2-2 • Environmental enamel hypoplasia. Same patient as depicted in Figure 2-1. Note the lack of enamel damage on bicuspids. (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Baltimore, 1999. Williams & Wilkins.)

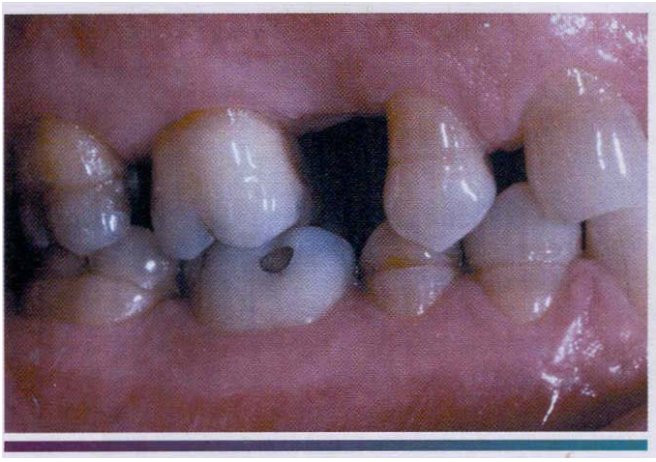

Figure 2-3 • Environmental enamel hypoplasia. Horizontal enamel hypoplasia of the bicuspids and second molars. Note sparing of the first molars. (From Neville BW, Damm DO. White OK: Cofor *atlas of clinical oralpathofogy.* ed 2. Baltimore. 1999, Williams & Wilkins.)

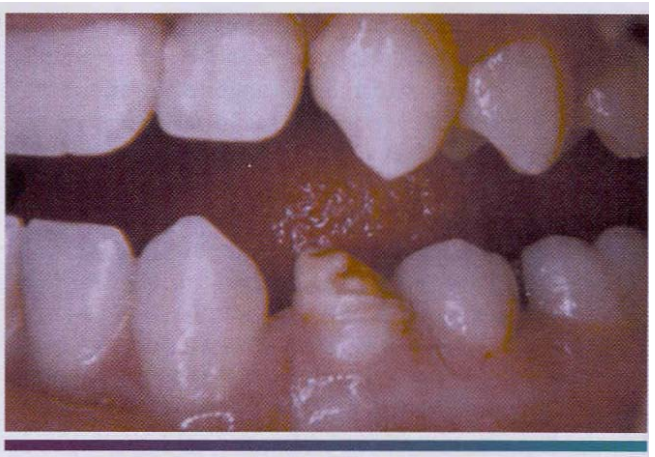

Figure 2-4 • Turner's hypoplasia. Extensive enamel hypoplasia of mandibular first bicuspid secondary to previous inflammatory process associated with overlying first deciduous molar. (From Halstead CL, Blozis CG. Drinnan AJ. et at: *Physical evaluation of the dental patient,* St Louis, 1982. Mosby.)

areas of white, yellow, or brown discoloration to extensive hypoplasia, which can involve the entire crown. The process is noted most frequently in the permanent bicuspids because of their relationship to the overlying deciduous molars (Figures 2-4 and 2-5). Anterior teeth arc 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 over*lying* 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 primary inflammatory disorders. traumatic injury to deciduous teeth also can cause significant alterations of the underlying dentition and the formation of Turner's 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 arc altered less frequently (Figure 2-6I. 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 reiation 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 86). 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 631). Similar levels of damage late in the formative process can lead to partial or total arrest in root formation.

Hypoplasia caused by antineoplastic therapy. As modern medicine increases its 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 under the age of 12 and most extensively in those under 5 years of age. 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

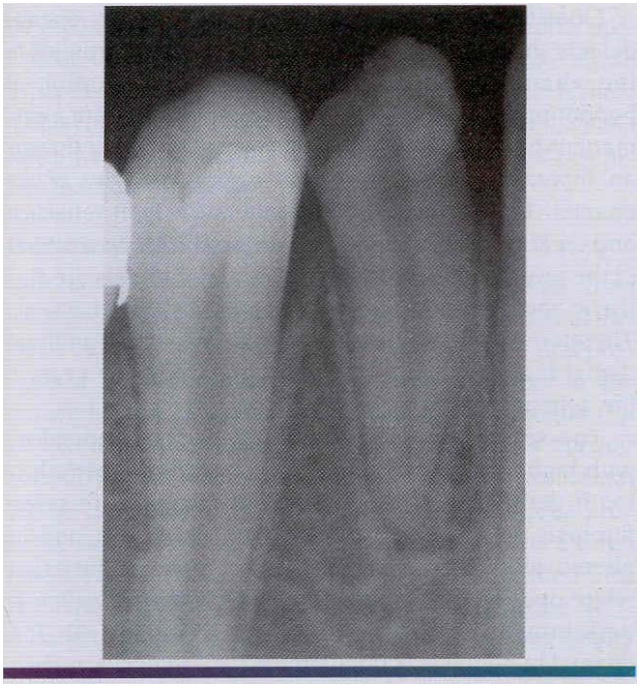

Figure 2-5 • **Turner's hypoplasia.** Radiograph of the same tooth depicted in Figure 2-4. Note the lack of significant enamel and irregularity of the dentin surface. (From Halstead CL, Blozis GG. Drinnan AJ, et al: *Physical evaluation of the dental patient,* St louis, 1982, Mosby)

developmental defects in both enamel and dentin, As the dose escalates, so does the impact on the developing dentilion and jaws, Frequently noted alterations include hypodontia, microdontia, radicular hypoplasia, and enamel hypoplasia (Figure 2-7). 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.**

*Denta! **fll/orosis.*** The **ingestion of excess amounts of** fluoride also can result in significant enamel defects known as dental fluorosis, In 1901, Dr. Frederick S. McKay suggested the association between this *mottled momel* and an agent in the Colorado Springs. Colorado, water supply during investigation of the *Colorado brown staill* seen in the teeth of many of his patients. Dr. F.L. **Robertson noted a similar association in many of his** patients in Bauxite, Arkansas (the home of bauxite mines for aluminum) in t909. tn t930, H.V. Churchill, a chemist in Bauxite who was employed by the Aluminum Company of America, discovered high concentrations of fluoride (13.7 ppm) in the water and contacted McKay for samples of the water in affected areas of Colorado. McKay's samples also demonstrated high levels of fluoride, and the final part of the puzzle was solved.

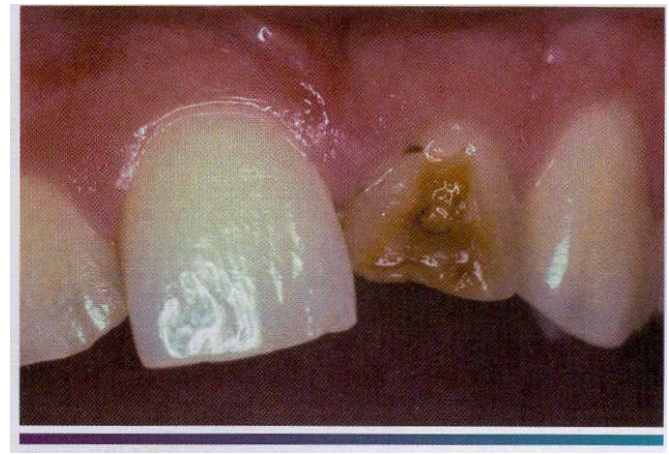

Figure 2-6. **Turner's hypoplasia.** Extensive coronal hypoplasia of permanent maxillary left central incisor secondary to previous trauma to deciduous central incisor.

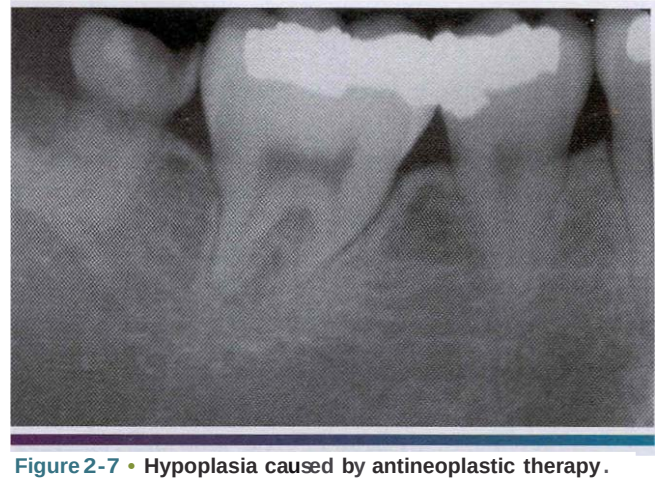

Figure 2-7 • **Hypoplasia caused by antineoplastic therapy. Developmental radicular hypoplasia and** microdontia **caused by radiation therapy. (From Neville BW, Damm DD, White DK: *Color atlas of clinical oral pathology,* ed 2, Baltimore, 1999, Williams &** Wilkins.)

Although the fluoride produced an unusual perma**nent dental stain, a resistance to caries also was noted.** In 1931, the National Institute of Health hired Dr. H, Trendley Dean to investigate the association between fluoride, the presence of dental fluorosis, and the prevalence of caries among children. Ultimately this led to the first water fluoridation clinical trial at Grand Rapids. Michigan. Because of the efforts of these pioneers and the simultaneous work of many others, it was discovered that fluoride in the water at 1.0 ppm reduced caries by 50% to 70%. In addition, this level of fluoride in the water

supply was associated with a low and mostly mild prevalence of mottled enamel. Since 1962, fluoridation of drinking water is recommended, with the optimum range being 0,7 to 1.2 ppm. The lower concentration is recommended for warmer climates where water consumption is higher.

Recently, an increased prevalence of dental fluorosis has been noted. In addition, the relative caries reduction in fluoridated communities has dropped between 8% to 37%. This has been attributed to the diffusion of fluoride to nonfluoridated areas through bottling and processing of foods and beverages with fluoridated water and the widespread use of fluoride toothpaste. Adult-strength fluoride toothpastes, fluoride supplements, infant foods, soft drinks. fruit juices, and industrial environmental emissions all represent potential sources of fluoride for children in their formative years. Infant formulas also used to contain significant amounts of fluoride. but more recent efforts have resulted in a dramatic decrease in the fluoride content from this source.

Because of this dissemination of fluoride, the need for supplements in nonfluoridated areas is declining. In patients who use fluoride toothpastes, the anticariogenic benefit of supplements is very small or nonexistent and the risk of fluorosis at the community level becomes a certainty. Several investigators have recommended strongly that children less than 7 years of age apply only a pea-sized amount of fluoride toothpaste on the toothbrush and discourage swallowing. In addition, fluoride supplements are recommended only in nonfluoridated areas in children who are at high risk for rampant caries. Finally, there currently is an effort to alter the 1962 recommendation and lower the optimum level of fluoride in the public water supply to 0.7 ppm.

Fluoride appears to create its significant enamel defects through retention of the amelogenin proteins in the enamel structure, leading to the formation of hypomineralized enamel. These alterations create a permanent hypomaturation of the enamel in which there is an increased surface and subsurface porosity of the enamel. This enamel structure alters the light reflection and creates the appearance of white. chalky areas. Most of the problems associated with dental fluorosis are aesthetic and concern the appearance of the anterior teeth. Therefore, the critical period for clinically significant dental fluorosis is during the second and third years of life, when these teeth are forming.

The severity of dental fluorosis is dose dependent, with higher intakes of fluoride during critical periods of tooth development being associated with more severe fluorosis. 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 (Figures 2-8 and 2-9). 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, and evidence of prior excessive fluoride intake or elevated levels of fluoride in the enamel or other tissues should be found.

Syphilitic hypoplasi«. Congenital syphilis (see page 170) 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's incisors and exhibit crowns that are shaped like straight-edge screwdrivers. with the greatest circumference present in the middle one third of

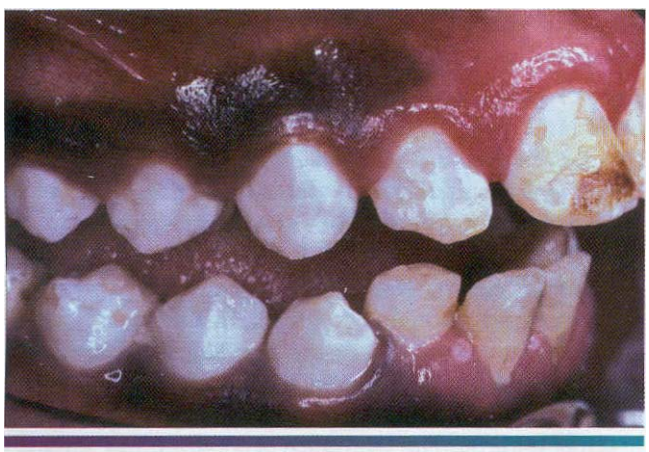

Figure 2-8 • Dental fluorosis. Dentition exhibiting lusterless. white, and opaque enamel.

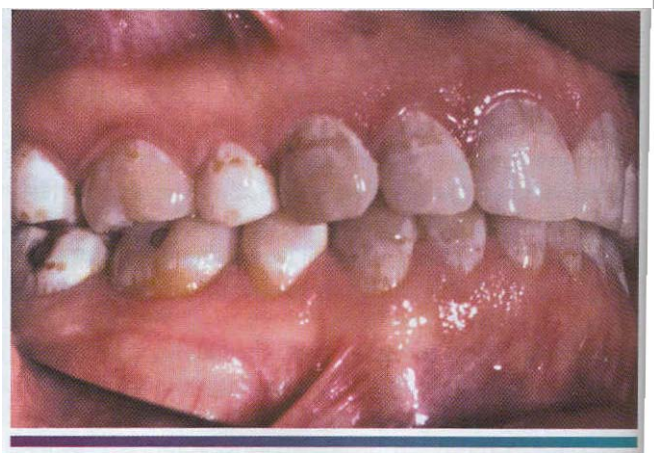

Figure 2-9 • Dental fluorosis. White opaque alteration of the bicuspids and second molars in a patient who also exhibits discoloration of the teeth secondary to tetracycline use. Patient moved to area of endemic fluorosis at 3 years of age.

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 that 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 create a loss of the continuous protective surface of enamel and may predispose the altered zone to caries. 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:

- 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 proeess 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. 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. Areas of dentin exposed by attrition or abfraction often are damaged further by the effects of erosion or abrasion. Areas softened by erosion are more susceptible to attrition, abrasion. and abfraction. It is important for the clinician to appreciate that acquired environmental loss of tooth structure often is multifactorial.

Generally. it is agreed 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. fresh fruits).

Attrition is the loss of tooth structure caused by tooth-to-tooth contact during occlusion and mastication. 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.

Tooth destruction can be accelerated by:

- Poor quality or absent enamel (c.g.• fluorosis, environmental or hereditary enamel hypoplasia. or dentinogenesis irnperfecta)
- Premature contacts (edge-to-edge occlusion)
- Intraoral abrasives. erosion. and grinding habits

Abrasion is the pathologic loss of tooth structure or restoration secondary to the action of an external agent. The most common cause of abrasion is toothbrushing that combines an 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 (hair grips). Chewing tobacco. biting 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 chemical process beyond that associated with bacterial interaction with the tooth. Typically. the exposure to an acid is to blame. but chelating agents are occasionally the primary cause. Although saliva aids remineraiization and contains bicarbonate with a significant buffering ability. this effect can be overwhelmed by excess acid (or the quantity and quality of saliva can be deficient and result in accelerated tooth loss>. The acidic source often is foods or drinks. but other causes include some medications (e.g.. chewable vitamin C. aspirin tablets) , swimming pools with poorly monitored pH. chronic involuntary regurgitation (e.g.. hiatal hernia, esophagitis, chronic alcoholism, pregnancy), voluntary regurgitation (e.g.. psychologic problems, bulimia, occupations that require low body weight). and industrial environmental exposure. Erosion from dental exposure to gastric secretions is termed pcrimolysis. Agreement on the prevalence of dental erosion does not exist. Some investiga-

tors believe erosion rarely is responsible solely for loss of tooth structure, although others list erosion as the leading cause of accelerated tooth wear.

Abfraction refers to the loss of tooth structure that results from repeated tooth flexure caused by occlusal stresses. 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. Once damaged, the cracked enamel can be lost or more easily removed by erosion or abrasion. Some investigators have suggested that the placement of occlusal restorations weakens the tooth's ability to resist the stresses of occlusion and predisposes to future abfractive lesions. Like erosion, agreement on the prevalence of abfraction does not exist. Some propose that abfraction causes most cervical tooth loss; others believe little evidence exists that this sequence of events actually occurs in the mouth.

Clinical Features

Attrition. Attrition can occur in both the deciduous and 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 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 (Figure 2-10).

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 (Figures 2-11 and 2-12). The defects usually have sharply defined margins and a hard, smooth surface. If acid also is present. the lesions will be more rounded and shallower. The degree of loss is greatest on prominent teeth (i.e.. cuspids, bicuspids, and teeth adjacent to edentulous areas) and 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 (Figures 2-13 and 2-14). The inappropriate usc of dental floss or toothpicks results in the loss of interproximal radicular cementum and dentin. Pulp exposure and dentin sensitivity are rare.

Erosion. In patients with erosion, the tooth loss does not correlate with functional wear patterns or with those typically associated with known abrasives. In contrast to abrasion, erosion commonly affects the facial surfaces of the maxillary antertors 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 (Figure 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 (Figure 2-16). Occasionally. entire buccal cusps are lost and replaced by ski slope-like depressions that extend from the lingual cusp to the buccal cementoenarnel junction (Figure 2-17). When palatal surfaces are affected. the

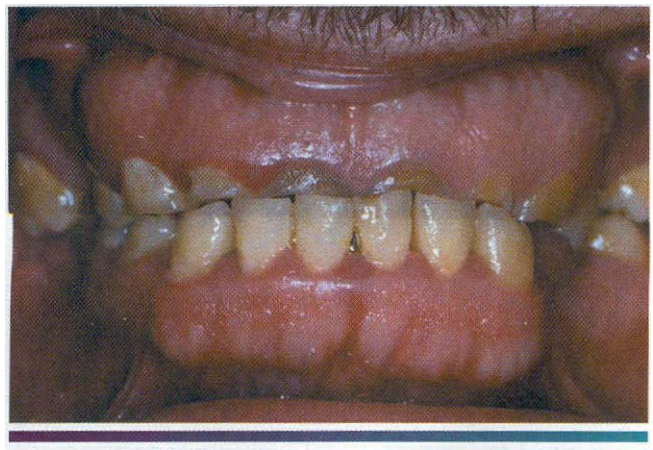

Figure 2-10. Attrition. Extensive loss of coronal tooth height without pulp exposure in patient with anterior edge-to-edge occlusion.

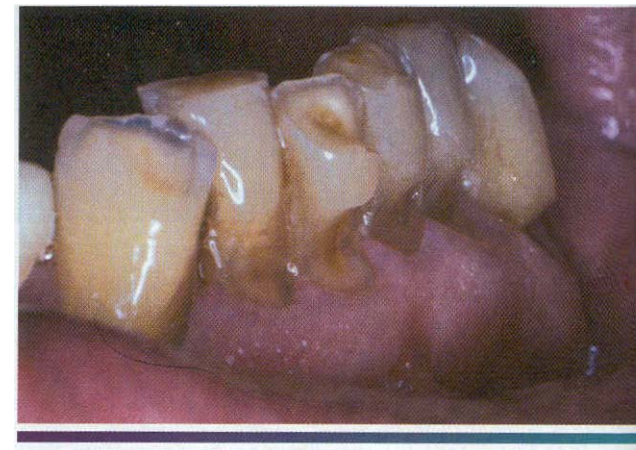

Figure 2-11 • Abrasion. Horizontal cervical notches on the anterior mandibular dentition.

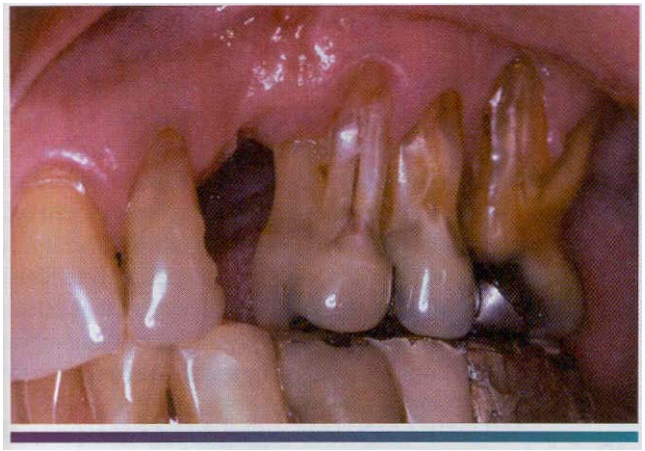

Figure 2-12 • Abrasion. Extensive recession and loss of buccal radicular dentin. Note visible pulp canals that have been filled with tertiary dentin.

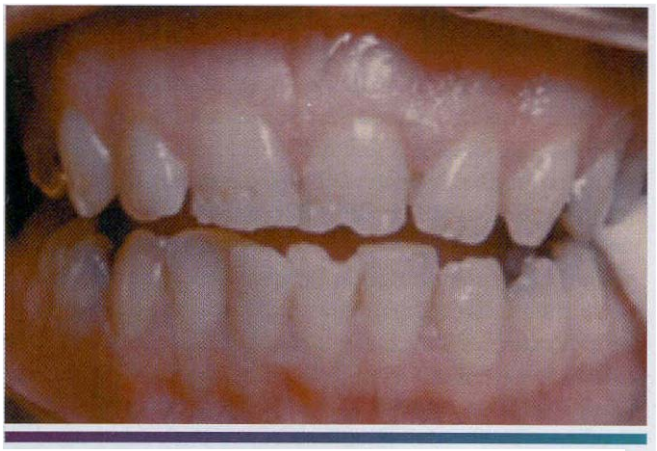

figure 2-13 . Abrasion. Notching of the right central incisor caused by improper use of bobby pins. The patient also exhibits environmental enamel hypoplasia of the anterior dentition. (Courtesy of Dr. Robert J. Gorlin.)

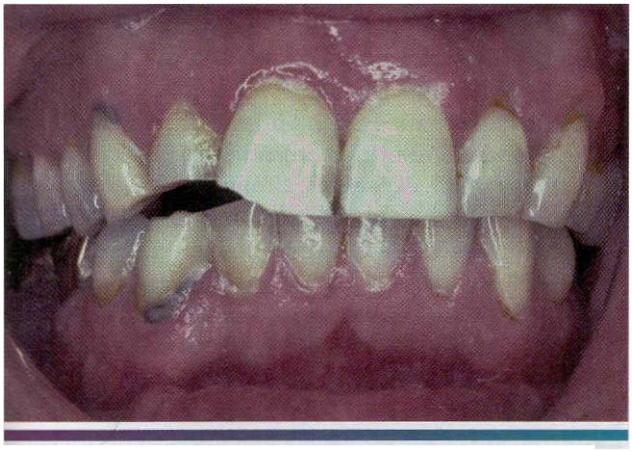

Figure 2-14 • Abrasion. Notching of the anterior dentition on the right side caused by long-term use of tobacco pipe.

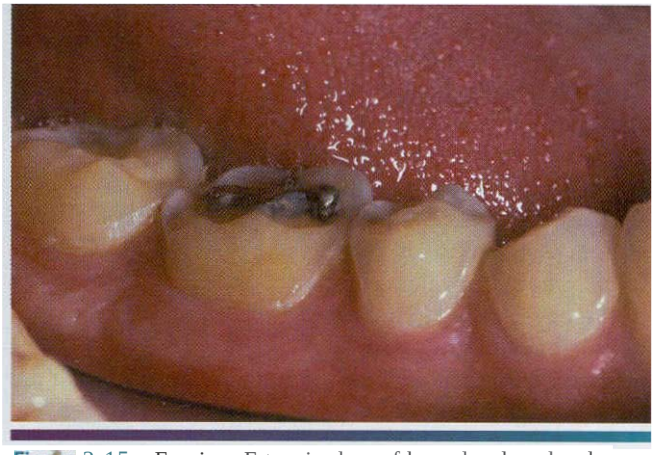

Figure 2-15 • Erosion. Extensive loss of buccal and occlusal tooth structure. Note that the amalgam margins are above the surface of the dentin.

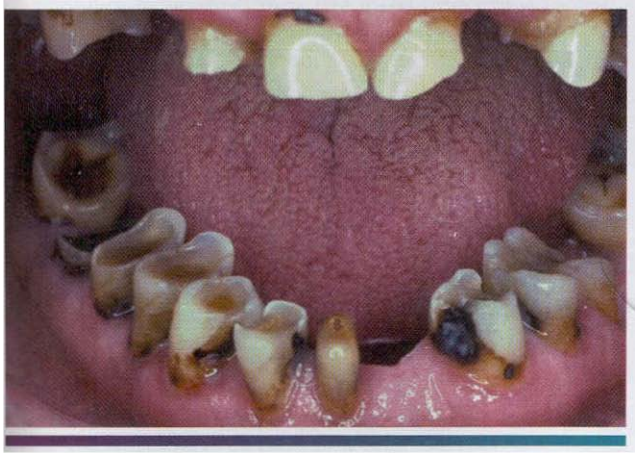

Figure 2-16 • Erosion. Occlusal surface of the mandibular dentition exhibiting concave dentin depressions surrounded by elevated rims of enamel.

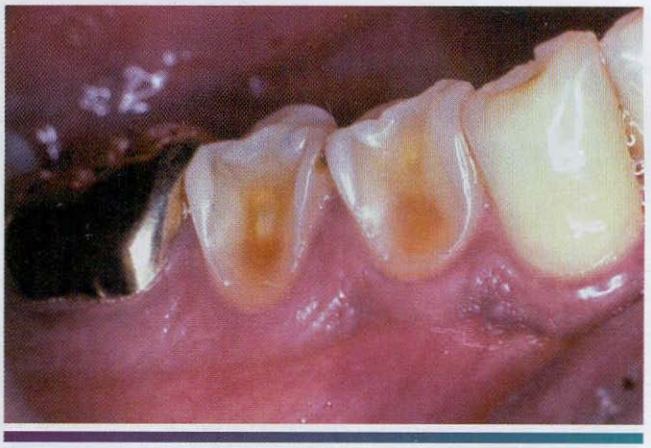

figure 2-17 . Erosion. Extensive loss of enamel and dentin on the buccal surface of the maxillary bicuspids. The patient had sucked chronically on tamarinds (an acidic fruit).

exposed dentin has a concave surface and shows a peripheral white line of enamel (Figure 2-18). 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 reliable completely. Although not common, erosion can proceed rapidly and result in dentinal sensitivity or pulp exposure.

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 (Figure 2-19). In addition, occasional lesions are subgingival, a site typically protected from abrasion and erosion. The lesions are seen almost exclusively on the facial surface and exhibit a much greater prevalence in those with bruxism. A higher frequency is noted in the mandibular dentition, presumably because the lingual orientation makes them more susceptible to the concentration of tensile stresses at the cervical regions.

Treatment and Prognosis

Before any definitive therapy, 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.

Patients should be informed of the potential for loss of tooth structure associated with the overuse of acidic foods and drinks, chronic regurgitation, and improper oral hygiene techniques. Mouth guards can be used to slow nocturnal attrition and to protect the teeth from frequent exposure to acid from regurgitation or industrial sources. 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. 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. In isolated teeth that continue to lose Class V restorations, continued abfraction is likely, and occlusal trauma should

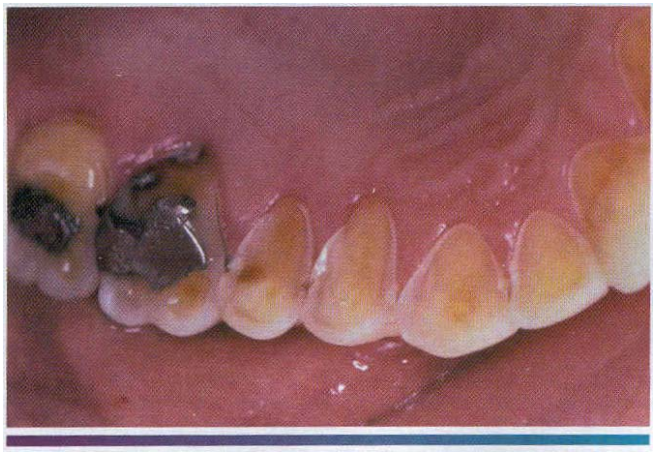

Figure 2-18 • Erosion. Palatal surfaces of the maxillary dentition in which the exposed dentin exhibits a concave surface and a peripheral white line of enamel. The patient suffered from bulimia.

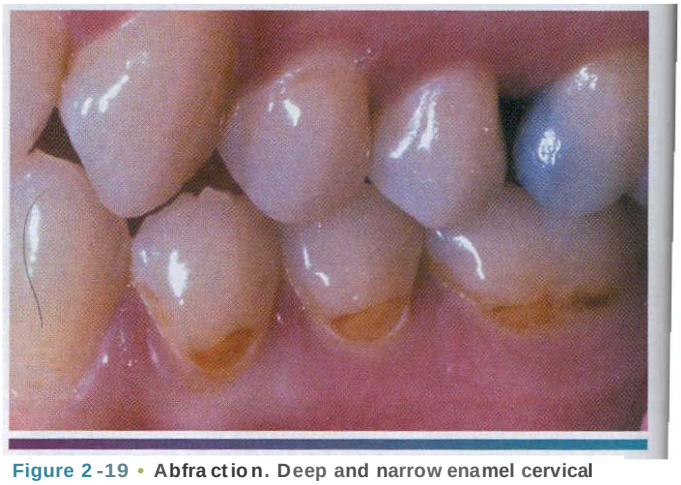

Figure 2-19 • Abfraction. Deep and narrow enamel cervical defects on the facial surface of the mandibular dentition. (From Neville BW, Damm DD, White OK: *Color atlas of clinical oral pathology*, ed 2, Baltimore, 1999, Williams & Wilkins.)

be eliminated. 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.

The body may adapt to loss of tooth structure by continual eruption of the teeth, appositional alveolar bone deposition. and compensatory skeletal growth. If the process of tooth loss is slow. the vertical dimension often is maintained; in patients with rapid destruction. there is a loss of facial length. Restoration of extensive loss of tooth structure is complex and should be performed only after a complete evaluation of the dentoalveolar complex.

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 (i.e., external resorption). Internal resorption is a relatively rare occurrence, and most cases follow 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 periodontal ligament.

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. 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 (such as 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 is usually asymptomatic and discovered through routine radiographs. Pain may be reported if the process is associated with significant pulpal inflammation. Two main patterns are seen: (I) inflammatory resorption and (2) replacement, or metaplastic absorption (Figure 2-20). 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

Box 2-3 ***Factors*** *Associated with External Resorption*

1. Cysts
2. Dental trauma
3. Excessive mechanical forces (e.g.. orthodontic therapy)
4. Excessive occlusal forces
5. Grafting of alveolar clefts
6. Hormonal imbalances
7. Intracoronal bleaching of putpless teeth
8. Local involvement by herpes zoster
9. Paget's disease of bone
10. Periodontal treatment
11. Periradicular inflammation
12. Pressure from impacted teeth
13. Reimplantation of teeth
14. Tumors

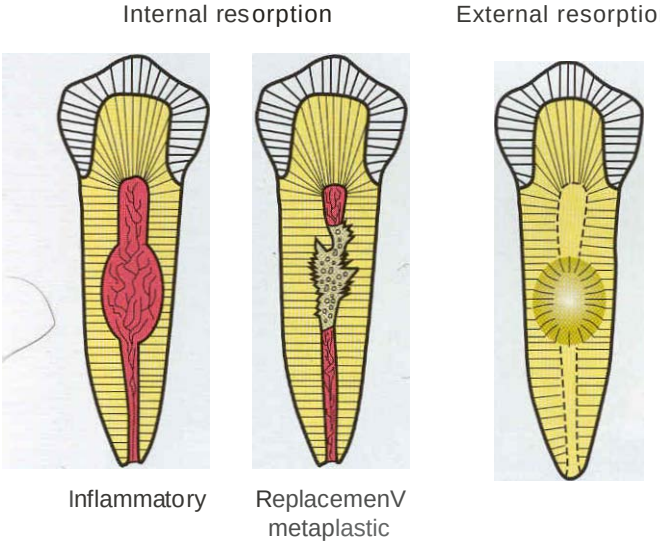

Figure 2-20 • Tooth resorption. Illustration contrasting the common patterns of internal and external tooth resorption.

Mummery) as the vascular resorptive process approaches the surface (Figures 2-21 and 2-22). When it occurs in the root, the original outline of the canal is lost and a balloonlike radiographic dilation of the canal is seen (Figure 2-23). Although most cases are progressive, some cases are transient 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 Figure 2-20). Radiographically, replacement resorption appears as an enlargement of the canal that 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 (Figures 2-24 to 2-27). If the lesion overlies the pulp canal, 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. 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.

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 (Figure 2-28). In some instances several teeth may be involved, and an under

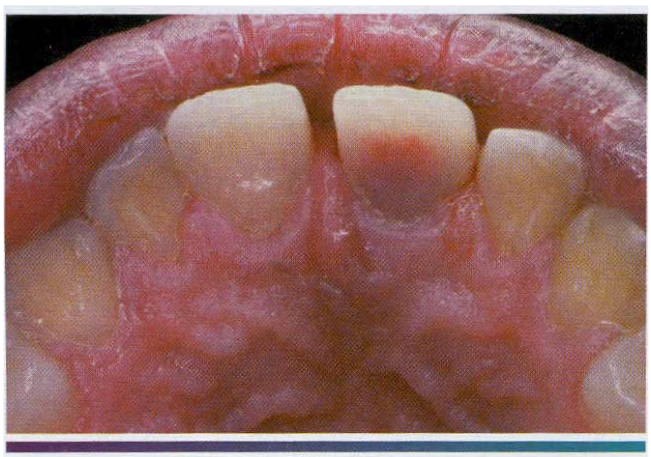

Figure 2-21 • Internal resorption (pink tooth of Mummery). Pink discoloration of the maxillary central incisor.

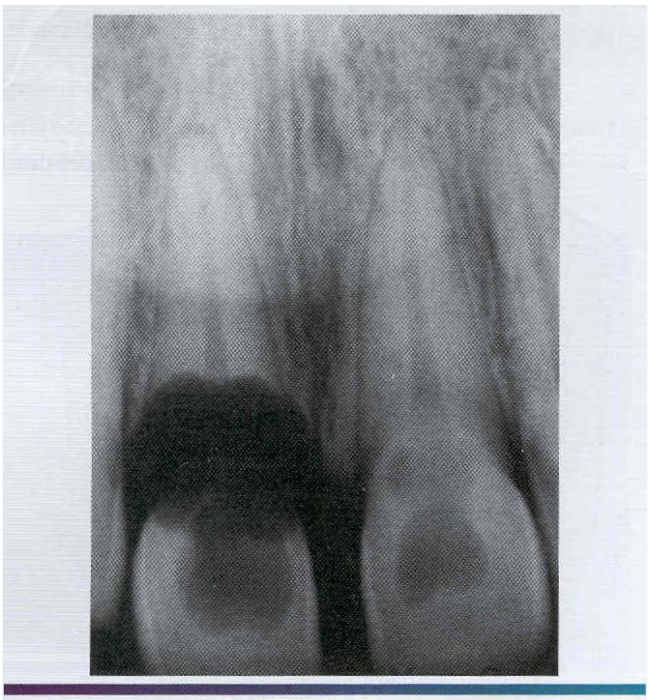

Figure 2-22 • Internal resorption. Same patient as depicted in Figure 2-21. Note extensive resorption of both maxillary central incisors.

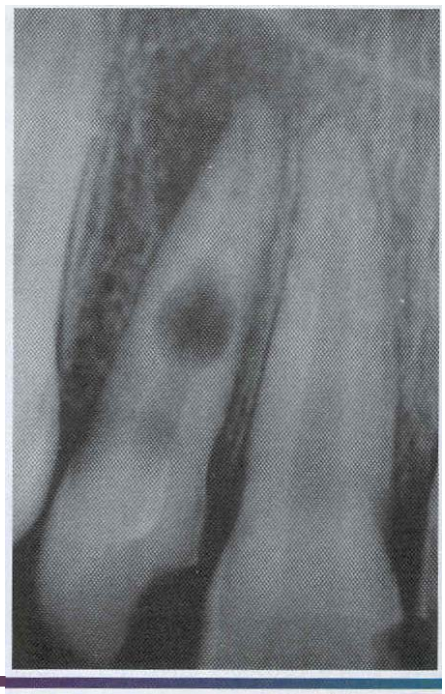

Figure 2-23 • Internal resorption. Balloonlike enlargement of the root canal.

lying cause for the accelerated destruction may not be obvious (multiple idiopathic root resorption).

If difficulty arises in distinguishing external from internal resorption, the mesial-buccal-distal rule can be used through two radiographic exposures: one perpendicular and one mesial (objects closer to the source of radiation will 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.

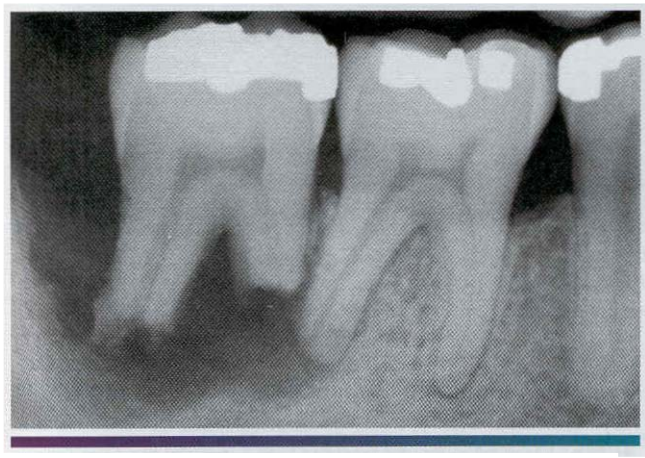

Figure 2-24 • **External resorption. Extensive irregular destruction of both roots of the mandibular second molar associated with chronic periodontitis. (Courtesy of Dr. Tommy Shimer.)**

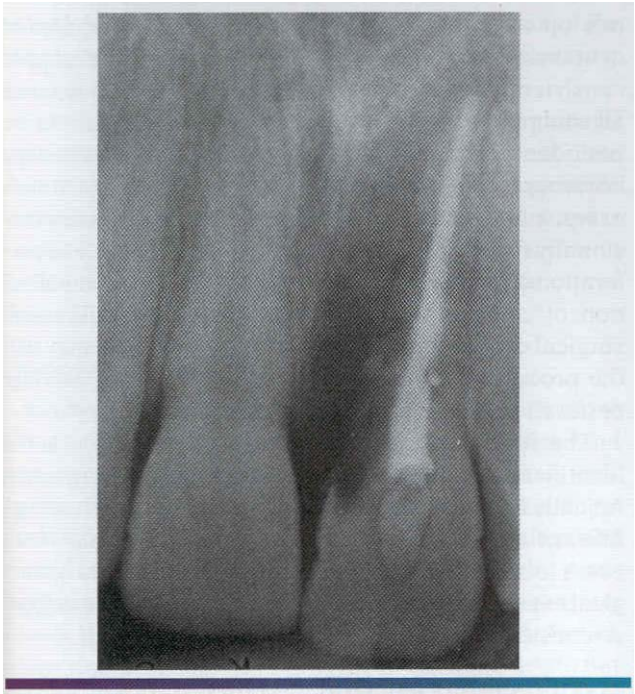

Figure 2-25 • **External resorption.** "Moth-eaten" **radiolucent alteration of the maxillary left central incisor. The tooth had been reimplanted after traumatic avulsion. (Courtesy of Dr. Harry** Meyers.]

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

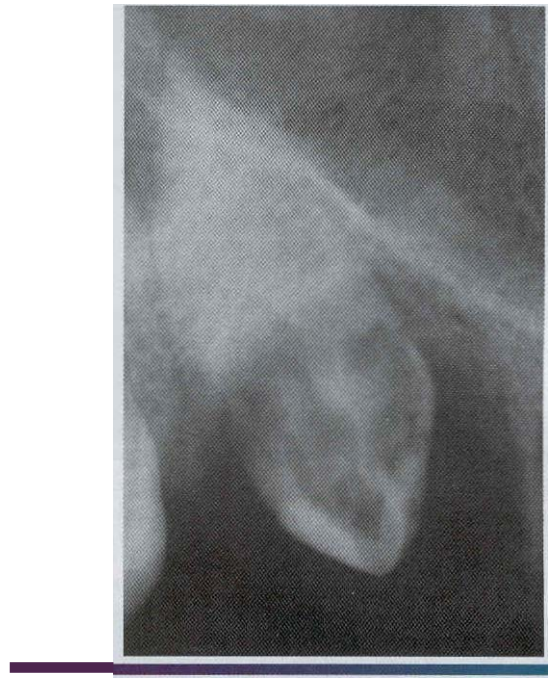

figure 2-26 • **External resorption. Extensive external** resorption **of the crown of the impacted right maxillary cuspid.** Histopathologic examination **revealed resorption without bacterial** contamination **or caries.**

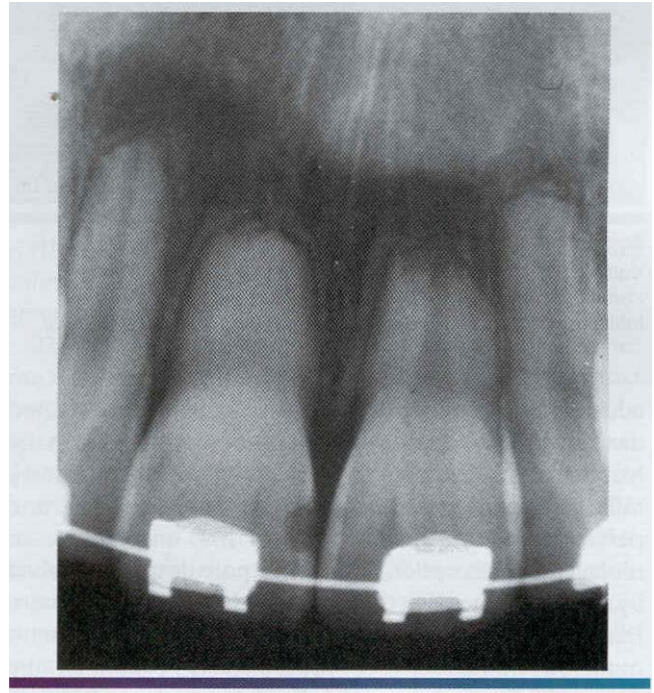

figure 2-27 • **External resorption. Diffuse external resorption of radicular dentin of maxillary dentition. This process arose after initiation of orthodontics.**

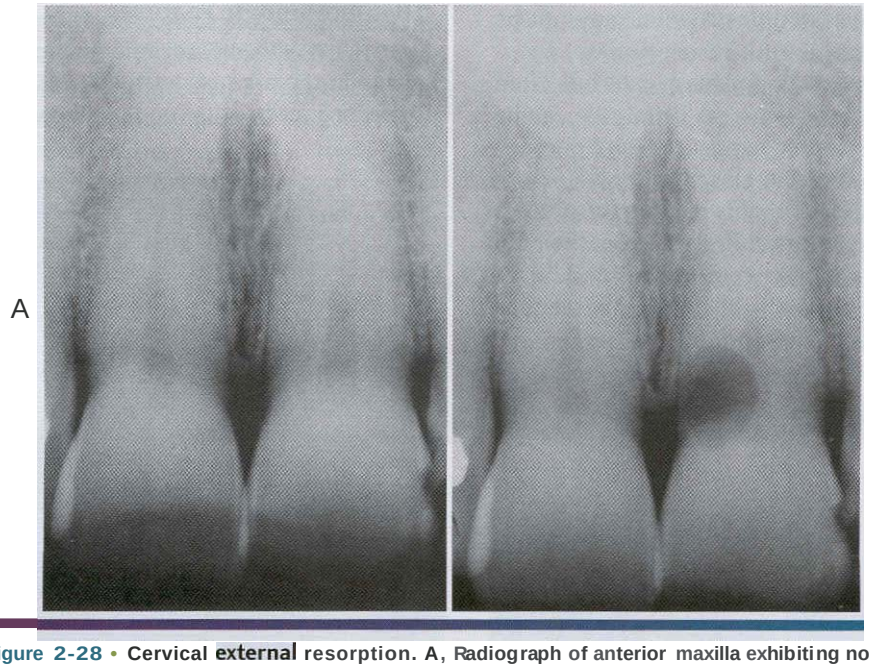

Figure 2-28 • Cervical external resorption. A, Radiograph of anterior maxilla exhibiting no signifieant areas of resorption. B. Well-defined radiolucent alteration of the cervical area noted three years after initial radiograph. (Courtesy of Dr. H. Dwaine Blakeman.)

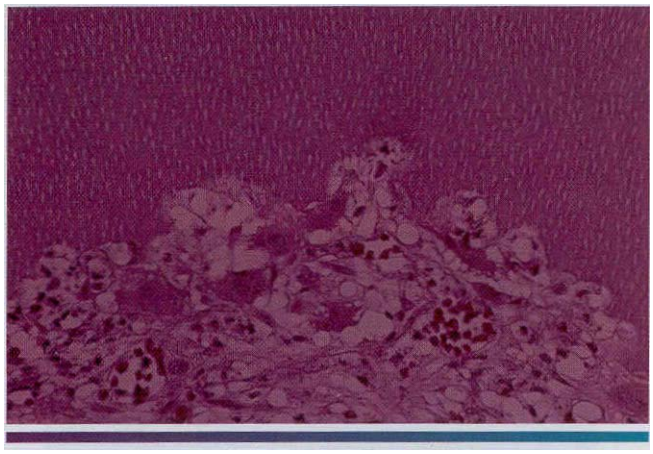

figure 2-29 • Internal resorption. Resorption of the inner dentinal wall of the pulp. Note cellular and vascular fibrous connective tissue, which exhibits an adjacent inflammatory infiltrate and numerous dentinoclasts within resorptive lacunae.

adjacent to the dentinal wall are numerous multinucleated dentinoclasts, which are histologically and functionally identical to osteoclasts (Figure 2-29), An inflammatory inflitrate 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 resorption is similar in appearance. with numerous multinucleated dentinoclasts located in the areas of structure loss. Areas of resorption often are** repaired through depositlon of osteodentin, In large defects, external inflammatory resorption results in dcp-**osition 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 periodontal ligament. Once perforation occurs, therapy becomes more difficult and the prognosis is poor, In such **cases, initial placement of calcium hydroxide paste occa**sionally may result in remineralization of the site of perforation **and stop the resorptive process. If remineralization of cervical sites of perforation is not successful,** 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 eliminatio n 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.

ENVIRONMENTAL DISCOLORATION OF TEETH

The color of normal teeth varies and depends on the shade, translucency, and thickness of the enamel. Trans-

Box 2-4 *Tootll Disco loratlons*

EXTRINSIC

1. Bacterial stains
2. Iron
3. Tobacco
4. Foods and beverages
5. Gingival hemorrhage
6. Restorative materials
7. Medications

INTRINSIC

1. Amelogenesis imperfecta
2. Dentinogenesis imperfecta
3. Dental fluorosis
4. Erythropoietic porphyria
5. Hyperbilirubinemia
6. Ochronosis
7. Trauma
8. Localized red blood cell breakdown
9. Medications

lucent enamel appears blue-white; opaque enamel is gray-white. Therefore, teeth with translucent enamel appear yellow at the cervical one third and blue-white at the incisal edge; those with opaque enamel are a more uniform gray-white. Abnormal colorations may be **extrinsic** (i.e., **arising from the surface accumulation of exogenous pigment) or intrinsic** (t.e., **secondary to** endogenous factors that result in the discoloration of the underlying dentin). Box 2-4 lists the most frequently documented causes of tooth discolorations.

Dental fluorosis is discussed under environmental effects on the structural development of the teeth (see page 53). The alterations associated with amelogenesis imperfecta (see page 89) and dentinogenesis impcrtecta (see page 94) are presented later in this chapter in the text devoted to primary developmental alterations of the teeth.

Clinical Features

Extrlnsic stains. **Bacterial stains are a common cause** of surface staining of exposed enamel. dentin. and **cementum. Chromogenic bacteria can produce col-**orations that vary from green or black-brown to orange. The discoloration occurs most frequently in children and is usually 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 suifide and iron in the saliva or gingival crevicular fluid.

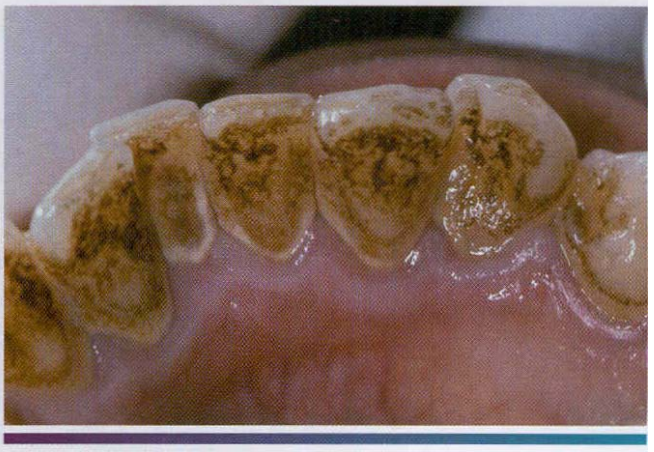

Figure 2-30 . Tobacco discoloration. Extrinsic brown stains of the enamel on the lingual surfaces of the anterior mandibular dentition secondary to long-term tobacco abuse.

Extensive use of tobacco products. tea. or coffee often results in significant brown discoloration of the surface enamel (Figure 2-30). 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 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.

Dental restorative materials. especially amalgam, can result in black-gray discolorations of teeth. This most frequently arises in younger patients who 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 discoloration, the clinician should not restore endodontically treated anterior teeth with amalgam (Figure 2-31).

A **large number of medications may result in surface** staining of the teeth. In the past, use of products con**taining high amounts of iron or iodine was associated with**

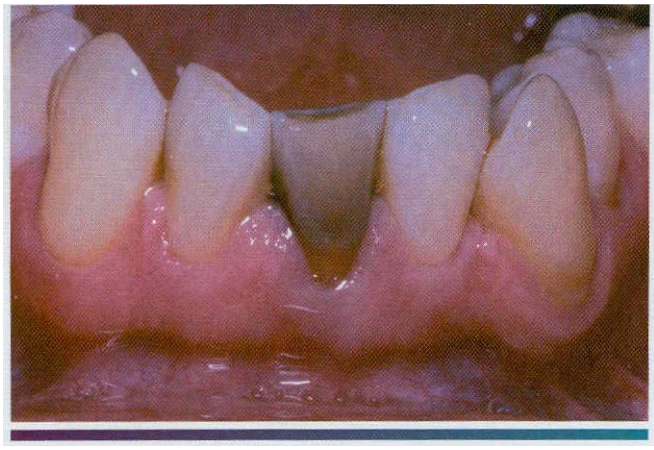

Figure 2-31 • Amalgam discoloration. Greenish-gray discoloration of mandibular central incisor, which had endodontic access preparation restored with amalgam.

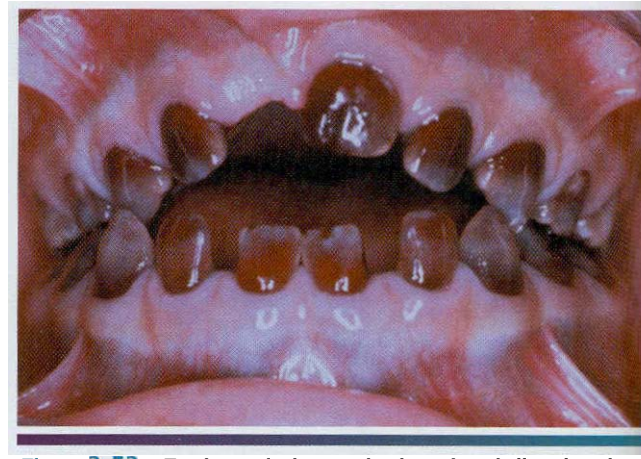

Figure 2-32 • Erythropoietic porphyria-related discoloration. Reddish-brown discoloration of the maxillary dentition.

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 or nickel may produce a green stain; cadmium may be associated with a yellow to golden-brown discoloration.

More recently, the most frequently reported culprits include stannous fluoride and chlorhexidine. Fluoride staining may be associated with the usc 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 yellowish-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. Chlorhcxidine is not alone in its association with tooth staining: many oral antiseptics, such as l.istcrine and sanguinarine, also may produce similar changes.

Intrinsic stains. Congenital erythropoietic porphyria (Gunther 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 (Figure 2-32). Affected teeth demonstrate a marked reddish-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. 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's 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 709). 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 01 hyperbilirubinemia during the neonatal period. The two most common causes are erythroblastosis fctalis and biliary atresia. Other diseases that less frequently dispiay intrinsic staining of this type include:

- Premature birth
- ABO incompatibility
- Neonatal respiratory distress
- Significant internal hemorrhage
- Congenital hypothyroidism
- Biliary hypoplasia
- Metabolic diseases (tyrosinemia. ai-antitrypsin deficiency)
- Neonatal hepatitis

Erythroblastosis fetalis is a hemolytic anemia of newborns secondary to a blood incompatibility (usually Rh factor) between the mother and the fetus. Currently. this disorder is relatively uncommon because of the use 01 antiantigen gamma globulin at delivery in mothers with Rh-negative blood.

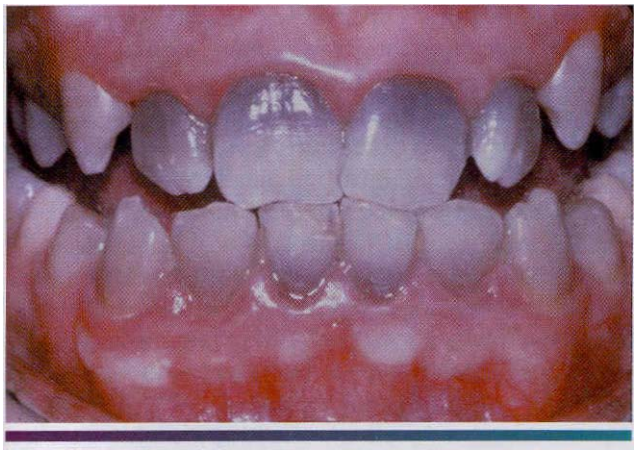

Figure 2-33 • Hyperbilirubinemia-related discoloration. Diffuse grayish-blue discoloration of the dentition. Cervical portions are stained most intensely. (Courtesy of Dr. John Giunta.)

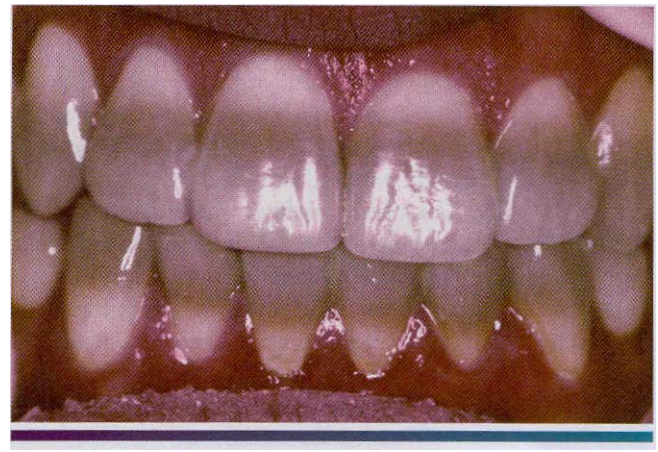

Figure 2-34 • Tetracycline-related discoloration. Diffuse brownish discoloration of the permanent dentition. (Courtesy of Dr. John Fantasla.]

Biliary atresia is a sclerosing process of the biliary tree that is the most important cause of death from hepatic failure in children in North America. However, many affected children live after successful liver transplantation.

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 (Figure 2-33). 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. Although pink and yellow discolorations are not indicative of pulp death. the dark-gray discoloration is associated with severe pulpal damage. 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 late yellow discoloration is indicative of pulpal obliteration, termed calcific metamorphosis, and is discussed more fully in Chapter 3 (see page 110). Although somewhat controversial. the dark-gray discoloration is believed by most investigators to signal significant pulpal degeneration that is. or eventually will become. necrotic. Such necrosis may be aseptic and not associated with significant tenderness to percussion• mobility, or associated periapical inflammatory disease.

A related process secondary to localized red blood cell destruction also can result in discoloration of the teeth. 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 176). Although controversial. some inyestigators 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.

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 ultraviolet light. showing a bright yellow fluorescence (Figure 2-34). The drug and its homologues can cross the placental barrier: therefore, administration must be avoided during pregnancy and in children up to 8 years of age. Homologues of tetracycline also associated with discoloration include chlortetracycline (gray-brown discoloration) and oxytetracycline (yellow).

One semisynthetic derivative of tetracycline. minocycline hydrochloride. has been shown to produce significant discoloration of the dentition and aiso may affect teeth that are fully developed. Minocycline is a widely used medication for the treatment of acne and also is occasionally prescribed to treat rheumatoid arthritis. Its prevalence *ot* usc 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. dermisl. 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 lust I month to several years.

In susceptible individuals. minocycline creates discoloration in the skin. nails. sclera. conjunctiva. thyroid. bone. and tceth. Coloration of the bone occasionally results in a distinctive blue-gray appcarance of the palate or anterior alveolar mucosa that represents the black bone showing through the thin. translucent oral mucosa (Figure 2-35). 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. The exposed roots of erupted teeth demonstrate a dark green discoloration. although the roots of developing teeth are stained dark black. Although the cutaneous staining fades after discontinuation of the medication, the dental discoloration remains.

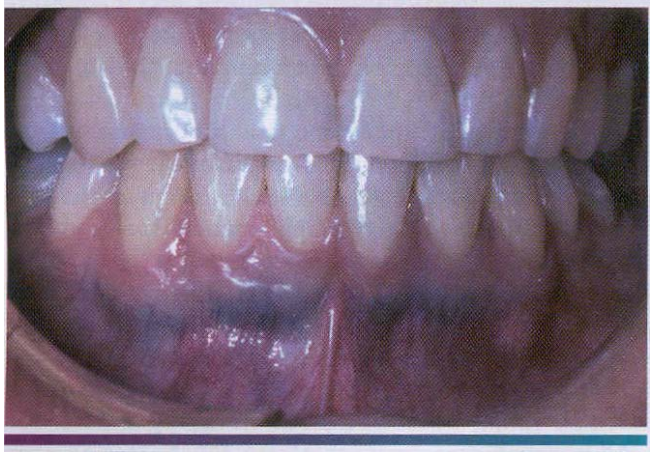

Figure 2-35 • Minocycline-related discoloration. Blue-gray discoloration of the facial surface of the anterior mandibular alveolus because stained alveolar bone is visible through the thin mucosa.

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 bicarbonated 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 solutions include full crowns. external bleaching of vital teeth. internal bleaching of nonvital teeth. bonded restorations. composite build ups. and laminate veneer 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

PRIMARY IMPACTION

Eruption is the continuous process of movement of a tooth from its developmental location to its functional location. Teeth that cease to erupt before emergence are impacted. Some authors subdivide these nonerupted 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

Primary impaction of deciduous teeth is extremely rare; when seen it most commonly involves second molars (Figure 2-36). Analysis of cases suggests that ankylosis plays a major role in the pathogenesis. In the permanent dentition. third molars are impacted most frequently. followed by maxillary cuspids. In decreasing order of frequency. impaction is seen 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. 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:

- **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 erupted partially 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: rncstoangular, distoangular, vertical. horizontal. or inverted.

Treatment and Prognosis

The choices of treatment for impacted teeth inciude:

- **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 mandate 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:**

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

The risks of intervention inciude:

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

Dental referral patterns provide a variety of perspectives of different dental practitioners. Many specialists (e.g.. oral 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. One **large review of pericoronal tissue submitted to an active** oral pathology service revealed that 32.9% of cases had pathologically significant lesions. In this o-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 exposure to significant pericoronal pathoses. such **specialists often choose extraction *over* close observation.**

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 will demonstrate fusion between the** affected tooth and the adjacent bone in almost all cases. Other terms for this process within the literature inciude **infraocclusion, secondary retention. submergence. reimpaction. and reinclusion. *Secondary retention* is an** acceptable term but may be confused with *retained pri-*

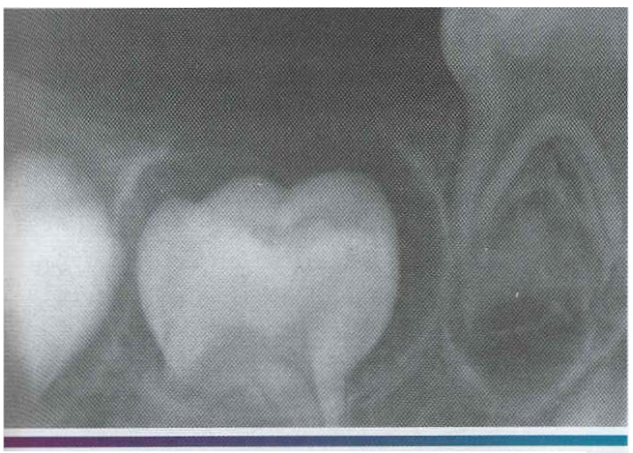

figure 2-36 • Primary impaction of deciduous tooth. The right secondary primary molar demonstrates delayed eruption and enlarged pericoronal radiolucency. **(Courtesy of Dr. G.** Thomas Kluemper.)

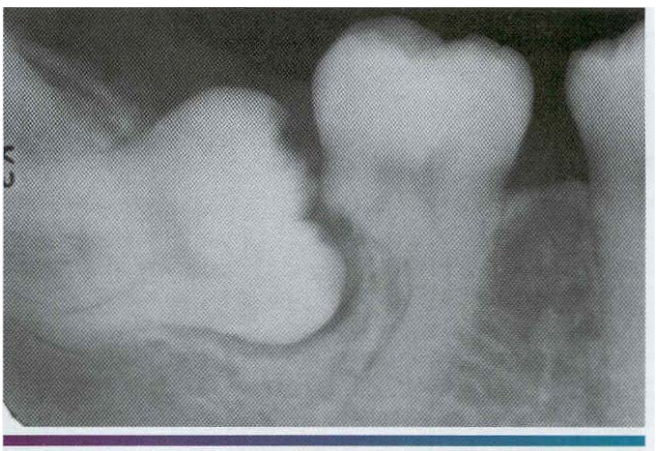

Figure 2-37 • Impaction-related tooth resorption. Mesic-**angular impaction of the right mandibular third molar associated with significant resorption of the distal root of the second molar. (Courtesy of Dr. Richard Brock.)**

may teeth, which maintain their emergence. *Submergence, retmpactton*, **and** *reinclusion* **connote an active depression.** and this is not the case.

The pathogenesis of ankyiosis 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 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** periodontal ligament gap. Other theories point to a disturbance between normal root resorption and hard-**tissue repair. Several investigators believe genetic pre-**disposition 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 it 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 tooth is the primary first molar: the majority of cases occur in the mandible. 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 (Figure 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 *ot* the periodontal ligament space may be noted: however. the area of fusion is often in the bifurcation and interradicular root surface. making radiographic detection most difficult (Figure 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 impaction of the underlying permanent tooth.

Treatment and Prognosis

Because they are fused to the adjacent bone. ankylosed teeth fail to respond to orthodontic forces. Recommended therapy for ankylosis of primary molars is variable and often determined by the scverity and timing of the process. When an undcrlying permanent successor is present. extraction of the ankylosed primary molar should not be performed until it is obvious that exfoliation is not proceeding normally or adverse occlusal changes are developing. In permanent teeth or primary teeth without underlying successors. a prosthetic buildup can be placed to augment the occlusal height. Severe cases in primary teeth are treated best with **extraction and space maintenance. Finally, 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 may result in the formation of a new fibrous ligament in the area of **previous fusion. In these cases, reevaluation in 6 months** is mandatory.

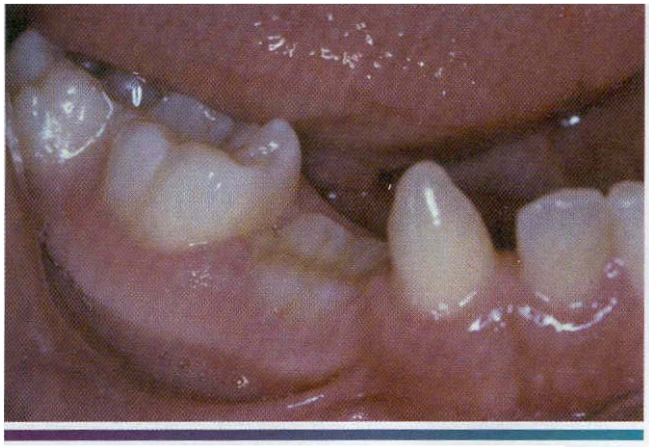

Figure 2-38 • Ankylosis. Deciduous molar well below the occlusal plane of the *adjacent* teeth.

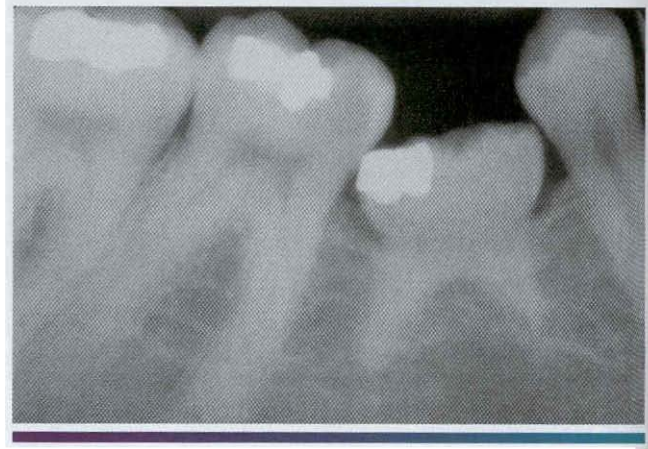

Figure 2-39 • Ankylosis. Radiograph of an ankylosed deciduous molar. Note the lack of periodontal ligament space.

Developmental Alterations of Teeth

Numerous developmental alterations of teeth can occur. Box 2-5 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,** dilaceration). For the sake of convenience, both the primary and 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. 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.

Genetic control appears to exert a strong influence on the development of teeth. Numerous hereditary syndromes have been associated with both hypodontia (Box 2-6) and hyperdontia (Box 2-7). In all of these syndromes, there Is an increased prevalence of hypodontla or hyperdontla, but the strength of the association varies. In addition, **many nonsyndromic numeric alterations of teeth** demonstrate a strong genetic correlation. Many cases of primary hypodontia appear to be autosomal dominant

Box 2-5 *Developmental Alterations of Teeth*

NUMBER
1. **Hypodontia**
2. **Hyperdontia**

SIZE
1. **Microdontia**
2. **Macrodontia**

SHAPE
1. **Gemination**
2. **Fusion**
3. **Concrescence**
4. **Accessory cusps**
5. **Dens invaginatus**
6. **Ectopic enamel**
7. **Taurodontism**
8. **Hypercementosis**
9. **Accessory roots**
10. **Dilaceration**

STRUCTURE
1. **Amelogenesis imperfecta**
2. **Dentinogenesis** Imperfects
3. **Dentin dysplasia type I**
4. **Dentin dysplasia type II**
5. **Regional odontodysplasia**

Box 2-6 *Syndromes Associated with Hypodolltia*

1. **Ankyloglossia superior**
2. **Böök**
3. **Cockayne**
4. Coffin-Lowry
5. **Cranio-oculo-dental**
6. **Crouzon**
7. **Down**
8. **Ectodermal dysplasia**
9. **Ectodermal dysplasia, cleft lip, cleft palate**
10. Ehlers-Danlos
11. Ellis-van **Creveld**
12. **Focal dermal hypoplasia**
13. **Freire-Maia**
14. Frontometaphyseal **dysplasia**
15. Goldenhar
16. **Gorlin**
17. **Gorlin-Chaudhry-Moss**
18. Hallertnann-Streiff
19. Hanhart
20. **Hurler**
21. Hypoglossia-hypodactylia
22. **Incontinentia pigmenti**
23. **Johanson-Blizzard**
24. **Lipoid proteinosis**
25. Marshaii-White
26. **Melanoleukoderma**
27. **Monilethrix-anodontia**
28. Orai-facial-digital, type I
29. Otodental dysplasia
30. **Palmoplantar keratosis. hypotrichosis. cysts of eyelid**
31. **Progeria**
32. **Rieger**
33. **Robinson**
34. Rothmund
35. 5turge-Weber
36. Tooth-and-nail
37. **Turner**

Box 2-7 *Syndromes Associated witl, Hyperdontia*

1. Apert
2. **Angio-osteohypertmphy**
3. Cleidocranial **dysplasia**
4. Craniometaphyseal **dysplasia**
5. Cro uzon
6. Curtlus
7. **Down**
8. **Ehlers-Danlos**
9. **Fabry-Anderson**
10. Fucosidosis
11. **Gardner**
12. Hallermenn-Strelff
13. Khppel-Trenaunay-weber
14. Laband
15. Nance-Horan
16. Oral-facial-digital, type I and III
17. Sturge-Weber
18. **Tricho-rhino-phalangeal**

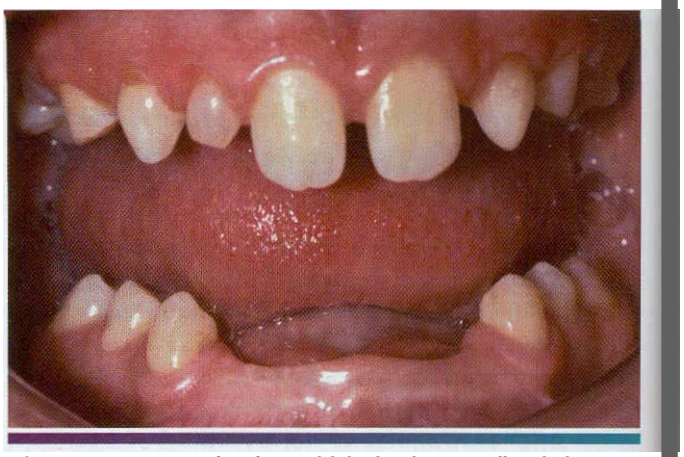

Figure 2-40. Hypodontia. Multiple developmentally missing permanent teeth and several retained deciduous teeth in a female adult.

with incomplete penetrance and variable expressivity, but **other cases exhibit support for an autosomal recessive or sex-linked pattern. The environment is not without its** influence, with occasional examples supporting multi-**factorial inheritance. Several investigators have reported** variable expression of hypodontia in monozygotic twins (confirmed by DNA fingerprinting). This discordance confirms the occasional muitifactorial nature of the process. overall, hypodontia most likely represents a variety of disorders caused by variable genetic and epigenetic factors. Less information is available on the genetics of hyperdontia, **but many cases also suggest an autosomal dominant pattern of inheritance wit h incomplete** penetrance. The variable expression and penetrance of the gene defects may be caused by environmental factors.

Some investigators have implied that hypodontia is a **normal variant. suggesting that humans arc in an inter-**mediate 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 pathogenesis of hyperdontia has been postulated to be caused by the development of excess dental lamina, which presumably leads to the formation of additional tooth germs. As expected, 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

ttypodontia. Developmental absent teeth are one of the most common dental developmental abnormalities with a reported prevalence of 3.5% to 8.0% (excluding third molars). A female predominance of approximately 1.5:I is reported (Figures 2-40 and 2-41). Anodontia is rare, and most cases occur in the presence of hereditary hypohidrotic ectodermal dysplasia (see page 644). Indeed, when the number of missing teeth is high or **involves the most stable teeth** (i.e., **maxillary central incisors, first molars), the patient should be** evaluated for ectodermal dysplasia. Hypodontia is uncommon in the deciduous dentition (less than I% of the population) and, when present, most frequently involves the mandibular incisors. Missing teeth in the permanent dentition are not rare, with third molars being the most commonly affected (20% to 23% of the population). After the molars, the second premolars and lateral incisors are absent most frequently (Figure 2-42). Hypodontia is associated positively with microdontia (see page 73). reduced alveolar development, increased freeway space, and retained primary teeth.

ityperdontia. The prevalence of supernumerary teeth **in Caucasians is between [% and** 3%. **with a slightly** higher rate seen in Asian populations. Approximately 76%

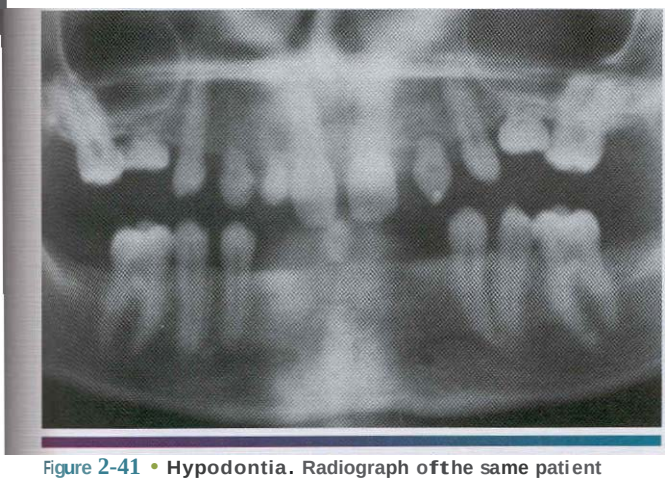

Figure 2-41 • **Hypodontia.** Radiograph of the same patient depicted in Figure 2-40. No unerupted teeth were noted within the jaws,

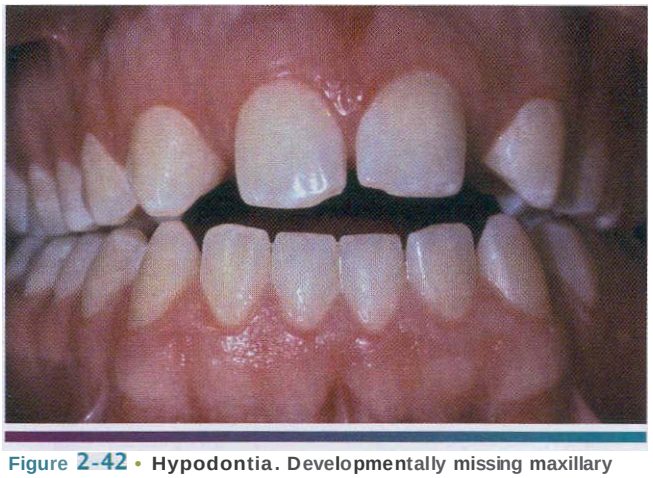

Figure 2-42 • **Hypodontia.** Developmentally missing maxillary lateral incisors. Radiographs revealed no underlying teeth, and there was no history of trauma or extraction.

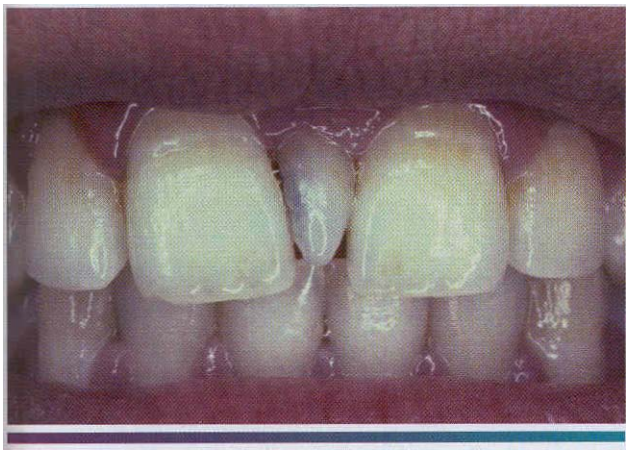

Figure 2-43. **Hyperdontia (mesiodens).** Erupted supernumerary, rudimentary tooth of the anterior maxilla.

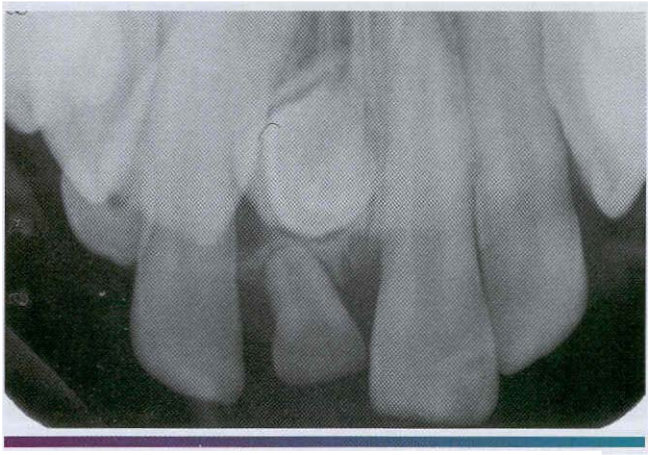

Figure 2-44 • Hyperdontia **(mesiodens). Unilateral supernumerary tooth of the anterior maxilla, which has altered the eruption path of the maxillary right permanent central incisor.**

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 90% present in the maxilla, with a strong predilection for the anterior region. The most common **site is the maxillary incisor region, followed** by maxillary fourth molars and mandibular fourth molars, premolars, canines, and lateral incisors (Figure 2-43). Although supernumerary teeth may be bilateral, most occur unilaterally (Figures 2-44 and 2-45). 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 (Figure 2-46).

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 73) 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 Figure 2-43); an accessory fourth molar is often called a distomolar or distodens. A posterior supernumerary tooth situated lingually or buccally to a molar tooth is termed **a paramolar** (Figures 2-47 and 2-48).

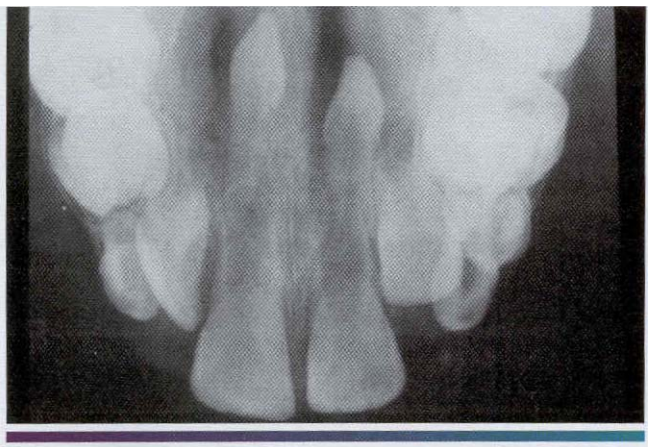

Figure 2-45 • Hyperdontia (mesiodens). Bilateral inverted supernumerary teeth of the anterior maxilla.

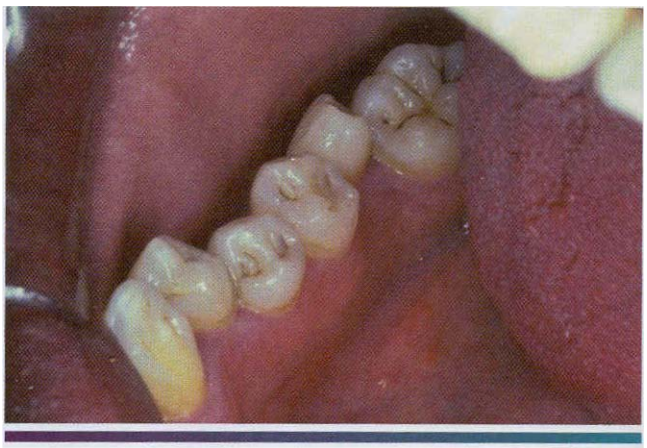

Figure 2-46 • Hyperdontia. Right mandibular dentition exhibiting four erupted bicuspids.

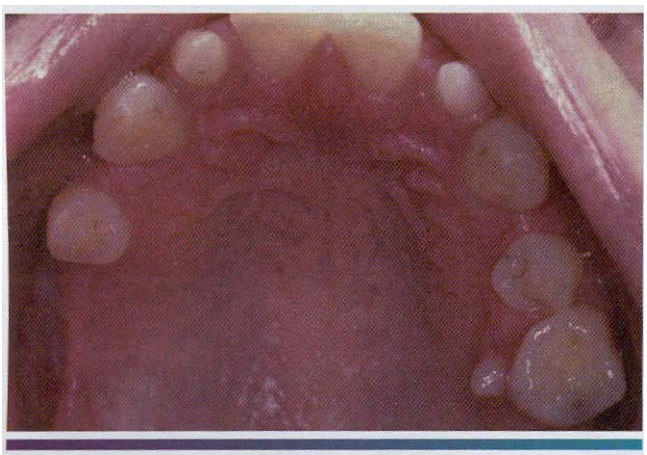

Figure 2-47 . Paramolar. Rudimentary tooth situated palatal to a maxillary molar in a patient who also exhibits hypodontia.

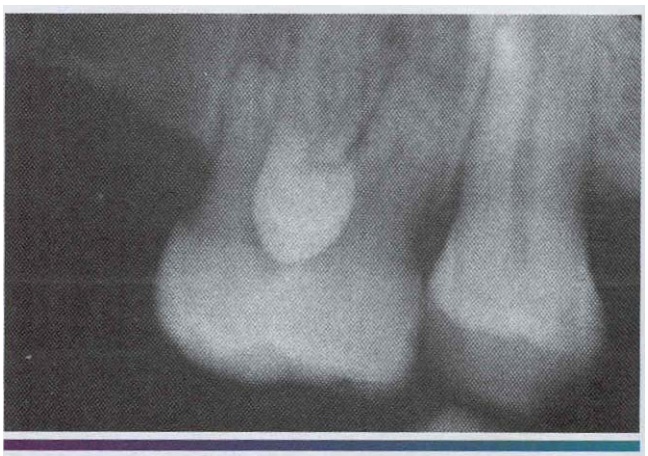

Figure 2-48 • Paramolar. Radiograph of the same patient depicted in Figure 2-47. Note the fully formed tooth overlying the crown of the adjacent molar.

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. The teeth involved most frequently in transposition are the maxillary canines and first premolars. 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* (Figure 2-49). 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.

Treatment and Prognosis

Sequelae associated with hypodontia include abnormal spacing of teeth, delayed tooth formation, delayed deciduous tooth exfoliation, and late permanent tooth eruption. 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 traditionai fixed prosthodontics, resin-bonded bridges, or osseoIntegrated implants with associated prosthetic crowns. For children and young adults, a resin-bonded bridge often is appropriate while waiting for full dental maturation.

The presence of supernumerary teeth should be suspected if there is a significant delay in the eruption of a localized portion of the dentition. In addition, supernumerary teeth may develop long after eruption of the permanent dentition. Several publications have documented supernumerary bicuspids arising up to II years after

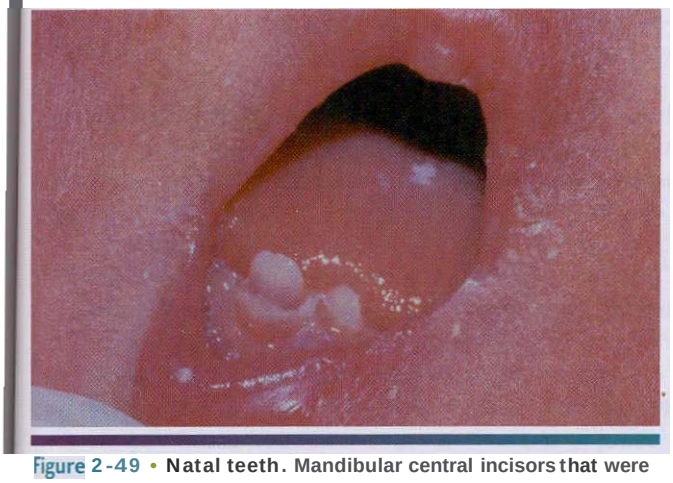

Figure 2-49 • Natal teeth. Mandibular central incisors that were erupted at birth.

completion of normal teeth development. In patients previously diagnosed with supernumerary teeth or 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 early removal of the accessory tooth. Complications created by anterior supernumerary teeth lend to be more significant than those associated with exira 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 1½ to 3 years.

A consequence of late therapy may include the delayed eruption or resorption of the adjacent teeth or the displacement of the teeth with associated crowding. malocclusion, or diastema formation. Supernumerary teeth also predispose the area to subacute pericoronitis, gingivitis. periodontitis. abscess formation. and the development of anyone 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.

Natal teeth must be approached individually. with sound clinical judgment guiding appropriate therapy. As Slated, 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. If mobility is not a problem and the teeth are stable, they should be retained. Traumatic ulcerations of the adjacent soft tissue (Riga-Fede disease) (see page 255) may occur during breast-feeding bU often can be resolved with appropriate measures.

DEVEIOPMENTAL 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, there is usually symmetry of the two sides of the jaws. In spite of 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 69); macrodontia often is seen in association with hyperdontia (see page 69), Females demonstrate a higher frequency of microdontia and hypodontia; males have a greater prevalence of macrodontia and hyperdontia.

Microdontia, The term mlcrodontia 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 micro**dontia, but it represents macrognathia (not micro**dontla). Diffuse true microdontia is uncommon but may occur as an isolated finding in Down syndrome. in pitu**itary dwarfism, and in association with a small number** of rare Ifereditary disorders that exhibit multiple abnormalities of the dentition (Figure 2-50).

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 (Figure 2-51). 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 pcnetrancc. In addition. isolated microdontia often affects third molars. Interestingly, both the maxillary lateral incisors and third **molars are among the most frequent teeth to be con**genitally missing. When a peg-shaped tooth is present, the remaining permanent teeth often exhibit a slightly smaller mesiodistal size.

Macrodontia. **Analogous to microdontia, the** term macrodontia (mcgalodontta, 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 macro-

dontla). 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 718) and pineal hyperplasia with hyperinsulinism. Macrodontia with unilateral premature eruption is not rare in hemifacial hyperplasia (see page 37). Authors have postulated that the unilateral bone growth resulting from this condition may also affect developing teeth on the altered side.

Treatment and Prognosis

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

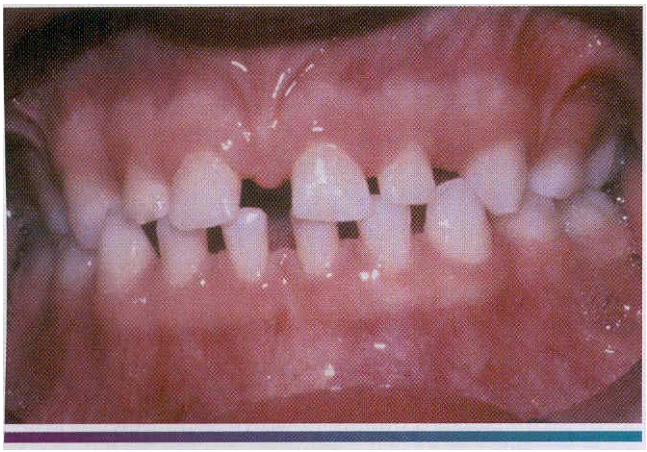

Figure 2-50 • Diffuse microdontia. Dentition in which the teeth are smaller than normal and widely spaced within the arch.

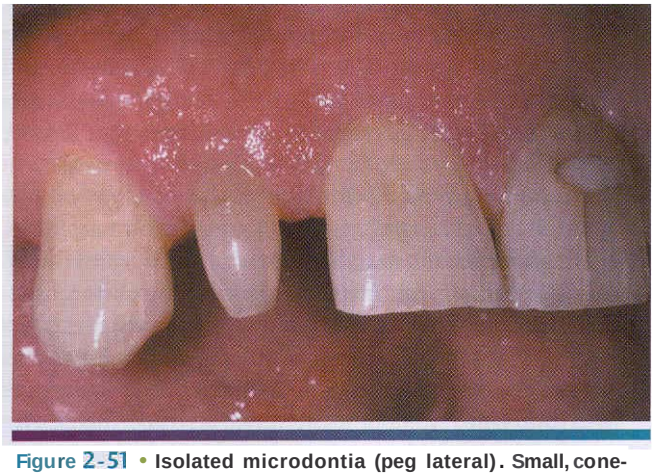

Figure 2-51 • Isolated microdontia (peg lateral). Small, cone-shaped right maxillary lateral incisor.

DEVELOPMENTAL ALTERATIONS IN THE SHAPE OF TEETH

GEMINATION, FUSION, AND CONCRESCENCE

Double 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, 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 rncsiodcns. 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).

Secondary to 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 [otned (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 [usion, Double teeth fgemination and fusion) occur in both the primary and permanent dentitions. with a higher frequency in the anterior and maxillary regions (Figures 2-52 to 2-56). Although the rate is variable in individual reports. the overall prevalence appears to be approximately 0.5% in the deciduous teeth and 0.1% in the permanent dentition. Bilateral cases are seen less frequently, with a *prevalence* of 0.02% in both dentitions (Figure 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 (Figure 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 crown may be seen overlying two completely separated roots. or the joined crowns may blend into one enlarged root with a single canal.

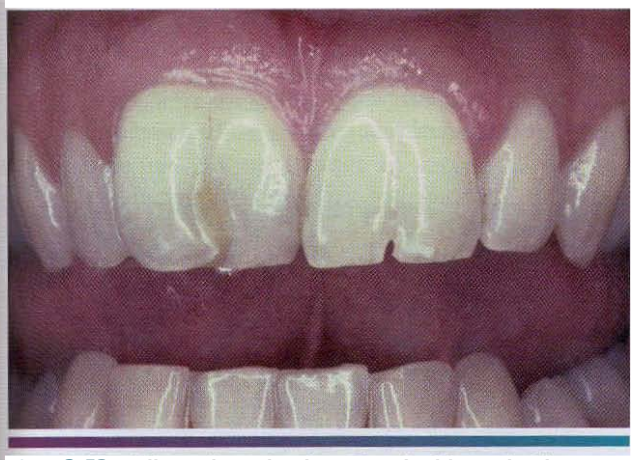

Figure 2-52 • Bilateral gemination. Two double teeth. The tooth count was normal when each anomalous tooth was counted as one.

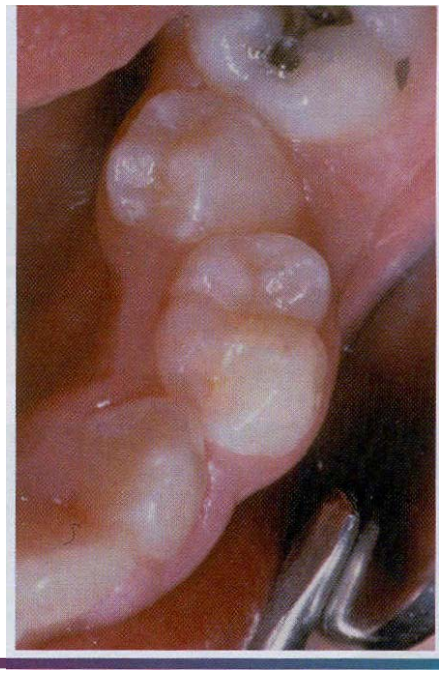

Figure *i -53* . Gemination. Mandibular bicuspid exhibiting bifid crown.

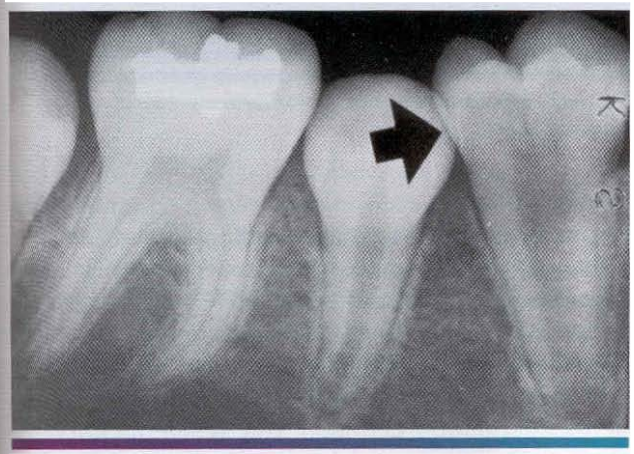

Figure 2-54 . Gemination. Same patient as depicted in Figure 2-53. Note the bifid crown and shared root canal.

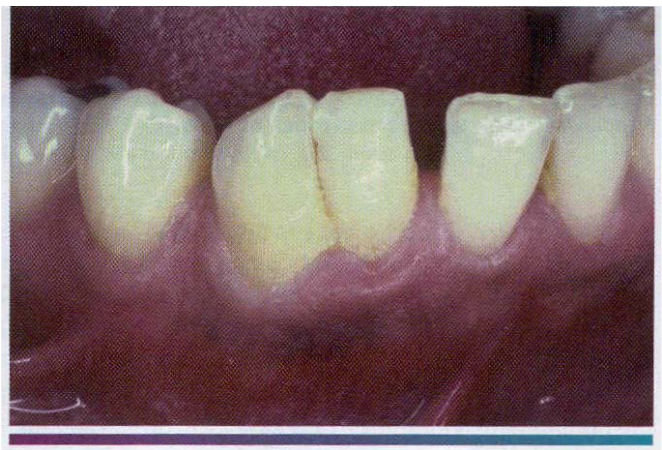

Figure 2-55 • Fusion. Double tooth in the place of the mandibular right lateral incisor and cuspid.

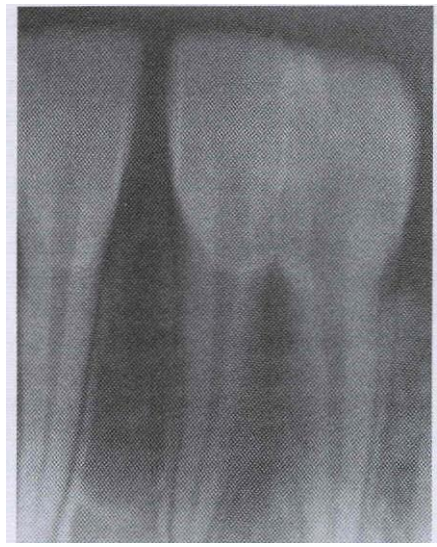

Figure 2-56 . Fusion. Radiographic view of double tooth in the place of the mandibular central and lateral incisors. Note separate root canals.

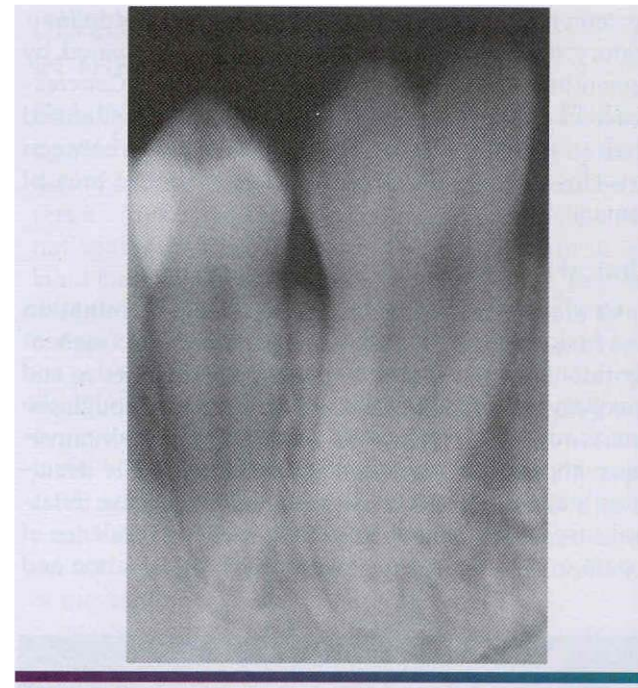

Figure 2-58 • Fusion. Radiograph of the same patient depicted in Figure 2-57. Note the bifid crown overlying the single root canal; the contralateral radiograph revealed a similar pattern.

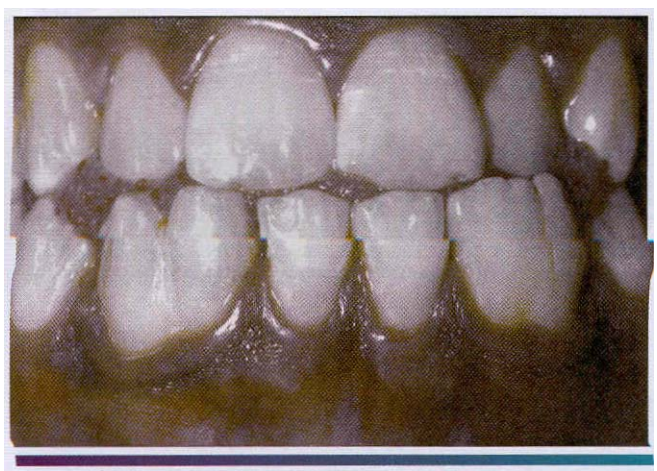

Figure 2-57 • Fusion. Bilateral double teeth in the place of the mandibular lateral incisors and cuspids.

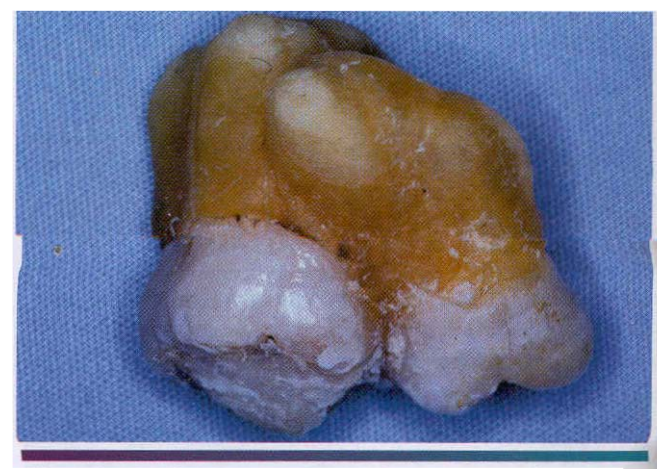

Figure 2-59 • Concrescence. Union by cementum of adjacent maxillary molars.

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 (Figure 2-59). The postinflammatory pattern frequently involves carious **molars in which the apices overlie the roots of horizon-**tally 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 resolution of a portion of the Intrabony pathosis. Cernental repair then occurs (Figures 2-60 and 2-6 1).

Treatment and Prognosis

The presence of double teeth (I.c.• 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

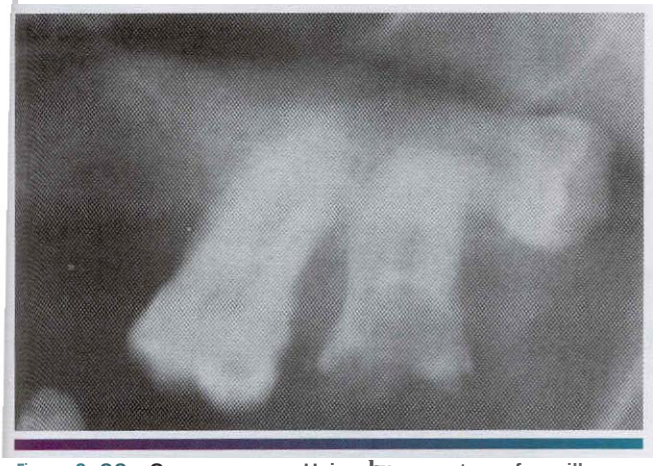

Figure 2-60 • Concrescence. Union by cementum of maxillary second and third molars. Note the large carious defect of the second molar.

observation. When appropriate, extraction may be necessary to prevent an abnormality in eruption.

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. Rare reports of successful surgical division have been documented. In most cases of surgical division, endodontic therapy was performed. 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.

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 (Figure 2-62). The cusp may be seen in the permanent or deciduous dentitions

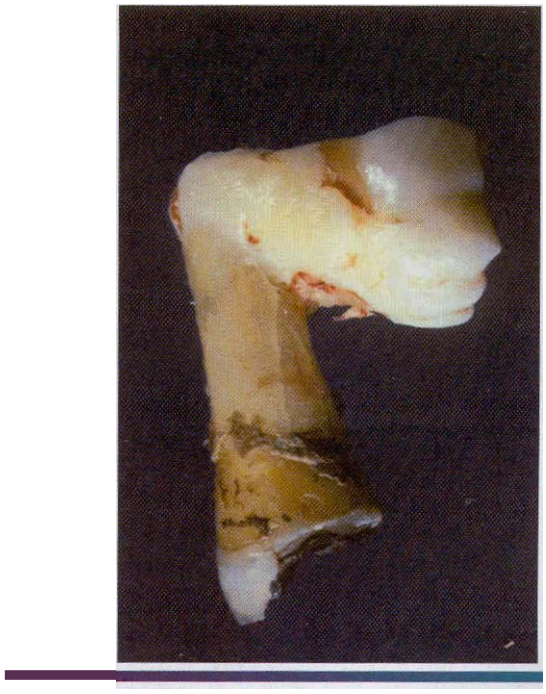

Figure 2-61 • Concrescence. Gross photograph of the same teeth depicted in Figure 2-60. Histopathologic examination revealed that union occurred in the area of cemental repair previously damaged by a periapical inflammatory lesion.

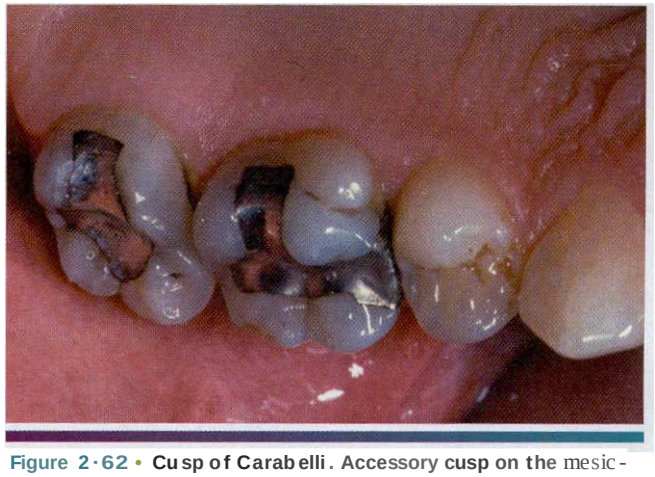

Figure 2-62 • Cusp of Carabelli. Accessory cusp on the mesiolingual surface of the maxillary first molar.

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 ceca-

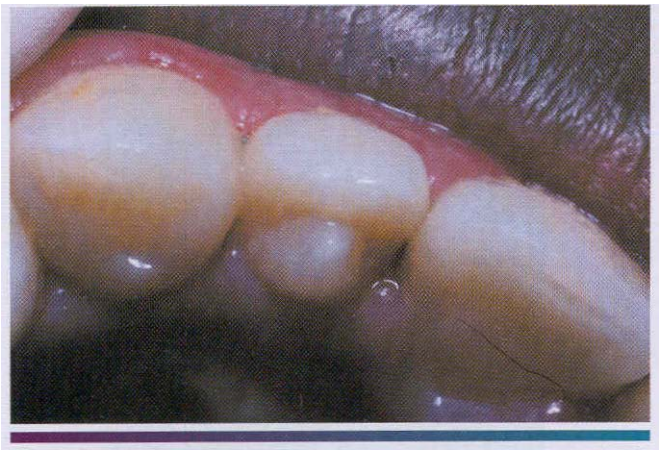

Figure 2-63 • Talon cusp. Accessory cusp present on the palatal surface of the maxillary left central incisor. Note the three-pronged pattern. which resembles an eagle talon.

sionally on the mesiobuccal cusp of a mandibular permanent or deciduous molar and is termed a protostylid.

Talon cusp, A talon cusp (dens evaginatus of anterior tooth) 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 cemcntoena mel junction to the incisal edge. 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%) (Figure 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 aecessory 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 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 (Figure 2-64). Only a few cases demonstrate visible pulpai extensions on dental radiographs.

Extensive *prevalence* studies have not been performed. but estimates suggest the frequency of talon cusp in the population ranges from less than i% to 8%. Variations within different population groups make a definitive calculation difficuit. Both sexes may be affected. and the occurrence may be unilateral or bilateral. The accessory cusp has been seen in association with other dental anomalies (c.g.. supernumerary teeth. odontomas. impacted teeth. peg-shaped lateral incisors. dens invaginatus. posterior dens evaginatus). Talon

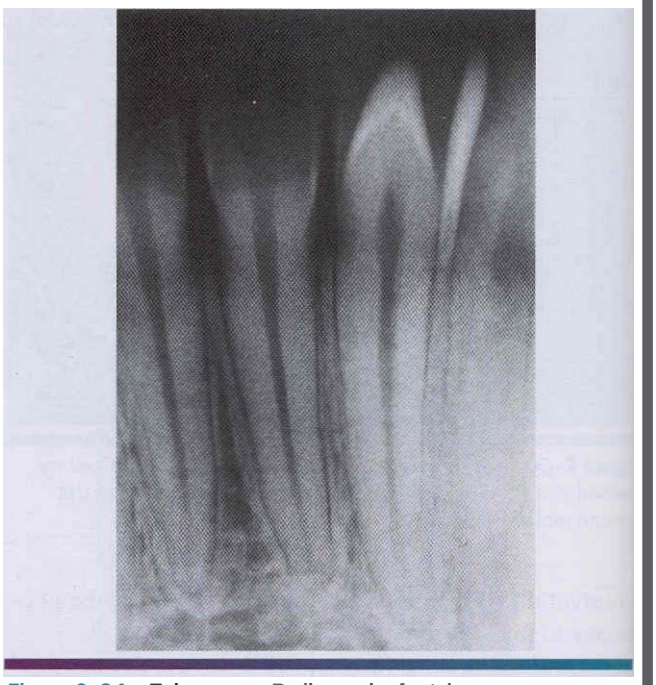

Figure 2-64 • Talon cusp. Radiograph of a talon cusp on a mandibular lateral incisor. Note the enamel and dentin layers within the accessory cusp.

cusps have been seen in patients with Mohr. Rubinstein-Taybi, and Sturge-Weber syndromes. In isolated cases. genetic influences appear to have an effect because identical talon cusps occasionally have been documented in twins.

Delis evaginatus. Dens evaginatus (central tubercle) is a cusplike elevation of enamel located in the central groove or linguai ridge of the buccal cusp of permanent premolar or molar teeth (Figure 2-65). Although this pal' tern of accessory cusps has been reported on molars. dens evaginatus typically occurs on premolar teeth. is usually bilateral. and demonstrates a marked mandibular predominance. The accessory cusp normally consists of enamel. dentin. and pulp. The process is rare in whites. but the prevalence has been reported to be as high as I5% in Asians. Radiographically. the occlusal surface exhibits a tuberculated appearance. and often a pulpal extension is seen in the cusp (Figure 2-66).

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 I5% in whites but close to 100% in native Americans and Alaskans. Affected incisors demonstrate prominent lateral margins. creating a hollowed lingual surface that resembles the scoop of a shovel (Figure 2-67). Typically. the thickened marginal ridges converge at the cingulum; not uncom-

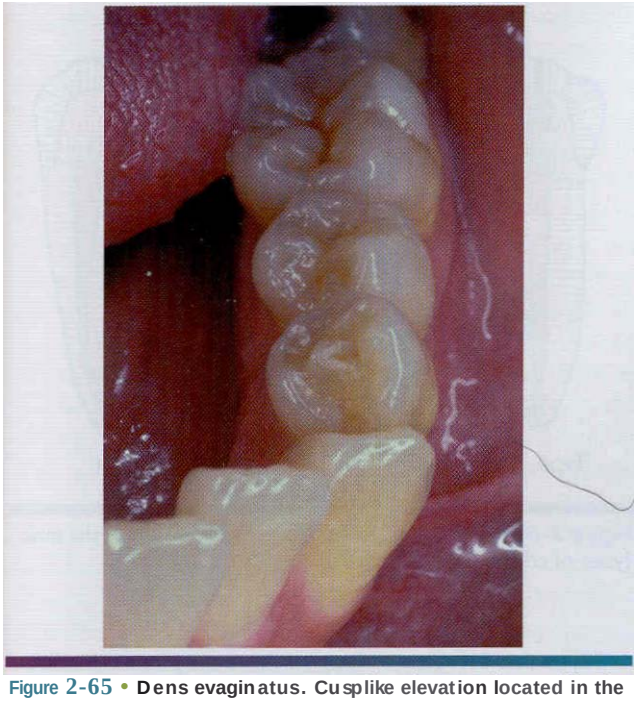

Figure 2-65 • Dens evaginatus. Cusplike elevation located in the central groove of mandibular first bicuspid.

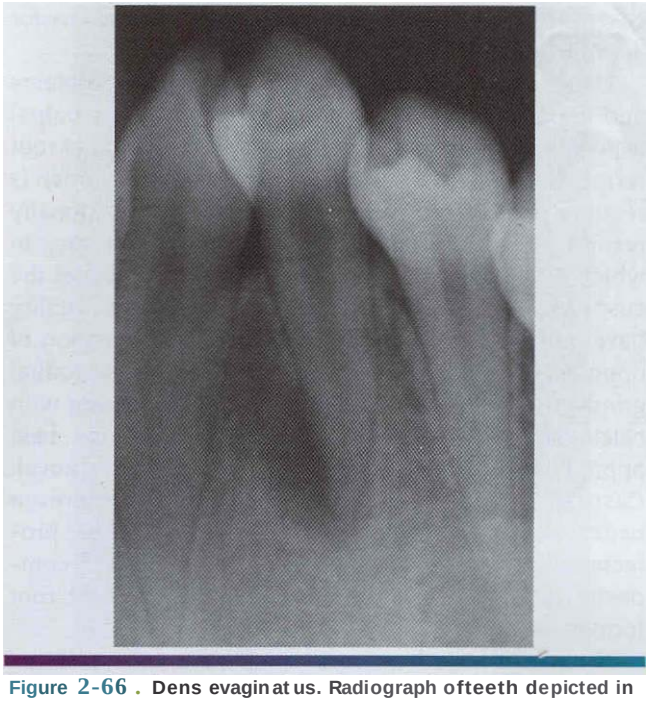

Figure 2-66 . Dens evaginatus. Radiograph ofteeth depicted in Figure 2-65. Note the tuberculated occlusal anatomy. Attrition on the accessory cusp led to pulpal necrosis and periapical inflammatory disease.

manly there is a deep pit. fissure. or dens invaginatus 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 present 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. After successful removal. the exposed dentin is covered with calcium hydroxlde. the peripheral enamel is etched. and a composite resin is placed.

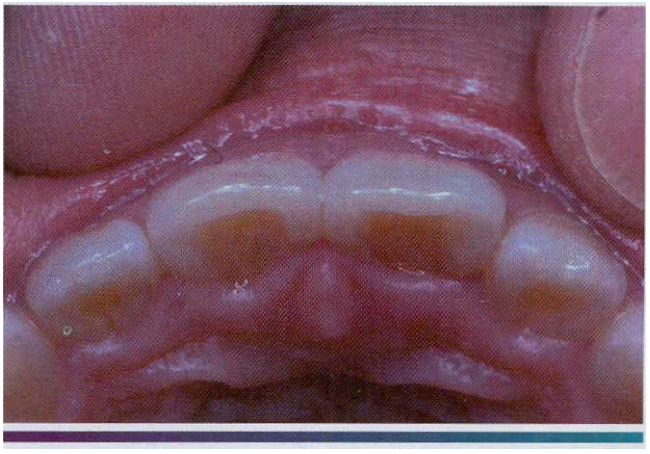

Figure 2-67 . Shovel-shaped incisors. Chinese patient exhibiting maxillary incisors with prominent lateral margins. which create a hollowed lingual surface.

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 often results in occlusal problems and is prone to fracture. frequently resulting in pulpal exposure. Pulpal necrosis results in the cessation of root formation; apexification with calcium hydroxide often is required to achieve closure. Extraction is occasionally recommended for *nonvital* teeth with an open apex in which apexification is unsuccessful. The *rcmovai* of the cusps often is indicated. but attempts to maintain vitality have met with only partial success. The elimination of opposing occlusal interferences. combined with gradual grinding of the tubercle and indirect pulp capping with calcium hydroxide. has been suggested as the best approach when the clinician is considering *removal*. Cuspal removal with direct pulp capping also has proven beneficial in some patients. Other investigators have protected the cusp from fracture by the placement of composite reinforcement around the projection until root formation is complete.

If shovel-shaped incisors arc present. the affected teeth 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.

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. A 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 (Figure 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 that mayor may not communicate with the adjacent dental pulp (Figures 2-69. 2-70. and 2-71). Large invaginations may become dilate and contain dystrophic enamel in the base of the dilata tion (Figure 2-72). Type ill extends through the root a perforates in the apical or lateral radicular area withd any immediate communication with the pulp. In thl latter type. the enamel that lines the invagination isoft replaced by cementum close to the radicular perforatio This perforation provides direct communication fromt oral cavity to the intraosseous periradicular tissuesa often produces inflammatory lesions in the presence 0 a vital pulp (Figures 2-73 and 2-74).

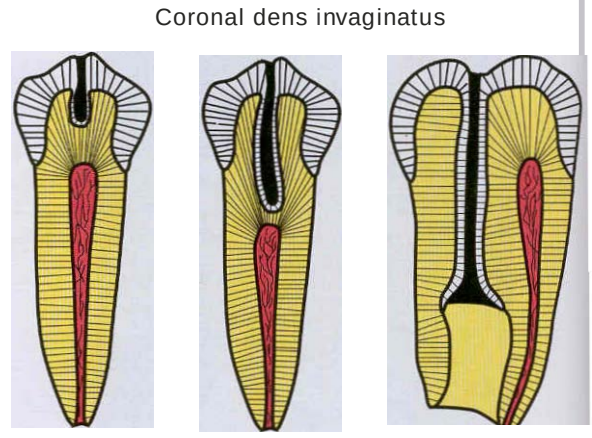

Figure 2-68 • Dens invaginatus. Illustration depicting the three types of coronal dens invaginatus.

Occasionally. the invagination may be rather large and resemble a tooth within a tooth. hence the term densil • dcnte. In other cases the invagination may be dilated an disturb the formation of the tooth. resulting in anomalo tooth development termed dilated odontome. Involment may be singular. multiple. or bilateral.

Radicular dens invaginatus is rare and thought to ari secondary to a proliferation of Herrwig:s root sheath. wit the formation of a strip of enamel that extends alongth surface of the root. This pattern of enamel depositioni similar to that frequently seen in association with radic ular enamel pearls (see *Ectopic Enamels*, Rather than pr trude from the surface (as seen in an enamel pearl). th altered enamel forms a surface invagination into th dental papilla (Figure 2-75). Cementum-lined invagina tions of the root have been reported. but these represen a simple variation of root morphology and should notb included under the term radicular dens invaginatus.

Radiographically. the affected tooth demonstratesa enlargement of the root. Close examination often reveal a dilated invagination lined by enamel. with the opcnin of the invagination situated along the lateral aspect the root.

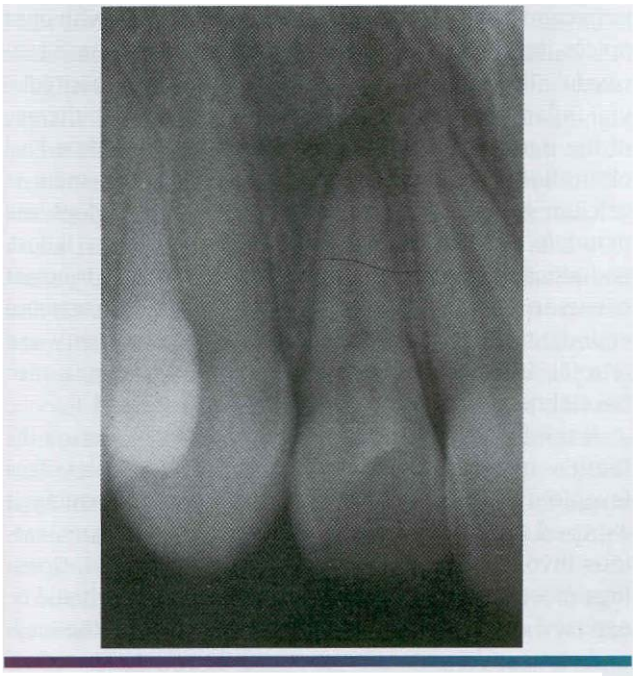

Figure 2-69 • Coronal dens invaginatus, type II. Maxillary lateral incisor exhibiting invagination of the surface enamel that extends slightly below the cementoenamel junction.

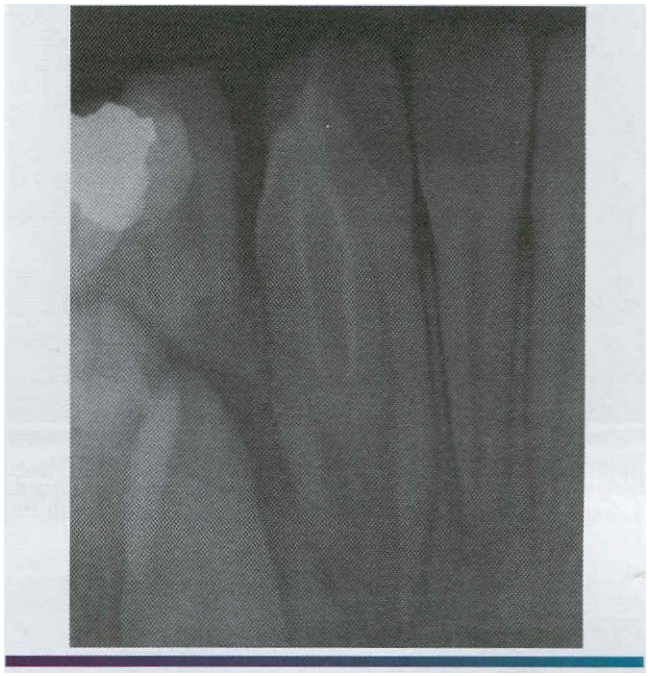

Figure 2-71 • Coronal dens invaginatus, type II. Radiograph of the mandibular lateral incisor depicted in Figure 2-70. Note the radiopaque and enamel-lined invagination extending below the level of the cementoenamel junction.

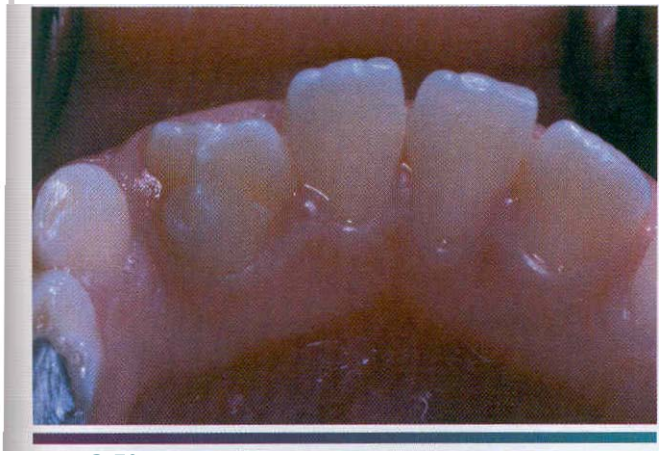

Figure 2-70 . Coronal dens invaginatus. type II. Mandibular lateral incisor exhibiting lingual bulbous enlargement at the site of coronal opening of enamel invagination.

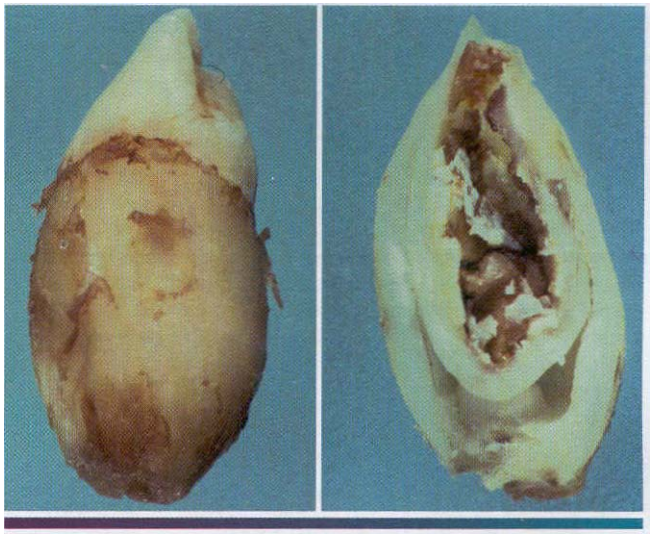

Figure 2-72 • Coronal dens invaginatus, type II. Gross photograph of a sectioned tooth. Note the dilated invagination with apical accumulation of dystrophic enamel.

Treatment and Prognosis

On eruption. the invagination of the affected tooth communicates with the oral cavity. and the soft tissue within the lumen undergoes necrosis (providing an excellent environment for growth of bacteria). In small type I invaginations. the opening of the invagination should be restored upon eruption in an attempt to prevent carious involvement and subsequent pulpal inflammation. If the invagination is not detected quickly. 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

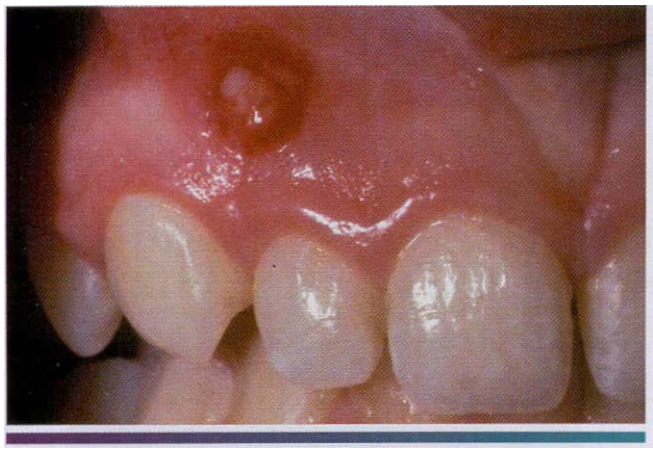

Figure 2-73 • Coronal dens invaginatus, type III. Parulis overlying vital maxillary cuspid and lateral incisor. The cuspid contained a dens invaginatus that perforated the mesial surface of its root.

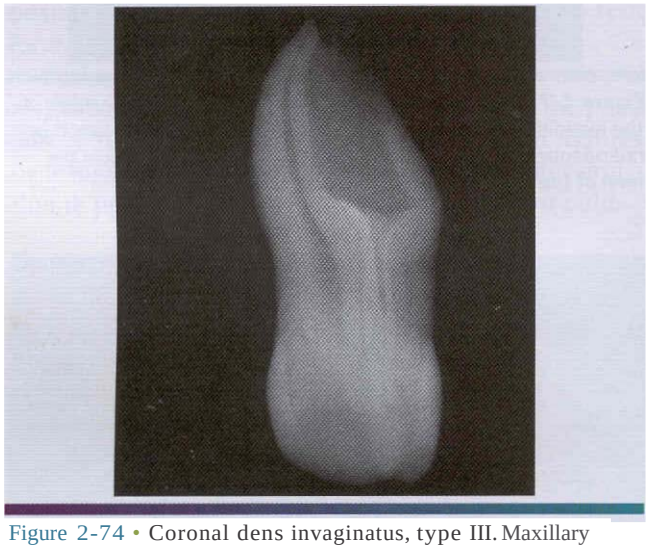

Figure 2-74 • Coronal dens invaginatus, type III. Maxillary cuspid exhibiting an enamel invagination that parallels the pulp canal and perforates the lateral root surface. (Courtesy of Dr. Brian Blocher]

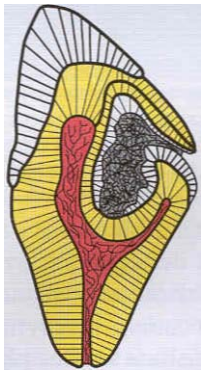

Figure 2-75 • Radicular dens invaginatus. Illustration depicting the radicular form of dens invaginatus.

pulp canal require endodontic therapy. In teeth with open apices, apexification with calcium hydroxide often is successful. 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 tooth's morphology, 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 thai may consist entirely of enamel or contain underlying dentin and pulp tissue. Most project from the surface of the rool and are thought to arise from a localized bulging of the odontoblastic layer. This bulge may provide prolonged contact between Hertwlg's 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 are found most frequently on the-roots of maxillary molars (mandibular molars are the second most frequent site). It is uncommon for maxillary premolars and incisors to be affected. *Involvement* of deciduous molars is not rare.

The prevalence of enamel pearls varies (1.1% 10 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 cemcntoenamel junction (Figure 2-76l.** Radiographically. pearls appear as well-defined. radiopaque nodules along the root's surface (Figure 2-77). Mature internal enamel pearls appear as well-defined circular areas of radiodensity extending from the dentinoenamel junction 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.

***Cervical** enamel extensions*. As mentioned previously, cervical enamel extensions are located on the buccal surface of the root overlying the bifurcation (Figure 2-78!. Mandibular molars are affected more frequently than are maxillary molars. The prevalence is greater in Asians and varies from 8.6% to 32.6% of all patients. depending on the population that is under study. In descending order. the teeth most frequently affected are the first. second. and third molars. respectively.

These apical extensions of enamel have been correlated positively to 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 involvemen!. 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 608). The association between cervical enamel extensions and this unique inflammatory cyst is controversial.

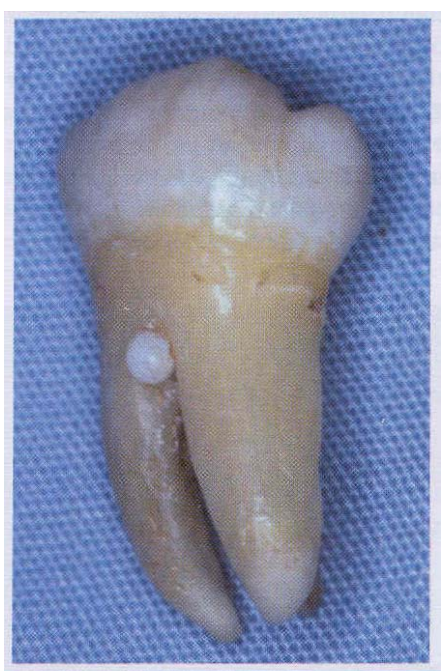

figure 2-76 . Enamel pearl. Mass of ectopic enamel located in the furcation area of a molar tooth. (Courtesy of Dr. Joseph Baird.)

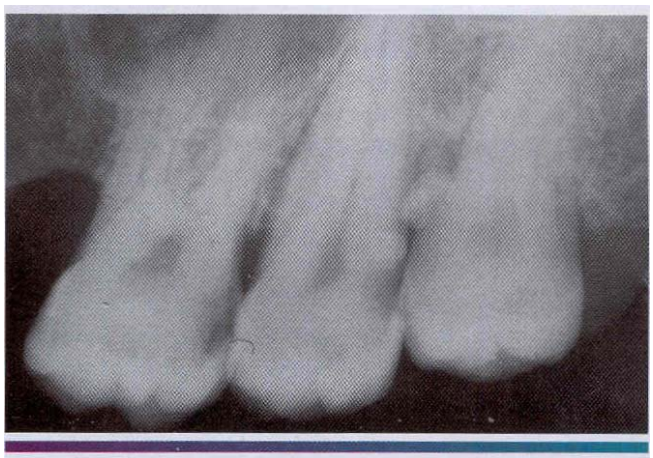

Figure 2-77 • Enamel pearl. Radiopaque nodule on the mesial surface of the root of the maxillary third molar. Another less distinct enamel pearl is present on the distal root of the second molar.

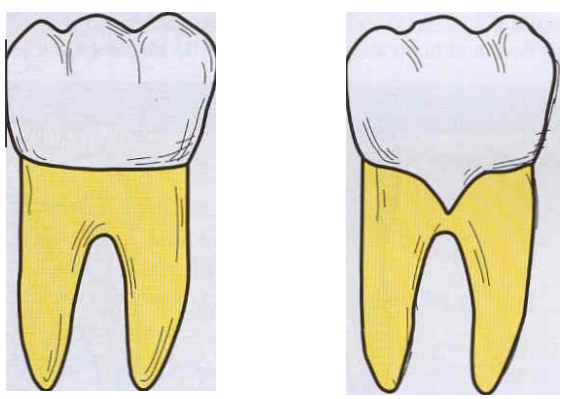

Figure 2-78 • Cervical enamel extension. Illustration of a normal molar adjacent to a molar exhibiting V-shaped elongation of enamel extending toward the bifurcation.

Treatment and Prognosis

When enamel pearls are detected radiographically. 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. If removal of the lesion is contemplated. the clinician must remember that enamel pearls occasionally contain 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 cxcisional 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-chewtng animals (*lauro* = bull and *dont* = tooth).

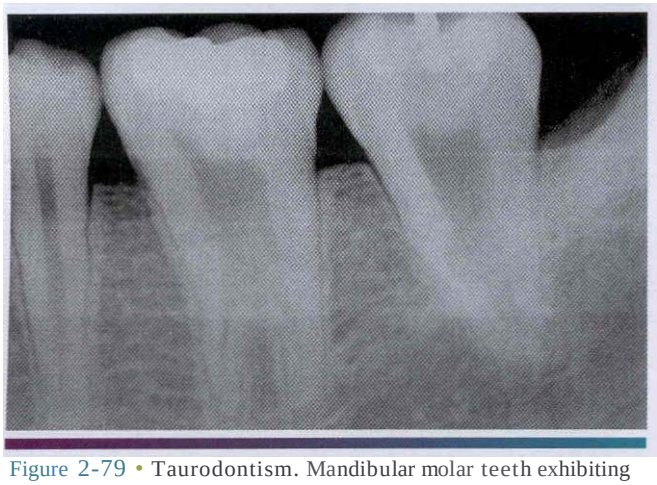

Figure 2-79 • Taurodontism. Mandibular molar teeth exhibiting increased pulpal apicoocclusal height with apically positioned pulpal floor and bifurcation. (Courtesy of Dr. Michael Kahn.)

Clinical and Radiographic Features

Affected teeth tend 10 be rectangular in shape and exhibit pulp chambers with a dramatically increased apicoocclusal height and a bifurcation close to the apex (Figure 2-79). The diagnosis usually is made subjectively from the radiographic appearance. The degree of taurodontlsm has been classified into mild (hvpotaurodontisrn), moderate (mcsotaurodonttsm), and severe (hypertaurodontism), according to the degree of apical displacement of the pulpal floor (Figure 2-80). Useful biometric criteria for the determination of taurodontism were presented by Witkop and colleagues and by Shifman and Chananel. 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

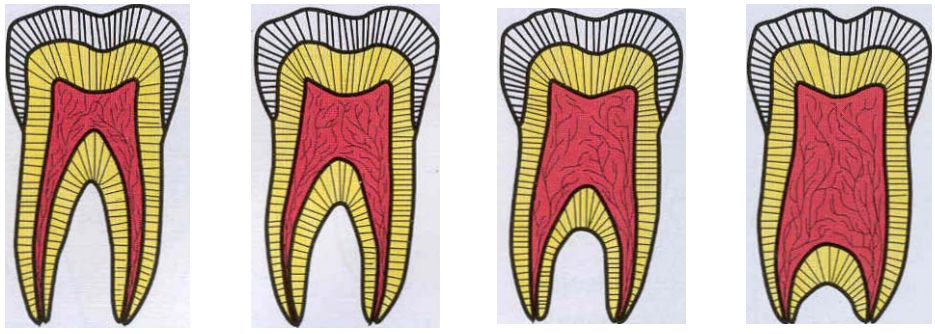

Figure 2-80 • Taurodontism. Illustration exhibiting the classification of taurodontism according to the degree of apical displacement of the pulpal floor.

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 a specific syndrome (Box 2-8). An increased frequency of taurodontism has been reported in patients with cleft lip or palate. Investigations have shown that taurodontism may develop in the presence of anyone 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.

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, but this hypothesis has not been verified. If endodontic therapy is required, the shape of the pulp chamber frequently increases the difficulty of locating, instrumenting, and obturating the pulp canals. One bit of good news is that patients have to demonstrate significant periodontal destruction before bifurcation involvement occurs.

HYPERCEMENTOSIS

Hypercementosis 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 (Figure 2-81). The enlarged root is surrounded by the radiolucent periodontal ligament space and the adjacent intact lamina dura. Hypercementosis may be isolated, may involve multiple teeth, or may appear as a generalized process. Premolar teeth are *involved* most frequently.

Hypercementosis occurs predominantly in adulthood, and the frequency increases with age. Its occurrence has been reported in younger patients, and many of these cases demonstrate a familial clustering, suggesting hereditary influence.

Box 2-9 lists several local and systemic factors that have been associated with an increased frequency of the cervental deposition. Of these factors, Paget's disease of bone (see page 542) has received the most attention. Numerous authors *have* reported significant hypercementosis in patients with Paget's disease, and this disorder should be considered whenever generalized hyper-

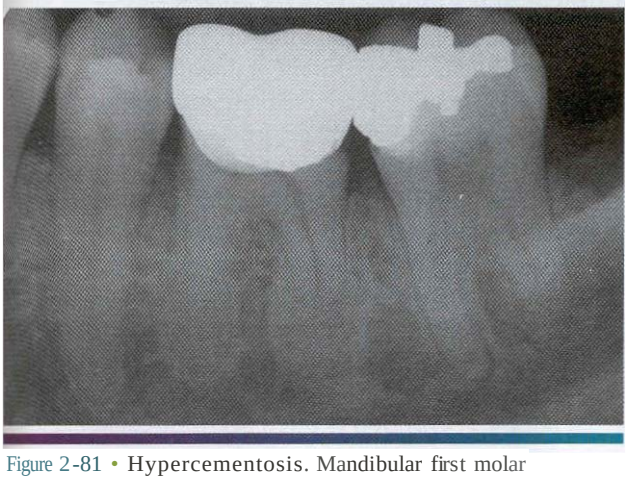

Figure 2-81 • Hypercementosis. Mandibular first molar exhibiting thickening and blunting of the roots.

Box 2-8 *Syndromes Associated with Taurodontism*

1. Amelogenesis imperfecta, hypoplastic, type IE
2. Amelogenesis imperfecta-taurodontism, type IV
3. Cranioectodermal
4. Ectodermal dysplasia
5. Hyperphosphatasia-oligophrenia·taurodontism
6. Hypophosphatasia
7. Klinefelter
8. Microdontia-taurodontia-dens invaginatus
9. Microcephalic dwarfism-taurodontism
10. Oculo-dento-digital dysplasia/
11. Oral-facial-digital, type II
12. Rapp-Hodgkin
13. Scanty hair-oligodontia-taurodontia
14. Sex chromosomal aberrations (e.g., XXX, XYY)
15. Down
16. Tricho-dento-osseous, types I, II, and III
17. Tricho-onycho-dental

Box 2-9 *Factors Associated with Hypercementosis*

LOCAL FACTORS

- Abnormal occlusal trauma
- Adjacent inflammation
- Unopposed teeth [e.g., impacted, embedded, without antagonist)

SYSTEMIC FACTORS

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

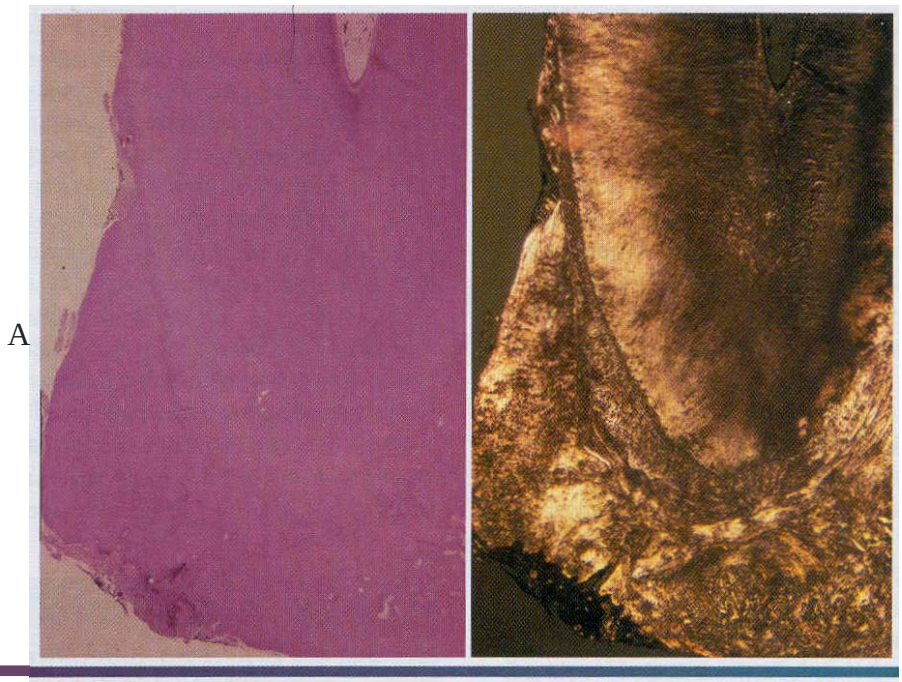

Figure 2-82 • Hypercementosis. A. Dental root exhibiting excessive deposition of cellular and acellular cementum. The dividing line between dentin and cementum is indistinct. **B.** Polarized light demonstrating the sharp dividing line between the tubular dentin and osteocementum.

cemcntosis 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.

Histopathologic Features

The periphery of the root exhibits deposition of an excessive amount of cementum over the original layer of primary cementum. The excessive cementum may be hypocellular or exhibit areas of cellular cementum that resemble bone (osreocc mcnturn). 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. the distinction between dentin and cementum often is difficult, but the use of polarized light clearly separates the two different layers (Figure 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 (Figure 2-83). Although a corroborating history may be absent, the majority 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 Intruslon of the overlying primary predecessor, an event that normally occurs before 4 years of age. Less frequently the bend develops secondary to the presence of an adjacent cyst. tumor. or odontogenic hamartoma (e.g.. odontoma, supernumerary tooth) (Figure 2-84). Some cases cannot be related to local injury and appear to be an idiopathic developmental disturbance (Figure 2-85).

Clinical and Radiographic Features

Although any tooth may be affected, the most frequently involved teeth are the permanent maxillary incisors, followed by the mandibular anterior dentition (Figure 2-86). Occasionally, involvement of the deciduous teeth is reported. and some have been associated with prior trauma secondary to neonatal laryngoscopy and endotracheal intubation. The age of the patient and the direction and degree of force appear to determine the extent of the tooth's malformation. The abnormal angulation may be present anywhere along the length of the tooth.

Altered maxillary anterior teeth frequently demonstrate the bend in the crown or the coronal half of the root; failure of eruption is often seen. Affected mandib-

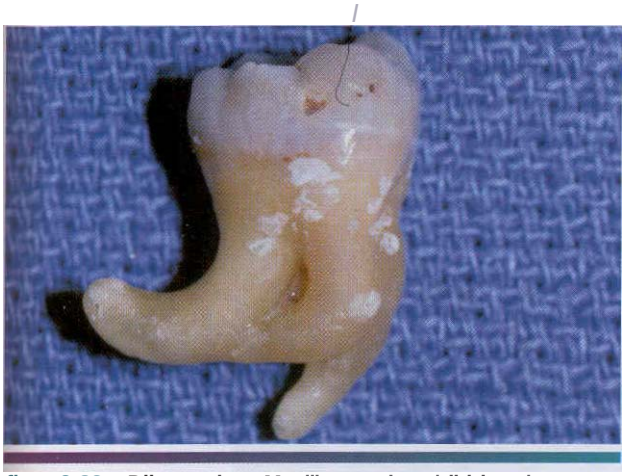

figure 2-83 • Dilaceration. Maxillary molar exhibiting sharp angulation of the roots. Note the interradicular bone.

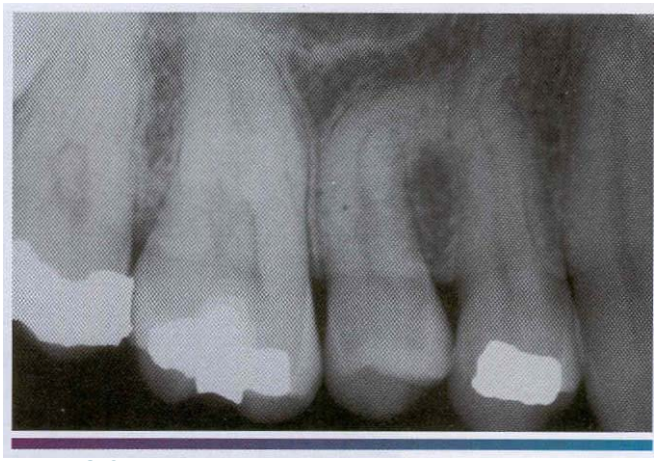

Figure 2-85 • Dilaceration. Maxillary second bicuspid exhibiting mesial inclination of the root. There was no history of local injury to the area. (Courtesy of Dr. Lawrence Bean.]

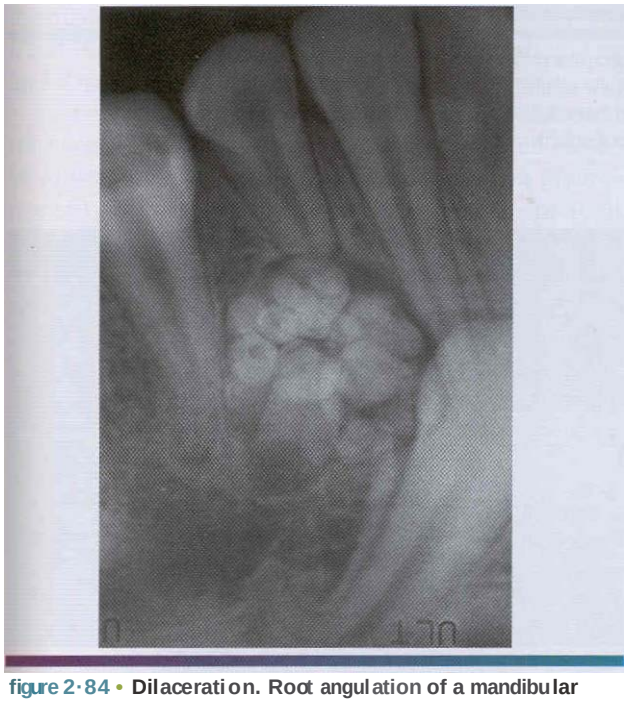

figure 2·84 • Dilaceration. Root angulation of a mandibular cuspid, Development has been altered by the presence of an adjacent compound odontoma. (Courtesy of Dr. Brent Bernard.)

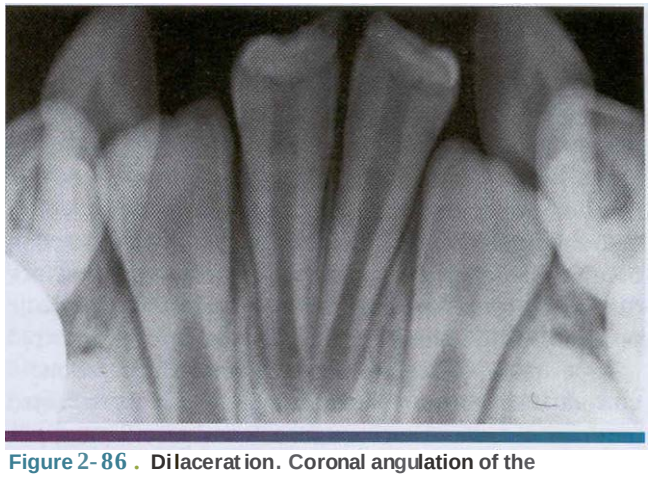

Figure 2-86 . Dilaceration. Coronal angulation of the mandibular central incisors has developed after trauma to the overlying deciduous dentition. (From Neville BW. Oamm DO. White DK: *Color atlas of clinical oral pathology.* ed 2. Baltimore. 1999. Williams & Wilkins.)

ular incisors also exhibit involvement of the crown or the superficial portion of the root. but more frequently they erupt into full occlusion. Those that achieve eruption often follow an altered path and present in a labial orlingual position. Many of the affected teeth, especially anterior mandibular teeth. are nonvital and associated with periapical inflammatory lesions. Typically. altered posterior teeth demonstrate involvement of the apical hall of the root and frequently do not exhibit delayed eruption.

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. In some cases, orthodontic therapy is not indicated because of extensive deformation of the affected tooth or the possibility. on repositioning, of perforation of the buccal alveolar ridge by the malpositioned root. Grossly

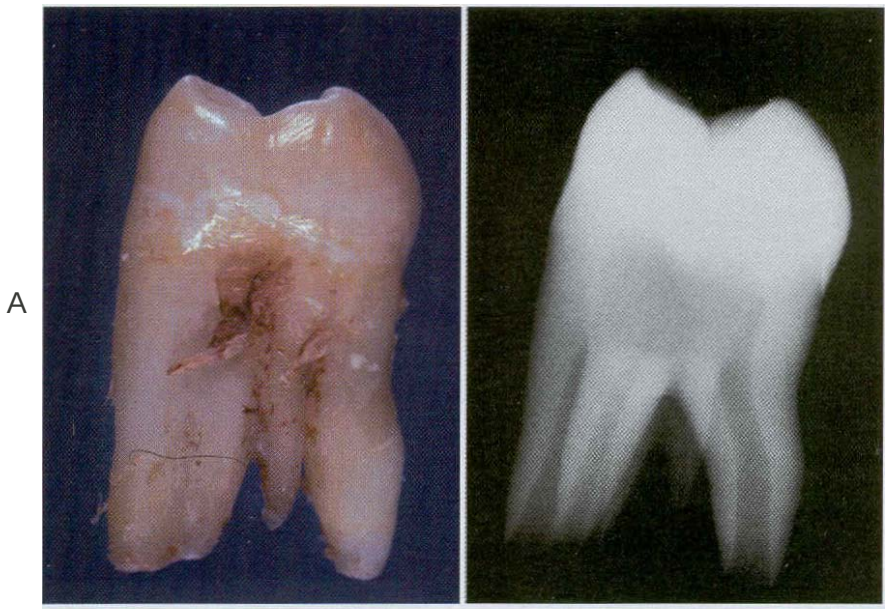

Figure 2-87 • Supernumerary root. A, Gross photograph exhibiting a maxillary molar with a small supernumerary root. B. Mesial-to-distal **radiographic view exhibiting the accessory root with central pulp** canal. If **a** buccal-to-lingual **radiographic view had been taken (as would be necessary in patient care), the additional root would not have been evident.**

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 dllacerared tooth to an adjacent tooth results in a multirooted abutment and overcomes the stress-related problems.

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 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 (Figure 2-87). 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 (Figure 2-88).

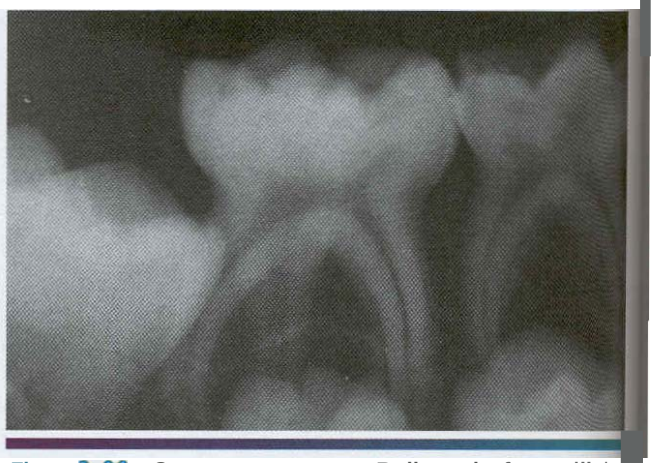

Figure 2-88 • Supernumerary root. Radiograph of a mandibular second deciduous molar, which exhibits divergent and easily discernible accessory root.

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. lust 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.

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. Box 2-2 (see page 50) lists several systemic diseases associated with enamel disorders that are not considered isolated amelogenesis Imperfecta.

At least 14 different hereditary subtypes of amelogenesis imperfecta exist. with numerous patterns of inheritance and a wide variety of clinical manifestations. As proof of the complicated nature of the process, several different classification systems exist. The most widely accepted is that developed by Witkop (Table 2- 1), and this part of the text adheres to this classification. The dissertation by Witkop and Sauk (and Witkop's more recent 1988 review) are works of art, and they should be used if more information is desired by the clinician.

It is necessary to point out that an ideal classilication system for amelogenesis imperfecta has not been established yet. Witkop's classification 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. Several investigators have suggested a classification system based on the phenotype and pedigree combined with scanning electron microscopic examination, biochemical methods, and molecular genetics. This system is a work in progress, with significant information available on only a few variants of amelogenesis imperfecta. In addition. this proposed classification system is impractical for most clinicians who must continue to rely on phenotype and pedigree to advise affected patients on the dentally related genetic implications of their disorder.

The formation of enamel is a multistep process, and problems may arise in anyone 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

The hereditary defects of the formation of enamel also are divided along these lines: hypoplastic, hypocalclftcd. and hypomaturation.

Clinical and Radiographic Features

The estimated frequency of amelogenesis imperfecta in the population varies between 1:718 and 1:14,000. As in any hereditary disorder, clustering of affected patients in certain geographic areas may occur (resulting in an increased prevalence of the disorder in those areas). Additionally. the stringency of the diagnostic criteria may influence the reported prevalence in any given study. In general. both the deciduous and permanent dentitions are diffusely involved.

Hypoplastic amelogenesis ***imperfecta.*** In patients with hypoplastic amelogenesis irnperfecta, the basic alteration centers on inadequate deposltlon of enamel matrix. Any matrix present is mineralized appropriately and radiographically contrasts well with the underlying

Table 2-1 *Classificatioll of Amelogenesis tmperfecta*

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
liB	Hypomaturation	Diffuse	Xvlinked recessive
IIC	Hypomaturation	Snow capped	X-linked
liD	Hypomaturation	Snow capped	Autosomal dominant?
lilA	Hypocalcified	Diffuse	Autosomal dominant
iliB	Hypocalcified	Diffuse	Autosomal recessive
IVA	Hypomaturatlcn-hypoplastic	Taurodontisrn present	Autosomal dominant
IVB	Hypoplastic-hypomaturation	Taurodontism present	Autosomal dominant

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 (Figures 2-89 and 2-90). 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 surrounded by a zone of hypocalcification. Typically. the altered area is located in the middle third of the buccal surfaces of the teeth. The incisal edge or occlusal surface usually is not affected. Both dentitions or only the primary teeth may be affected. All 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 (type Ie) is more severe and typically demonstrates involvement of all teeth in both dentitions.

In the autosomal dominant smooth pattern. the enamel of all teeth exhibits a smooth surface and is thin. hard, and glossy (Figure 2-91). The absence of appropriate enamel thickness results in teeth that are shaped **like crown preparations and demonstrate open contact** points. The color of the teeth varies from opaque white **to translucent brown. Anterior open bite is not** rare. Radiographically, the teeth exhibit a thin peripherai outline of radiopaque enamel (Figure 2-92). Often. unerupted teeth exhibitlng resorption are seen.

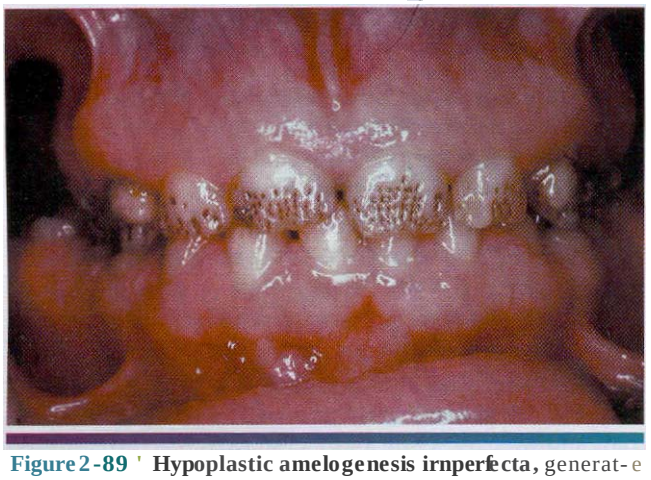

Figure 2-89 ' Hypoplastic amelogenesis irnperfecta, generat-e **ized pitted pattern. Note the numerous pinpoint pits scattered across the surface of the teeth. The enamel between the pits is of normal thickness. hardness. and coloration. (From Stewart RE, Prescott GH: *Dratfacial genetics*. 5t louis. 1976, Mosby.)**

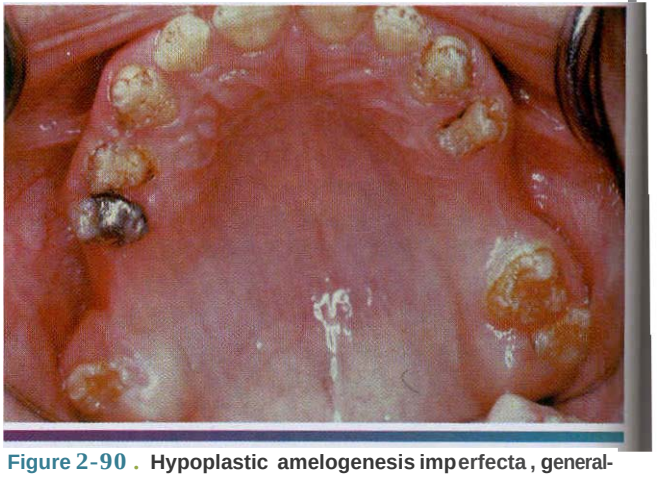

Figure 2-90 . Hypoplastic amelogenesis imperfecta, generalized pitted pattern. Same patient as depicted in Figure 2-89. Note diffuse involvement of all maxillary teeth, which is inconsistent with environmental damage. (Courtesy of Dr. Joseph S. Giansanti.)

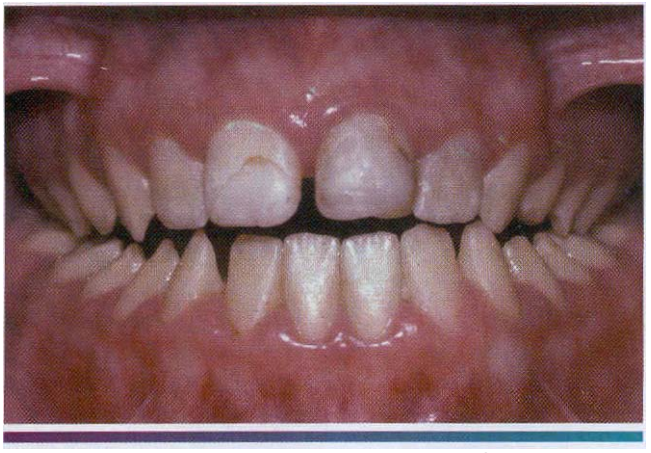

Figure 2-91 • Hypoplastic amelogenesis imperfecta, autosomal dominant smooth pattern. Small. yellowish teeth **exhibiting hard, glossy enamel with numerous open contact points and anterior open bite.**

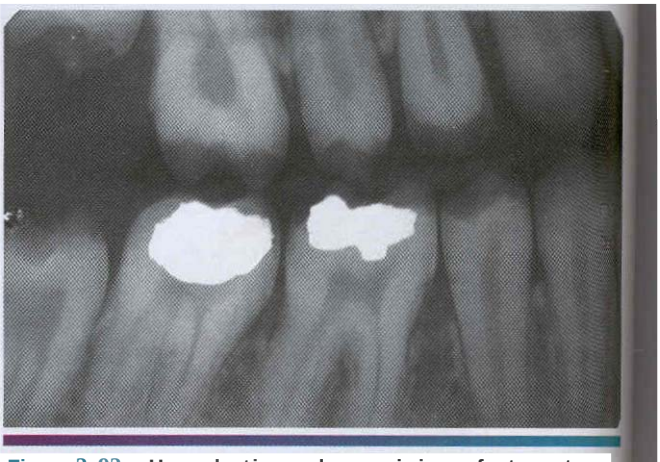

Figure 2-92 • Hypoplastic amelogenesis imperfecta, autosomal dominant smooth pattern. Radiograph of the same **patient depicted in Figure 2-91. Note the thin peripheral outline of radiopaque enamel. (Courtesy of Dr. John G. Stephenson.)**

The x-lmked dominant smooth pattern is a lesson inthe lyonization effect. On approximately the sixteenth day of embryonic life in all individuals wi th 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 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, the teeth would exhibit alternating zones of normal and abnormal enamel.

Males with the X-linked dominant smooth pattern exhibit diffuse thin, smooth. and shiny enamel in both dentitions. The teeth often have the shape of crown preparations, and the contact points are open. The color varies from brown to yellow-brown. Radiographs demonstrate a peripheral outline of radiopaque enamel. Unerupted teeth may undergo resorption. On the other hand, females exhibit vertical furrows of thin hypoplastic enamel, alternating between bands of normal thickness. The banding often is detectable with dental radiographs. An open bite is seen in almost all males and in a minority offemales.

In the rough pattern. the enamel is thin, hard, and rough surfaced. As in the smooth forms, the teeth taper toward the incisal-occlusal surface and demonstrate open contact points (Figure 2-93). The color varies from white to yellow-white. The enamel Is denser than that seen in the smooth patterns, and the teeth are less vulnerable to attrition. Radiographs exhibit a thin peripheral outline of radiodense enamel (Figure 2-94). Unerupted teeth. often undergoing resorption, may be seen. An anterior open bite is common.

As the name implies. enamel agenesis demonstrates atotal lack of enamel formation. The teeth are the shape and color of the dentin. with a yellow-brown hue, open contact points, and crowns that taper toward the incisal-occlusal surface. The surface of the dentin is rough, and an anterior open bite is seen frequently. Radiographs demonstrate no peripheral enamel overlying the dentin. A lack of eruption of many teeth with significant resorption frequently occurs.

llypomalllratioll amelogenesis impetfecta. In a person with hypomaturation amelogenesis trnpcrfccta, the enamel matrix is laid down appropriately and begins to mineralize; however, there is a defect in the maturation of the enamel's crystal structure. Affected teeth are normal in shape but exhibit a mottled. opaque white-brown-yellow discoloration (Figure 2-95). The enamel is softer than normal and tends to chip from the underlying dentin. Radiographically. the affected enamel exhibits a radiodensity that is similar to dentin.

In the pigmented 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. These cases often demonstrate extensive calculus deposition.

The X-linked 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; the permanent teeth are opaque yellow-white and may darken with age. The enamel tends to chip and often can be pierced with a dental explorer point. The degree of enamel loss is more rapid than that in normal teeth but does not approach that seen in the hypocalcified forms. Focal areas of brown

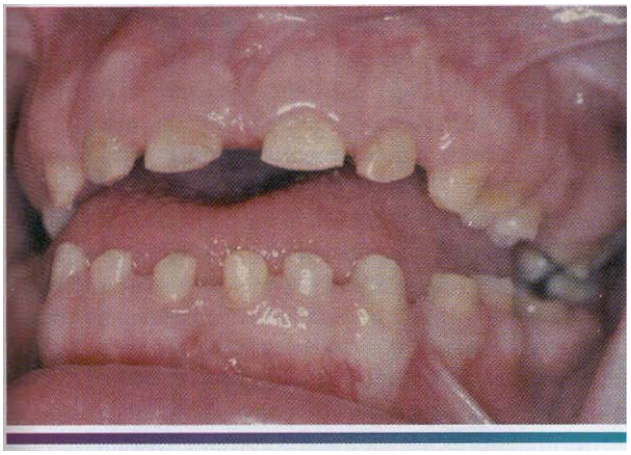

Figure 2-93 • Hypoplastic amelogenesis imperfecta, rough pattern. Small, yellow teeth with rough enamel surface, open contact points, significant attrition, and anterior open bite.

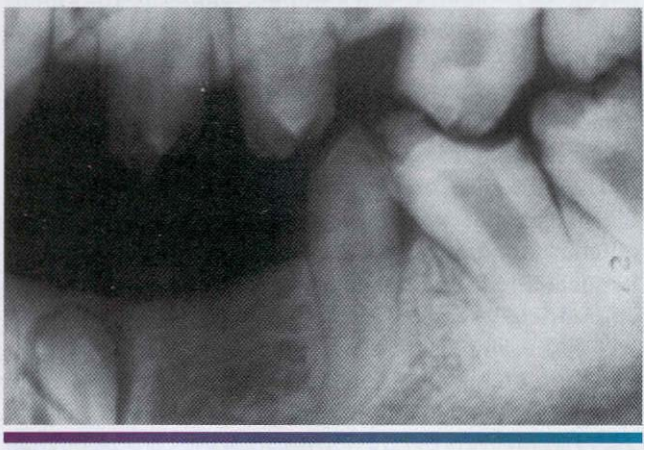

Figure 2-94 • Hypoplastic amelogenesis Imperfecta. rough pattern. Radiograph of the same patient as depicted in Figure 2-93. Note the impacted tooth and the thin peripheral outline of radiodense enamel.

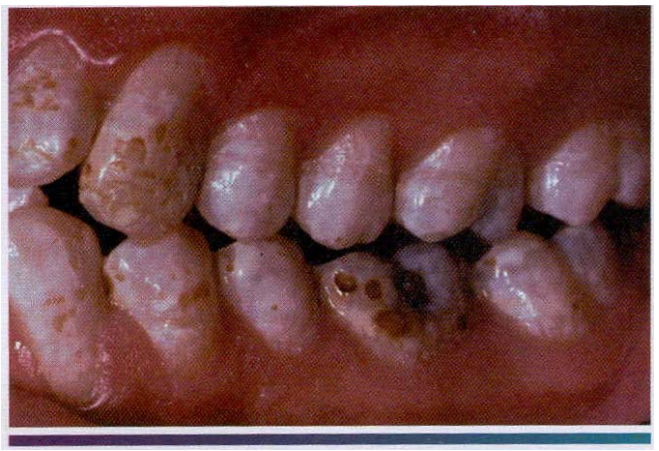

Figure 2-95 • Hypomaturation amelogenesis imperfecta. Dentition exhibiting mottled, opaque white enamel with scattered areas of brown discoloration.

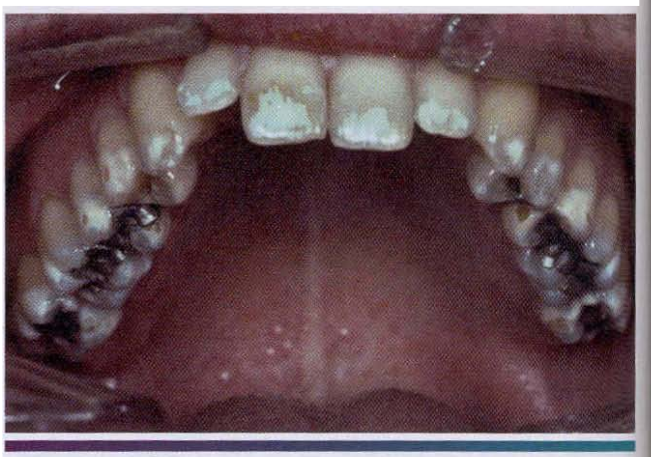

Figure 2-96 . Hypomaturation amelogenesis imperfecta, snowcapped pattern. Dentition exhibiting zone of white opaque enamel in the incisal and occlusal one fourth of the enamel surface. {Courtesy of Dr. Heddie O. Sedano}

discoloration may develop within the white opaque enamel. Radiographically, the contrast between enamel and dentin is reduced.

Female patients exhibit a similar pattern in both dentitions. The teeth demonstrate vertical bands of white opaque enamel and normal translucent enamel; the bands are random and asymmetric. The banding is not obvious under regular lighting, and transillumination often is required to demonstrate the pattern. Radiographically, the band is not perceptible, and the contrast between enamel and dentin is within normal limits.

The snow-capped patterns exhibit a zone of white opaque enamel on the incisal or occlusal one quarter to one third of the crown (Figure 2-96). 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 antertor-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 permanent dentitions are affected. Most cases demonstrate an X-linked pattern of inheritance, but there possibly is an autosomal dominant form.

Hypocalcified amelogenesis imperfecta. In this type the enamel matrix is laid down appropriately but no significant mineralization occurs. In both patterns of hypocalcified amelogenesis Irnperfecta, 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 (Figure 2-97>. 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. Both patterns are similar, but the autosomal recessive examples are generally more severe than the autosomal dominant cases. Radiographically, the density of the enamel and dentin are similar. Before eruption the teeth are normal in shape; however. after a period of function much of the cuspal enamel is lost, with the occlusal surface becoming the most irregular (Figure 2-98),

Hypomaturation/hypoplastic amelogenesis imperfed•. This type of amelogenesis irnperfecta exhibits enamel hypoplasia in combination with hypomaturation. Both the deciduous and permanent dentitions are involved diffusely. I\vo patterns are recognized that are similar but differentiated by the thickness of the enamel and the overall tooth size. Both patterns have been reported in a single kindred, and these may represent a range of the same process.

In the hypomaturation-hypoplastic pattern, the predominant defect is one of enamel hypomaturation in which the enamel appears as mottled yellowish 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; the enamel that is present demonstrates hypomaturation. Except for the decrease in the thickness of the enamel, this pattern is radiographically similar to the hypomaturation-hypoplastic variant.

Both patterns are seen in the systemic disorder, trichodento-osseous syndrome. This autosomal dominant

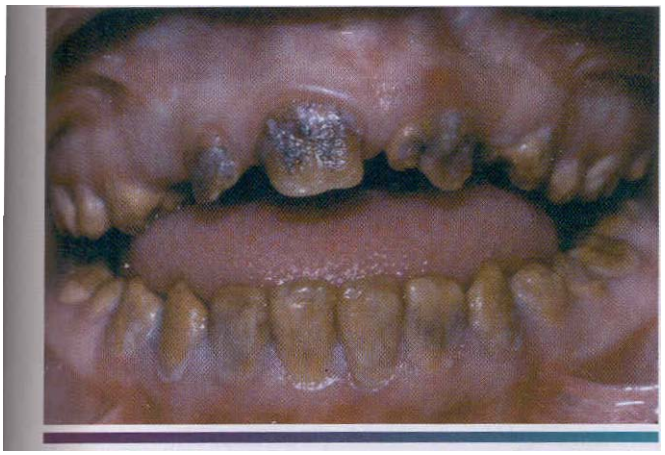

Figure 2-97 • **Hypocalcified amelogenesis imperfecta. Dentition exhibiting diffuse yellow-brown discoloration. Note numerous teeth with loss of coronal enamel except for the cervical portion.**

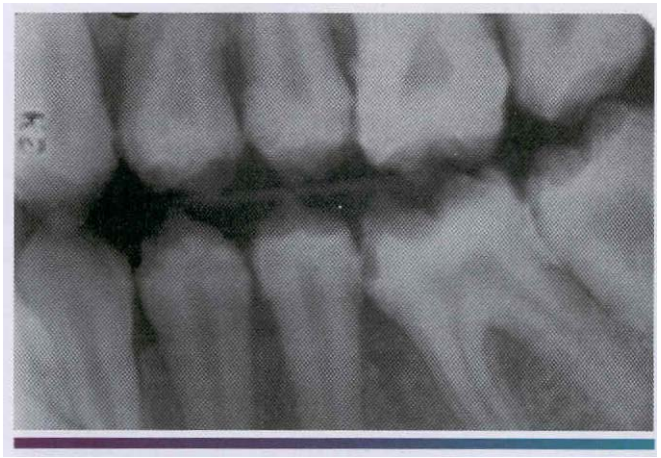

Figure 2-98 • **Hypocalcified amelogenesis imperfecta. Radiograph of the same patient depicted in Figure 2-9Z Note the extensive loss of coronal enamel and the similar density of enamel and dentin.**

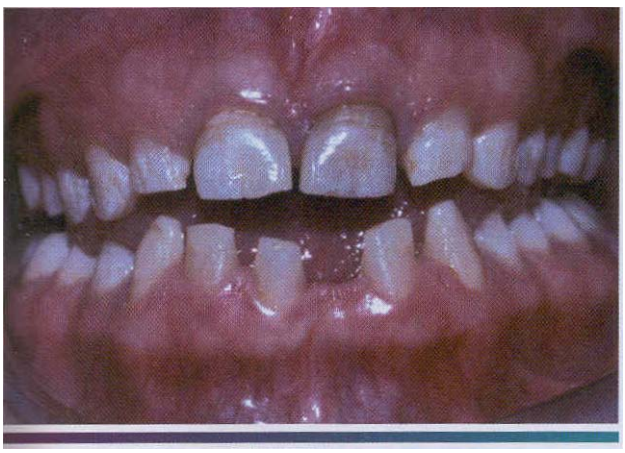

Figure 2-99 • **Tricho-dento-osseous syndrome. Dentition exhibiting diffuse enamel hypoplasia and hypomaturation. At birth, the patient exhibited a kinky "steel wool" texture to her hair; with time, the hair straightened. A high index of suspicion was required to arrive at the diagnosis.**

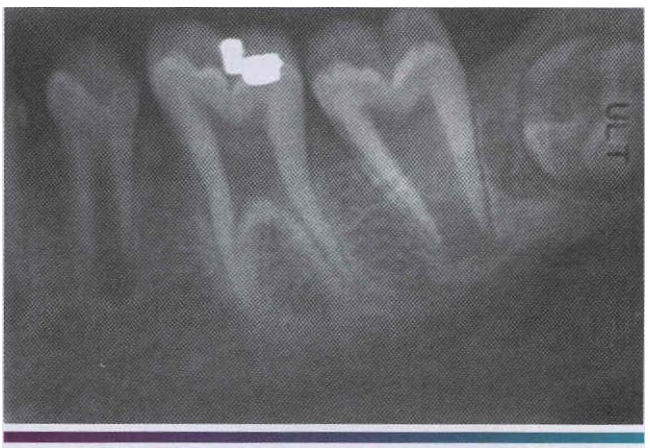

Figure 2-100 • **Tricho-dento-osseous syndrome. Radiograph of the same patient depicted in Figure 2-99. Note significant taurodontism of the first molar and the enamel. which is thin and similar in density to the dentin.**

syndrome is mentioned here because the diagnosis may not be readily apparent without a high index of suspicion (Figure 2-99). 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 suggest that hypomaturation-hypoplastic amelogenesis imperfccta may represent partial **expression of the** trlcho-dcnto-osseous **syndrome. More** recently, the gene mutation responsible for trlcho-dento-osseous syndrome has been isolated and shown not to be present in cases of hypomaturation-hypoplastic amelogenesis irnperfecta. If only dental changes are seen in the absence of hair or bone changes, either in the individual or within the family, the diagnosis of amelogenesis Imperfecta appears appropriate. In addition to the **genetic difference, another investigator reviewed the** controversy and believes the disorders can be distinguished by the degree of taurodontism present in the mandibular first molars. This review indicated that no **severe taurodontism of the mandibular first molar was** found in cases of hypomaturation-hypopiastic amelogenesis lrnperfccta: however, all examples of trlcho-dento-**osseous syndrome demonstrated severe hypertaurodon-**tism of this tooth (Figure 2-100).

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 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 impcrfecta there is an increased prevalence of caries. anterior** open bite, delayed eruption, tooth impaction. or associated gingival inflammation.

Types ID, IE, IG. IIA. liIA. IIIB, and IVB demonstrate very thin enamel or highly defective enamel. which leads to 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 (overdcnturcs in some cases) often become the only satisfactory approach.

The other types of amelogenesis irnperfecta 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 usc of glass-ionomer **cements with dentinal adhesives often overcomes this weakness.**

DENTINOGENESIS IMPERFECTA (HEREDITARY OPALESCENT DENTIN; CAPDEPONT'S TEETH)

Dentinogenesis imperfecta is a hereditary developmental disturbance of the dentin in the absence of any systemic **disorder. Similar dental changes may be seen in con**junction with the systemic hereditary disorder of bone. osteogenesis imperfecta (see page 534). Like amelogenesis impcrfccta, the disorders of dentin also involve **disagreements in** classificatlon. **Two systems, one by** Witkop and the other by Shields. are well accepted but not totally satisfactory (Table 2-2l. This text docs not adhere strictly to either. It is evident that the third type of dentinogenesis imperfecta (Shields' type III or Witkop's **Brandywine isolate) is not a separate disease and merely represents a variation of expression of** Shields' type II.

The best nomenclature system was suggested by Levin. Analogous to amelogenesis Irnperfecta, the diagnosis of dentinogenesis imperfecta should be reserved for defective dentin formation with opalescent teeth (deciduous and permanent) in the absence of systemic disease. Appropriately, dentin defects associated with the sys**temic bone disease are termed osteogenesis impcrfeeta** with opalescent teeth. Extensive pedigrees of individuals with dentinogenesis imperfecta have been studied. and none have exhibited other changes suggestive of osteogenesis imperfecta. Therefore. dentinogenesis imperfecta **is clearly a disorder distinct from osteogenesis** Imperfecta, Arguably the dentin dysplasias could be included under the heading of isolated dentin defects. but such a confusing disruption of the nomenclature is undesirable.

Clinical and Radiographic Features

The prevalence of dentinogenesis imperfecta 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 I:8000 whites in the United States.

The dental alterations in dentinogenesis imperfecta and osteogenesis imperfecta with opalescent teeth are similar clinically, radiographically. and histopathologically. All teeth in both dentitions are affected. The severity of the dental alterations varies with the age at which the tooth developed. 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 (Figure 2- 101, The enamel frequently separates easily from the underlying defective dentin. Once exposed, the dentin often demon-

Table 2-2 *Det/lit/ogmesis* ***Imperfecta***

SIIIELD5	CLINICAL PRESENTATION	WITKOP
Dentinogenesis imperfecta I	**Osteogenesis imperfeeta with opalescent teeth**	**Dentinogenesis imperfecta**
Dentinogenesis imperfecta II	**Isolated opalescent teeth**	**Hereditary opalescent teeth**
Dentinogenesis imperfecta III	**Isolated opalescent teeth**	**Brandywine isolate**

strates significantly accelerated attrition (Figure 2-102). Radiographically, the teeth have bulbous crowns, cervical constriction, thin roots, and early obliteration of the root canals and pulp chambers (Figure 2-103).

The trait exhibits close to 100% penetrance but variable expressivity. Significant clinically obvious enamel hypoplasia is noted in some patients. The enamel abnormality is thought to be a secondary defect and not a direct expression of the dentinogenesis imperfecta gene (Figure 2-104). Although the pulps are usually obliterated by excess dentin production, some teeth may show normal-sized pulps or pulpal enlargement *(shell teeth).*

Shell teeth demonstrate normal-thickness enamel in association with extremely thin dentin and dramatically enlarged pulps (Figure 2-105). The 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. 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.

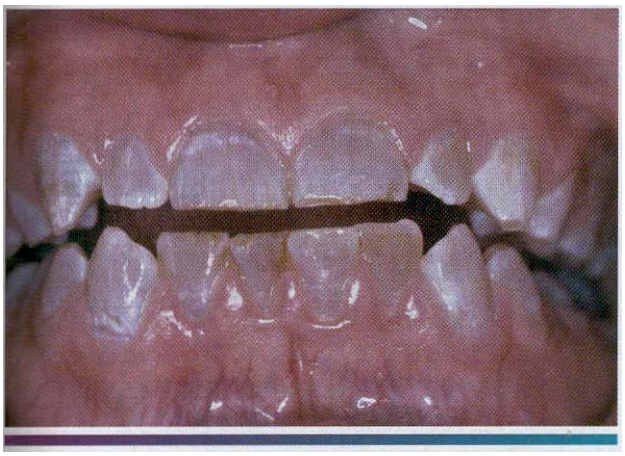

figure 2-101 • **Dentinogenesis imperfecta. Dentition exhibiting diffuse brownish discoloration and slight translucence.**

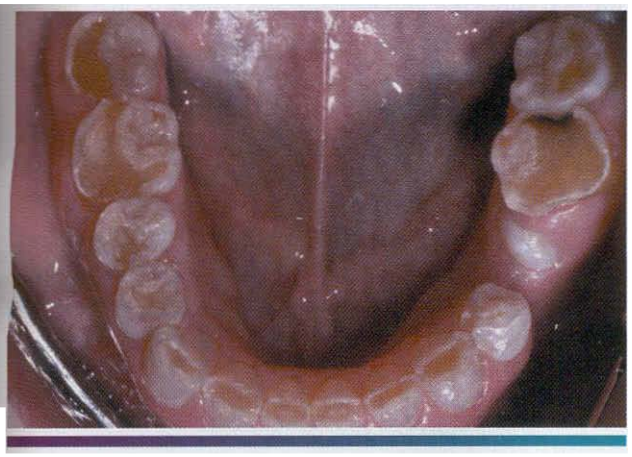

Figure 2-102 • **Dentinogenesis imperfecta. Dentition exhibiting grayish discoloration with significant enamel loss and attrition.**

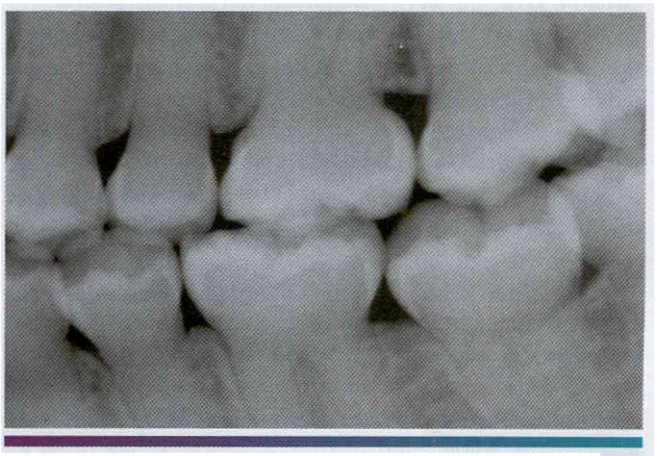

Figure 2-103 • **Dentinogenesis imperfecta.** Radiograph of dentition exhibiting bulbous crowns, cervical constriction, and obliterated pulp canals and chambers.

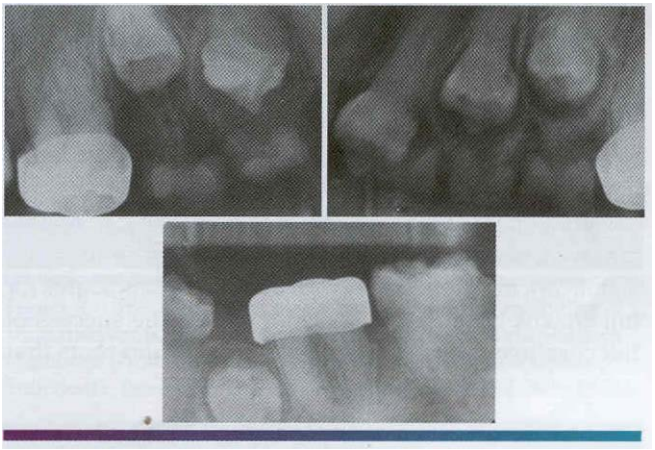

Figure 2-104. **Dentinogenesis imperfecta.** Radiograph of dentition exhibiting bulbous crowns, early obliteration of the pulp, and enamel hypoplasia. (From Levin LS, Leaf SH, [elmine RJ, et al: Dentinogenesis imperfecta in the Brandywine isolate (01 type III): clinical, radiologic, and scanning electron microscopic studies of the dentition, *Oral Surg Oral Med Oral Pathol* 56:267-274, 1983.)

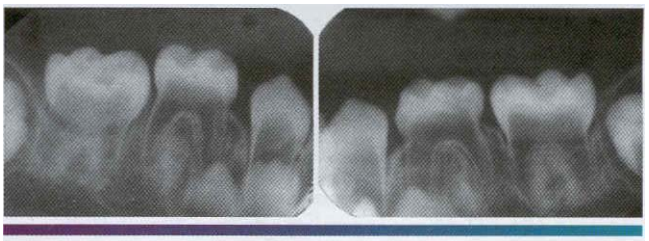

Figure 2-105 • **Shell teeth.** Dentition exhibiting normal thickness enamel, extremely thin dentin, and dramatically enlarged pulps.

Initially. this pulpal enlargement was discovered in the large Maryland Brandywine isolate and thought to be a new variant of dentinogenesis imperfecta (type III or Brandywine isolate). Current evidence strongly supports the Brandywine isolate representing nothing more than variable expressivity of the gene for dentinogenesis imperfecta. A review of the isolate revealed only 8% of the kindred with enlarged pulp chambers. Investigators have documented affected people with enlarged pulps in association with parents and children with classic dentinogenesis imperfecta. Finally. identical patterns of variable expressivity have been seen in other large affected kindreds with no connection to the Brandywine isolate.

Histopathologic Features

As expected. affected teeth demonstrate altered dentin. 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 (Figure 2-106). 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; however. about one third of the patients have hypoplastic or hypocalcified defects.

Treatment and Prognosis

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 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.

Additional therapeutic approaches have been used. but long-term follow-up is incomplete. In patients with extensive attrition. the vertical dimension has been 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 . most of those affected are candidates for full dentures or implants by 30 years of age in spite of the numerous interventions. Newer materials and interventions may alter this outlook.

Figure 2-106 • Dentinogenesis imperfecta. Coronal dentin exhibiting short misshapen tubules within atypical granular dentin matrix.

DENTIN DYSPLASIA

Dentin dysplasia was initially categorized in 1939. There are two major patterns: type I and type II. By definition. dentin dysplasia should have no correlation with systemic disease or dentinogenesis irnperfecta. An unusual combination of type I and type II dentin dysplasia has been reported. but these cases represent variable pulpal anatomy that has been documented well in dentin dysplasia type I. Systemic diseases reported to be associated with similar dentin changes are listed in Box 2-10.

Clinical and Radiographic Features

*Dentin **dysplasia type** I.* Dentin dysplasia type I (radicular dentin dysplasia; rootless teeth) 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 exhibits an approximate prevalence of 1:100.000. The enamel and coronal dentin are normal clinically and well formed (Figure 2-107). but the radicular dentin loses all organization and subsequently is shortened dramatically (Figure 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

Box 2-10 *Systemic Diseases Correlated with Dentin Dysplasia-Like Alterations*

1. Calcinosis universalls
2. Rheumatoid arthritis and vitaminosis D
3. Sclerotic bone and skeletal anomalies
4. Tumoral calcinosis

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 radicular strength of the dentin is reduced. with the teeth being predisposed to fracture during extractions.

Radiographically. the deciduous teeth are affected severely. with little or no detectable pulp and roots that are markedly short or absent. The permanent teeth vary according to the proportion of organized versus disorganized dentin (Figure 2-t09). With early disorganization. no pulp can be detected and the roots are extremely short or absent. With somewhat later disorganization, crescent or chevron-shaped pulp chambers can be detected overlying shortened roots that exhibit no pulp **canals. Late disorganization results in normal pulp** chambers overlying roots. each of which exhibits a large pulp stone. The root is flared at the site of the stone. and the canal is constricted apical to the stone. Those teeth without root canals frequently develop periapical inflammatory lesions without obvious cause. The inflammatory lesions 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 that are normal clinically. Radiographically the **teeth are normal in shape but demonstrate a radiodense** product filling the pulp chambers and canals. in contrast

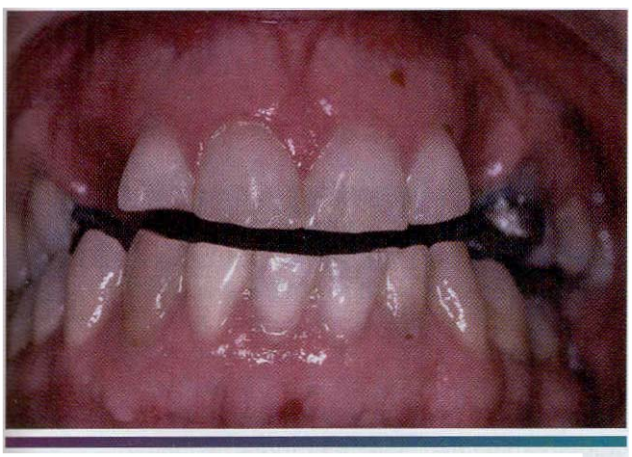

Figure 2-107. **Dentin dysplasia type I.** Dentition exhibiting attrition but otherwise normal coronal coloration and morphology.

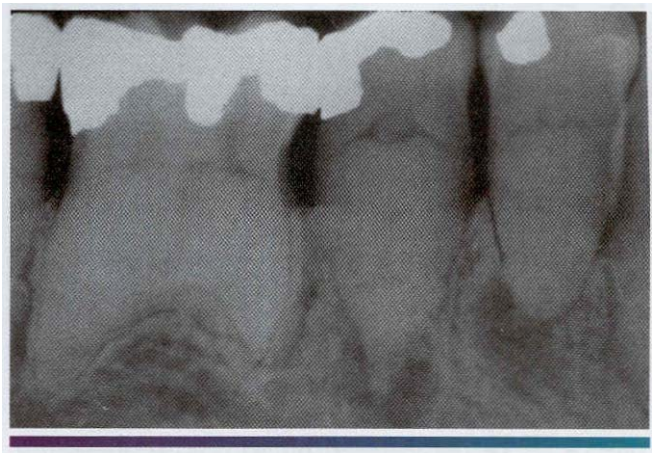

Figure 2-108 • **Dentin dysplasia type I.** Dentition exhibiting shortened roots, no pulp canals. and small crescent-shaped pulp chambers. (From Tidwell E, Cunningham CJ: Dentinal dysplasia. Endodontic treatment. with case report.j *Endod* 5:372-376. 1979.)

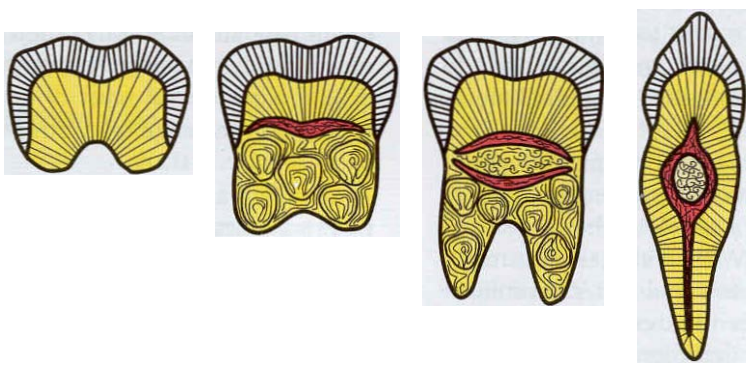

Figure 2-109 • **Dentin dysplasia type I.** Illustration demonstrating the variability of the radiographic appearance according to the degree of dentin disorganization within the root.

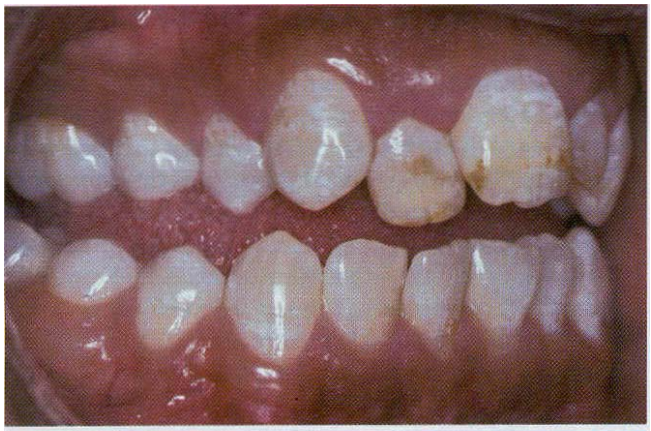

Figure 2-110 • Dentin dysplasia type II. Permanent dentition that does not exhibit translucence, as noted in the deciduous teeth. The patient also exhibits mild fluorosis of the enamel.

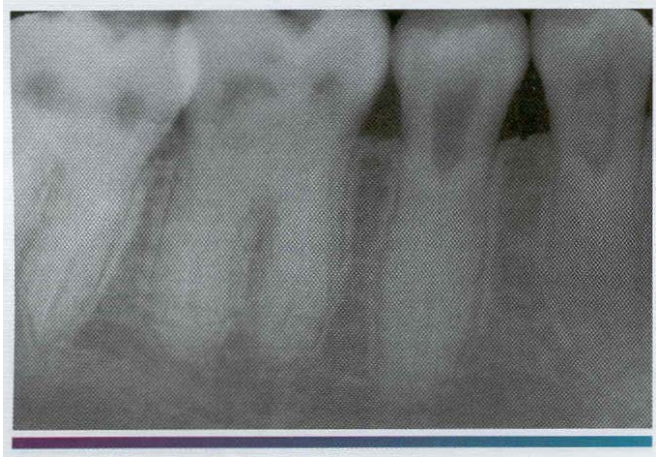

Figure 2-111 • Dentin dysplasia type II. Radiographic appearance of the dentition depicted in Figure 2-110. Note thistle tube-shaped enlargements of the pulp chambers and numerous pulp stones.

to dentinogenesis imperfecta, small foci of radiolucency can be seen in the pulp. In contrast to dentin dysplasia type I, no crescent pulp chambers and no decrease in root length are seen. The radiodense intrapulpal material consists of fibrotic dentin.

Dentin dysplasia type II. Dentin dysplasia type II (coronal dentin dysplasia) exhibits numerous features of dentinogenesis imperfecta, and although reclassification was not recommended. Witkop suggested it might be a form of that disease. Autosomal dominant inheritance is seen. In contrast to dentin dysplasia type I, the root length is normal in both dentitions. The deciduous teeth closely resemble those of dentinogenesis imperfecta. Clinically, the teeth demonstrate a blue-to-amber-to-brown translucence. Radiographically, the dental changes include bulbous crowns, cervical constriction, thin roots, and early obliteration of the pulp. The permanent teeth demonstrate normal clinical coloration; however, radiographically, the pulp chambers exhibit significant enlargement and apical extension. This altered pulpal anatomy has been described as thistle tube-shaped or flame-shaped (Figures 2-11o and 2-11m). Pulp stones develop in the enlarged pulp chambers.

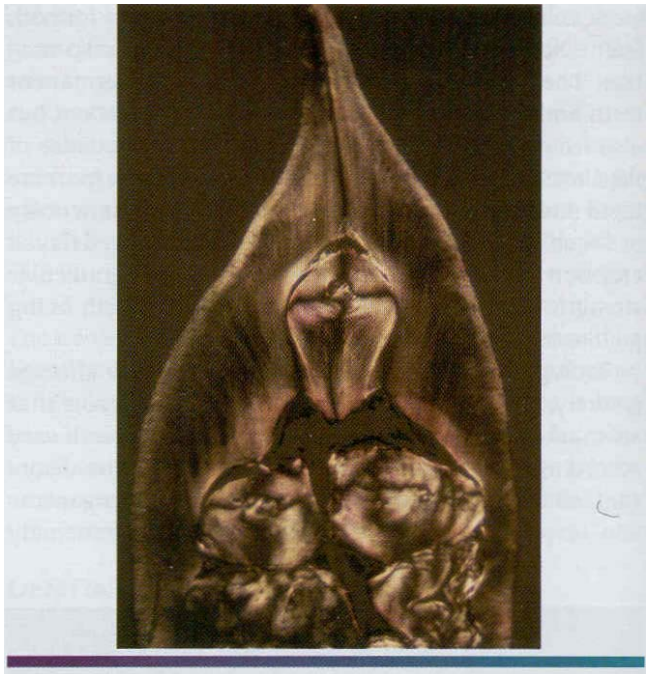

figure 2-112 • Dentin dysplasia type I. Polarized light view of affected tooth demonstrating a classic *stream flowing around boulders* appearance.

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 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" (Figure 2-112).

In patients with dentin dysplasia type II, the deciduous teeth demonstrate the pattern described 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 (Figure 2-113).

Treatment and Prognosis

In patients with dentin dysplasia type I, preventive care is of foremost importance. Perhaps as a result of short-

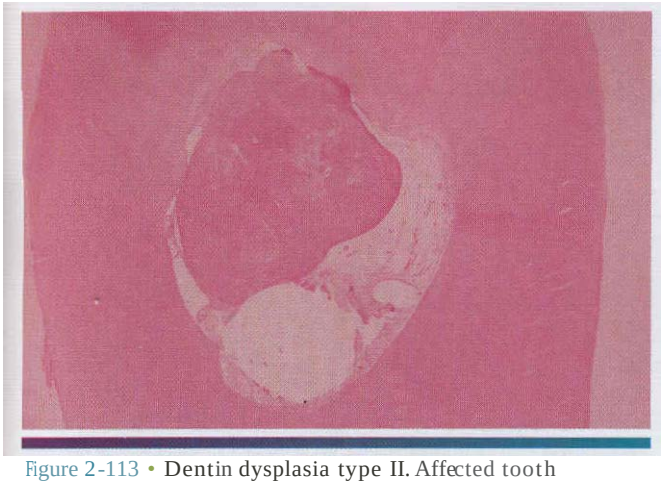

Figure 2-113 • Dentin dysplasia type II. Affected tooth exhibiting large pulp stone within the pulp chamber.

encd 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 therapeutic choice is guided by the root length. 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.

Dentin dysplasia type II demonstrates similar problems. and meticulous oral hygiene must be established. Thedeciduous teeth can be approached in a manner similar to that used for dentinogenesis imperfecta. In the permanent teeth. an increased risk of pertaplcal inflammatory iesions is also seen. Because the pulp canals are not usually obliterated completely. endodontic therapy is accomplished more readily.

REGIONAL ODONWDYSPLASIA (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 2-11). A number of causes have been proposed (Box 2-12). 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.

Box 2-11 *Pathoses Noted ill Association with Regional Odontodyspiasia*

1. Ectodermal dysplasia
2. Epidermal nevi
3. Hypophosphatasia
4. Hydrocephalus
5. Ipsilateral facial hypoplasia
6. Neurofibromatosis
Z Orbital coloboma
8. Rhesus incompatibility
9. Vascular nevi

Box 2-12 *Proposed Causations for Regiona! Odontodysplasia*

1. Abnormal migration of neural crest cells
2. latent virus
3. local circulatory deficiency
4. local trauma or infection
5. Hyperpyrexia
6. Malnutrition
7. Medication used during pregnancy
8. Radiation therapy
9. Somatic mutation

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 (1.4: I). 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 II years) dentitions. Typically. the process affects a focal area of the dentition. with involvement of several contiguous teeth. There is a maxillary predominance (2.5: I) and 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. Involvement of more than two quadrants is rare. Involvement of the deciduous dentition is typically followed by similarly affected permanent teeth. In the area of altered teeth. the surrounding bone often exhibits a lower density.

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

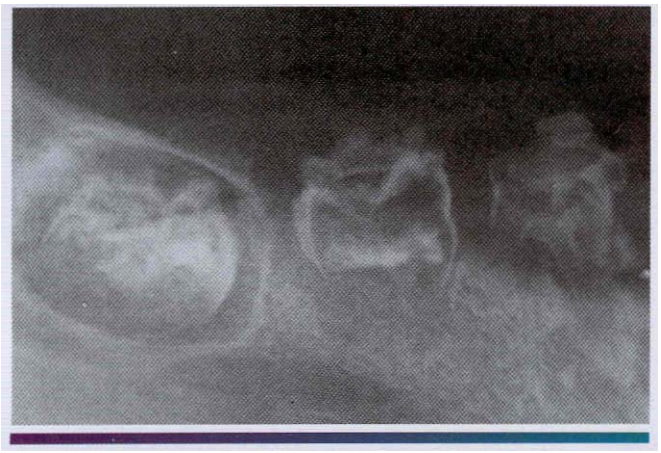

Figure 2-114. **Regional odontodysplasia (ghost teeth).** Posterior mandibular dentition exhibiting enlarged pulps and extremely thin enamel and dentin. (Courtesy of Dr. John B. Perry.)

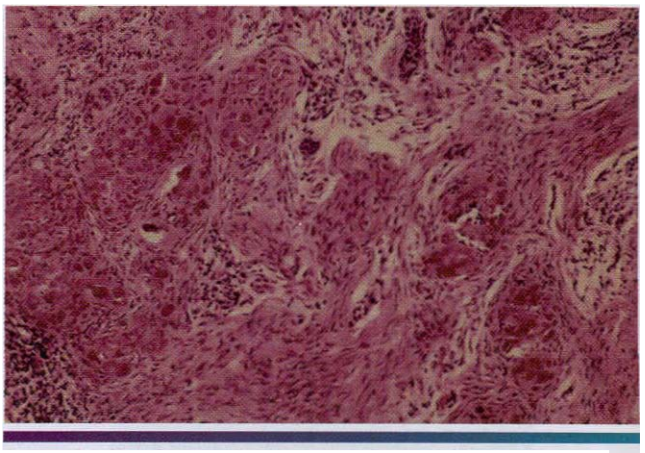

Figure 2-115 • **Regional odontodysplasia. Follicular tissue contains scattered collections of enameloid conglomerates and islands of odontogenic epithelium.**

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 (Figure 2-114). There is a lack of contrast 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 gingiva' 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 (Figure 2-115). 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

The basic approach to therapy of regional odontodysplasia is directed toward retention of the aItered teeth. whenever possible. to allow for appropriate development and preservation of the surrounding alveolar ridge. Endodontic therapy on nonvital teeth that have sufficient hard tissue to allow restoration has been performed successfully. 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. In one report. normal bicuspids were autotransplanted into the extraction sites of the abnormal dentition. After a 6-year follow-up period. this therapy successfully restored masticatory function. allowed appropriate facial development. and prevented ridge atrophy and supereruption of the opposing dentition.

Although vitality of the abnormal dentition often is difficult to maintain. such efforts may bring significant rewards. Several investigators have shown continued dentinal development of teeth affected by regional odontodysplasia. In cases followed for many years. the teeth lost their ghostly appearance and revealed a resultant decrease in pulp size. a significant increase in *dentin* thickness. and ultimate relative normalization of the radicular anatomy. In contrast. the enamel remained hypoplastic. The surrounding bone became well developed and lost its diminished density. Only a few reports of this phenomenon exist. however. most likely because the prior treatment of choice has been extraction.

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CHAPTER 3

Pulpal and Periapical Disease

CHAPTER OUTLINE

PULPITIS

The initial response of the dental pulp to injury is not significantly different from that seen in other tissues. However, the final result can be dramatically different because of the rigid dentinal walls of the pulp chamber. When external stimuli reach a noxious level, degranulation of mast cells, decreased nutrient flow, and cellular damage occur. Numerous inflammatory mediators (e.g., histamine, bradykinin, neurokinins, neuropeptides, prostaglandins) are released. These mediators cause vasodilation, increased blood inflow, and vascular leakage with edema. In normal tissue, increased blood flow promotes healing through removal of inflammatory mediators, and swelling of the injured tissue usually occurs. However, the dental pulp exists in a very confined area. The active dilation of the arterioles leads to increased pulpal pressure and secondary compression of the venous return, which can lead to strangulation of the arterial inflow. The increased pressure appears to be confined to the area of the pulp receiving the noxious stimulus. The increased pulpal pressures, combined with the accumulation of mediators, can lead to vessel damage, pulpal inflammation, and tissue necrosis. Severe localized pulpal damage can spread progressively to involve the more apical portion of the pulp.

Four main types of noxious stimuli are common causes of pulpal inflammation:

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.**

Pulpitis can be classified as:

- **Acute or chronic**
- Subtotal or generalized
- Infected or sterile

The best classification system 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

Reversible puipitis, When exposed to temperature extremes, teeth with reversible pulpitis exhibit a sudden mild-to-moderate pain of short duration. Although heat may initiate pain, the affected tooth responds most to cold stimuli (e.g.• ice, beverages, cold air). Contact with **sweet or sour foods and beverages also may cause pain.** The pain does not occur without stimulation and subsides within seconds after the stimulus is removed. 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. If the pulpitis is allowed to progress, the duration of the pain upon stimulation can become longer and the pulp may become affected irreversibly.

Irreversible pulpltis. Patients with early irreversible pulpitis generally have sharp, severe pain upon thermal stimulation. **and the pain continues after the stimulus is** removed. Coid 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 pulpltis, the pain often can be localized easily to the individual offending tooth; **with increasing discomfort. however, the patient is unable** to identify the offending tooth within a quadrant.

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) the symptoms may resolve, only to return if the drainage ceases.

The dramatic and painful cases of acute pulpitis are the ones that arc recalled most easily by both patients and clinicians. In spite of this, the process may take years, the pattern of symptomatology is highly variable, and often the patient may have no symptoms. In some **cases, severe pulpitis with abscess (ormation and** necrosis may be asymptomatic, although mild puipitis **may cause excruciating pain.**

chronic hyperplastic plllpilis. 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 infiammation that produces hyperpiastic granulation tissue that extrudes from the chamber and often fills the associated dentinal defect (Figures 3-1 to 3-3). The apex may be open and reduces the chance 01 **pulpal necrosis secondary to venous compression.** The tooth is asymptomatic except for a possible feeling of **pressure when it is placed into masticatory function.**

Histopathologic Features

Basically. the histopathology is primarily of academic interest and does not usually affect treatment signifi**cantly. Numerous investigations have shown a surprising** lack of correlation between histopathologic findings and the clinical symptoms in the majority of puips examined.

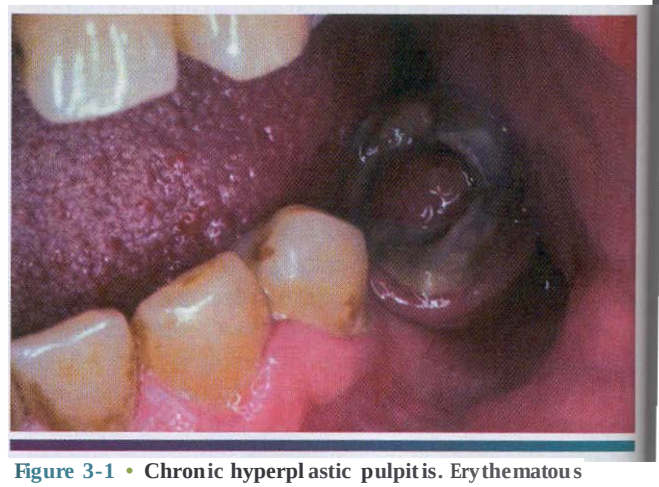


Figure 3-1 • Chronic hyperplastic pulpitis. Erythematous granulation tissue extruding from the pulp chamber of the mandibular first molar.

In patients with reversible pulpitis, the pulp usually shows hyperemia, edema, and a chronic inflammatory cellular infiltrate underlying the area of affected dentinal tubules (Figure 3-4). Reparative secondary 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 histiocyres (Figure 3-5). The surrounding pulp tissue usually exhibits fibrosis and a mixture of plasma cells, lymphocytes, and histiocytes (Figure 3-6).

Chronic hyperplastic pulpitis demonstrates a cap of subacutely inflamed granulation tissue resembling that seen in a pyogenic granuloma (see page 447). 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 (sec Figure 3-3). The deeper pulp tissue demonstrates a chronic inflammatory infiltrate.

The diagnosis is made from a combination of the clinical presentation and the response to percussion, thermal stimuli, and electric pulp testing. The predictive value of these tests is less than desired. When the procedures demonstrate that the pulp is disease-free, results are highly reliable. However, when a pulp tests *positive* for irreversible pulpitis, histopathologic examination frequently demonstrates a disease-free state. The practitioner should use all *available* tests, clinical information, and personal judgment in an attempt to arrive at an appropriate diagnosis. Future improvements in diagnostic methods. such as laser Doppler flowmetry, may help to increase accuracy.

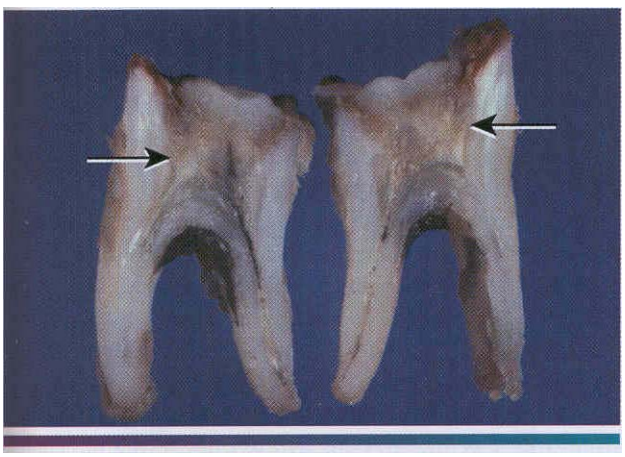


Figure 3-2 • Chronic hyperplastic pulpitis. Gross photograph demonstrating hyperplastic pulp tissue filling a large coronal carious defect. Arrows delineate the previous roof of the pulp chamber.

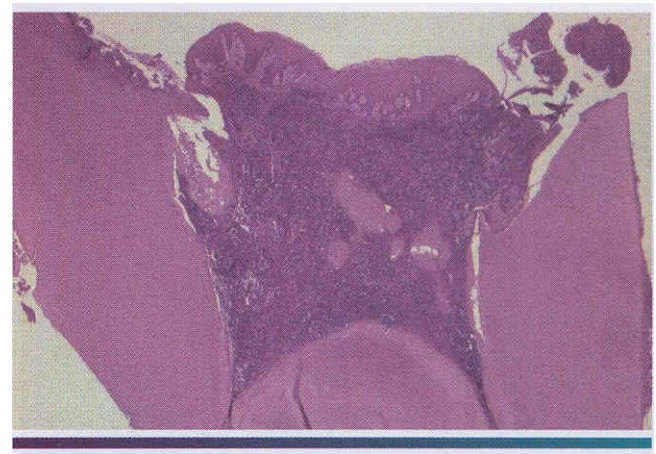


Figure 3-3 • Chronic hyperplastic pulpitis. Same tooth as depicted in Figure 3-2. Chronically inflamed granulation tissue fills the coronal defect. Note surface stratified squamous epithelium.

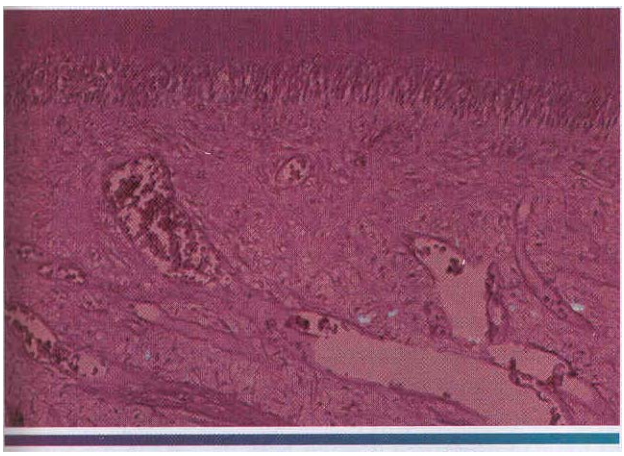


Figure 3-4. Reversible pulpitis. Dental pulp exhibiting hyperemia and edema. The adjacent dentin was cut recently during placement of a dental restoration.

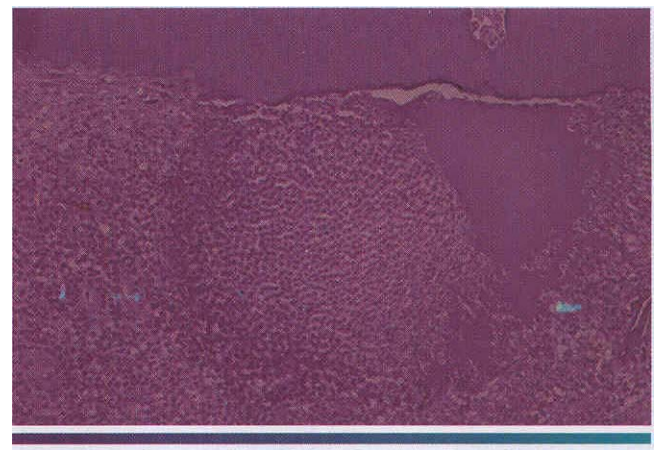


Figure 3-5 • Irreversible pulpitis. Dental pulp exhibiting acute inflammatory infiltrate consisting predominantly of polymorphonuclear leukocytes.

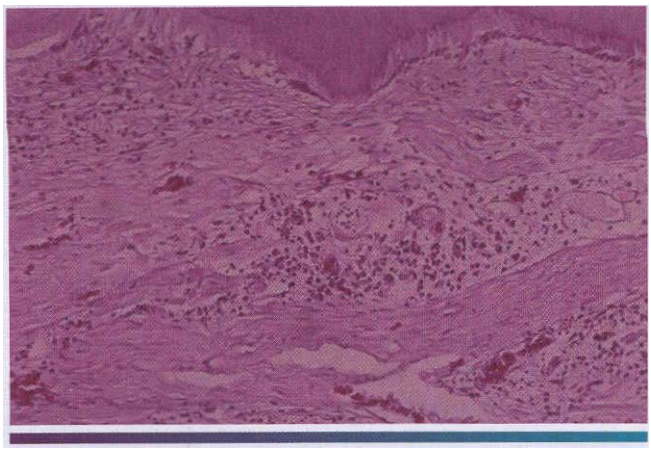


Figure 3-6 • Irreversible pulpitis. Same tooth as depicted in Figure 3-5. The dental pulp exhibits an area of fibrosis and chronic inflammation peripheral to the *zone* of abscess formation.

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 tooth should be tested for vitality after the symptoms have subsided to ensure that irreversible damage has not occurred.

Irreversible and chronic hyperplastic pulpitis are treated by extraction of the tooth or by root canal therapy.

SECONDARY 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, deposition of secondary dentin leads to smaller pulp chambers and canal systems. The deposition of dentin is slow and gradual but does increase after the age of 35 to 40. Early widespread formation of secondary dentin has been seen in association with progeria, a condition associated with accelerated aging. On occasion, significant traumatic injury can lead to early obliteration of the pulp chamber and canal (Calcific metamorphosis) in the affected tooth.

In functioning teeth, deposition begins in the coronal portions of the tooth and proceeds to the apical areas. This type of dentin is thought by many investigators to occur as a result of aging and has been termed physiologic secondary dentin. A significantly decreased amount of secondary dentin has been described in impacted teeth, suggesting that the deposition is promoted by functional forces of occlusion. Interestingly, the deposition in impacted teeth appears to begin in the apical areas and spreads coronally.

Although production of physiologic secondary dentin and a resultant decrease in pulpal size are related most strongly to aging, the process is more advanced in males and has been associated positively with calcification-related diseases (e.g., arthritis, gout, kidney stones, gall stones, atherosclerosis, hypertension). Deposition within the pulp chamber often is not totally uniform. In posterior teeth, deposition is seen greatest 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.

Localized secondary dentin also is laid down in areas of focal injury. This dentin is more haphazardly organized and is termed reparative secondary (irregular, tertiary) dentin. This localized dentin formation may occur in response to:

- 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 reparative secondary dentin formation. If the stimulus is mild to moderate, the dentin is typically produced by *surviving* odontoblasts and is more regular in appearance. When the stimulus is more intense, the dentin is more irregular and often is secreted by a new generation of odontoblast-like cells recruited from undifferentiated cells in the pulp. If the damage is *severe*, the odontoblasts may die, resulting in dentinal tubules filled with degenerated odontoblastic processes known as dead tracts. These tubules are usually sealed off by formation of reparative dentin along the pulpal wall of these tracts.

Clinical and Radiographic Features

As noted on periapical radiographs, the deposition of secondary dentin results in diminishing size of pulp chambers and canals. In addition to being used as an estimate of age, 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 (Figure 3-7). Teeth affected by calcific metamorphosis often are discovered

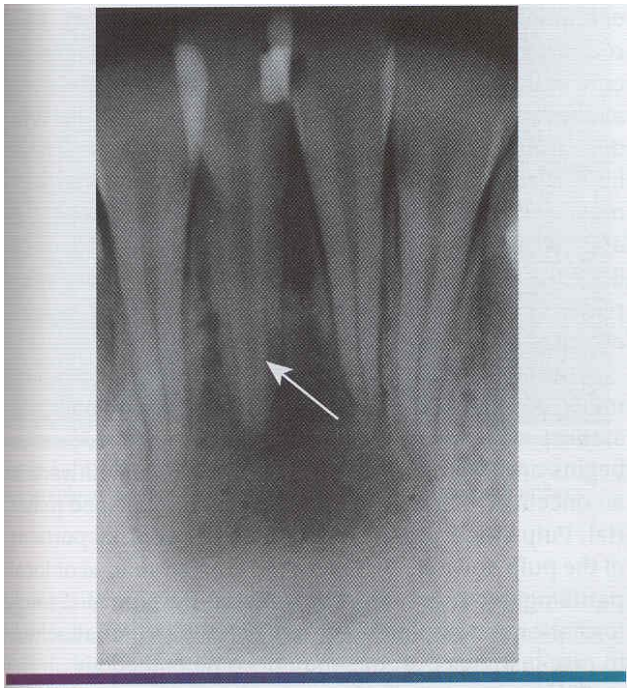


Figure 3-7. Physiologic secondary dentin. Periapical abscess with all four teeth nonresponsive to electric pulp testing. Increased deposition of physiologic secondary dentin on the right central incisor *(arrow)* delineated the origin of the infection; endodontic treatment of this tooth resolved the lesion.

clinically by a yellow discoloration of the crown; radiographically, the affected teeth exhibit an accelerated closure of the pulp chamber and canal when compared to adjacent or contralateral teeth (Figures 3-8 and 3-9). In such cases, the pulpal space may be obliterated completely or reduced dramatically.

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 noted by a bending of the tubules (Figure 3-10). With advancing age, as the odontoblasts undergo degenerative changes, the physiologic secondary dentin **becomes more irregular with fewer tubules.**

The quality and appearance of reparative secondary dentin depend on the severity of the noxious stimulus that promoted its formation. This dentin is localized to the pulpal end of the odontoblastic processes that were affected (Figure 3-11). With a mild stimulus, such as abrasion or attrition, the deposition is slow and demonstrates only slightly irregular tubules. With more *severe* damage (e.g., a rapidly progressing carious lesion), **the formation is rapid and consists of very** irregular dentin with widely scattered, disorganized tubules.

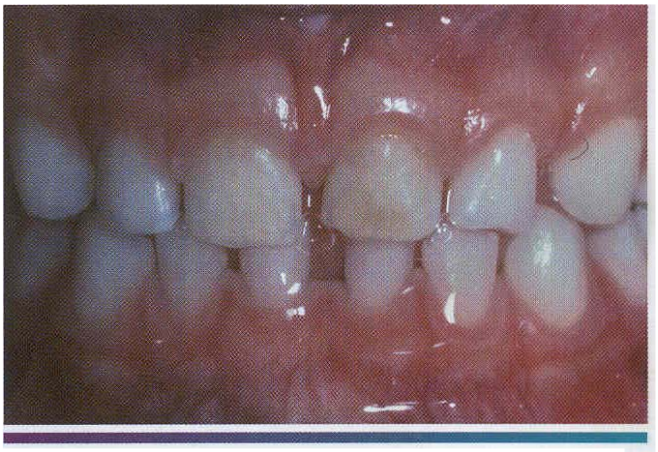


Figure 3-8 • Calcific metamorphosis. Left deciduous maxillary central incisor exhibiting yellow discoloration. (Courtesy of Dr. Jackie L. Banahan.)

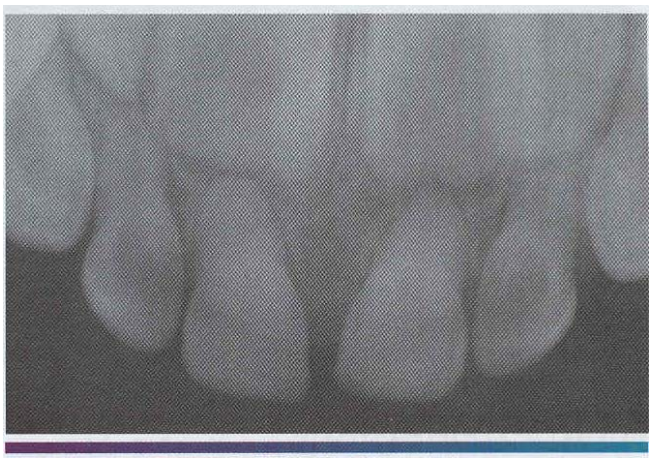


Figure 3-9 • Calcific metamorphosis. Same patient as depicted in Figure 3-8. Deciduous maxillary incisors exhibit total calcification of the pulp chambers and canals. (Courtesy of Dr. Jackie L. Banahan.)

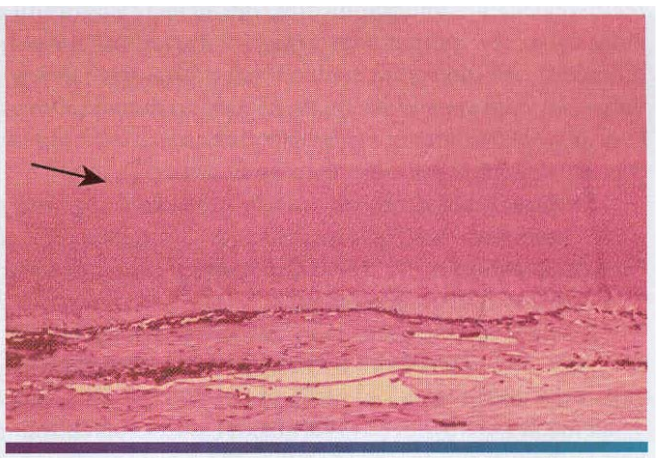


Figure 3-10 • Physiologic secondary dentin. Primary dentin and physiologic secondary dentin are separated by a distinct line of demarcation *(arrow)*.

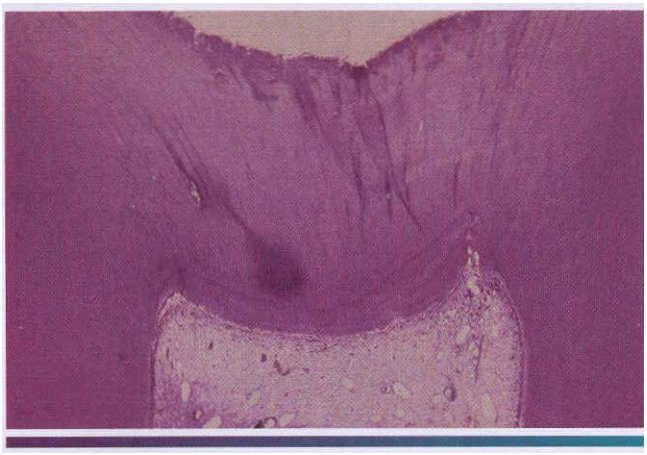


Figure 3-11 • Reparative secondary dentin. Localized deposition of secondary dentin *(bottom)* at the pulpal end of the dentinal tubules affected by the carious process.

Treatment and Prognosis

In permanent teeth exhibiting features of calcific metamorphosis. endodontic therapy should be performed if periapical pathosis or negative vitality testing is present. Even if a canal space cannot be identified. conventional root canal therapy can usually locate and negotiate the pulp canal. If unsuccessful. periapical surgery can be performed in those cases with evidence of periapical inflammatory disease. If vitality testing is positive. 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

Cakifications 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 urn in diameter, the prevalence in a histopathologic review would be expected to be much higher. Increased numbers of calcifications are seen in older teeth and those that have been exposed to trauma or caries.

The three types of pulpal calclflcatlons are:

- Denticles
- Pulp stones
- 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. Denticles form during the period of root development and occur in the root canal and the pulp chamber adjacent to the furcation areas of multirooted teeth. Because denticle development typically precedes completion of the primary dentin. most dcntlclcs become attached to or embedded in the dentin.

Pulp stones are thought 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 calcined 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. Most pulp stones develop after tooth formation is completed and are usually free or attached. In rare instances, stones may become embedded.

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 calclflcatlons 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 (Figure 3-12). Diffuse calcifications are not detectable radiographically.

Other than rare difficulties during endodontic procedures, pulpal calciftcations 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. On occasion. the pulpal calcifications may become very large and may interfere with root formation. possibly leading to early periodontal destruction and tooth loss. Prominent pulpal calcifications have been noted in association with certain disease processes. such as the following:

- Dentin dysplasia type II (see page 96)
- Pulpal dysplasia (see page 98)
- Tumoral calcinosis
- Calcinosis universalis
- Ehlers-Danlos syndrome (see page 655)

Histopathologic Features

Denticles consist of tubular dentin surrounding a central nest of epithelium. With time. the central epithelium

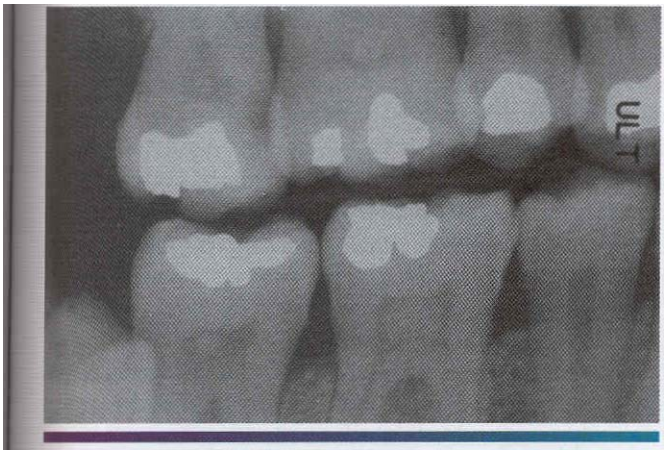


Figure 3-12 • **Pulp stones. Multiple teeth demonstrating radiographically obvious calcifications within the pulp chambers.**

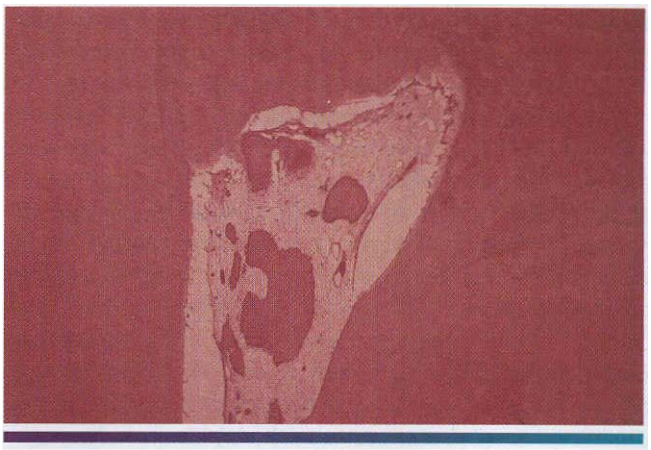


Figure 3-13 . Pulp stones. Multiple stones within the pulp chamber.

degenerates and the tubules undergo sclerosis. making their detection difficult. Most denticles arc 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 (Figure 3-13). 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 (Figure 3- 14). This material often is deposited in a linear fashion along the course of a blood **vessel or nerve.**

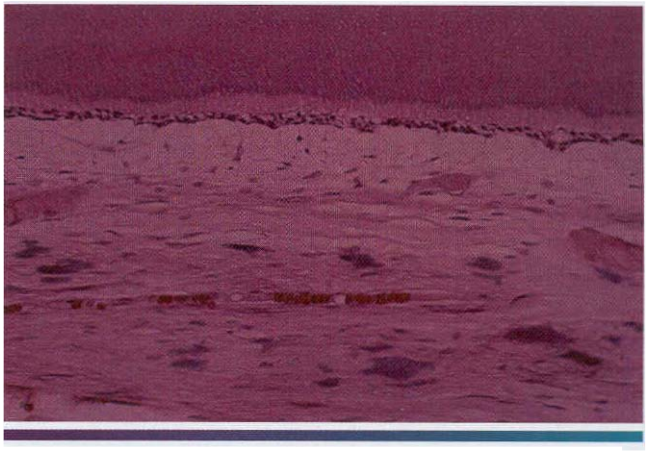


Figure 3-14 • Diffuse linear pulpal calcifications. Fine. fibrillar calcifications parallel the course of the neurovascular channels within the pulp canal.

Treatment and Prognosis

No treatment is required. Most pulpal calcifications arc not associated with any significant clinical alterations.

PERIAPICAL GRANULOMA (CHRONIC APICAL PERIODONTITIS)

The term periapical granuloma refers to a mass of chronically 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 bacteria 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.

Periapical granulomas may arise after quiescence of a periapical abscess or may develop as the initial periapical pathosis. These lesions arc not static and may **transform into periapical cysts or may demonstrate acute exacerbations with abscess formation.**

Clinical and Radiographic Features

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. Periapical granulomas represent approximately 75% of apical inflammatory lesions and 50% of those that have failed to respond to conservative endodontic measures.

Most lesions are discovered on routine radiographic examination. A radiolucency of variable size is present. and the affected tooth shows loss of the apical lamina dura. The lesion may be circumscribed or ill-defined. The size is variable, ranging from small, barely perceptible **lesions to lucencies exceeding 2 cm in diameter (Figures** 3-15 to 3-17). Root resorption is not uncommon (Figure 3-18). Although lesions greater than 200 mm² 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.

Histopathologic Features

Periapical granulomas consist of inflamed granulation **tissue surrounded by a fibrous connective tissue** wall. The granulation tissue demonstrates a variably dense lymphocytic infiltrate that is intermixed frequently with neutrophils, plasma cells, histiocytes, and, less frequently, mast cells and eosinophils (Figure 3-19). When **numerous plasma cells are present, scattered eosinophilic globules** of gamma 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

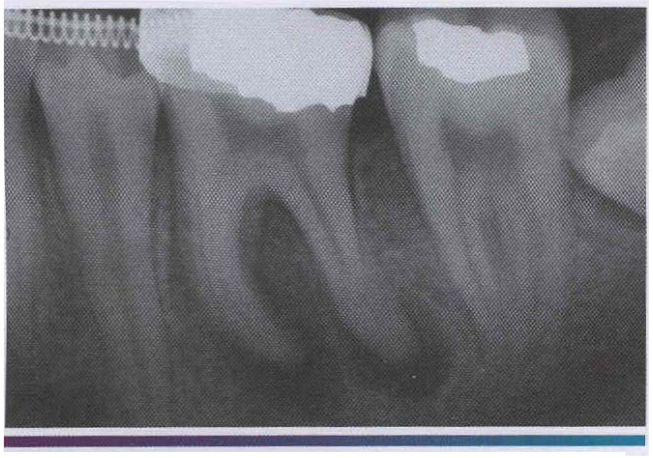


Figure 3-15 • Periapical granulomas. Discrete periapical radiolucencies associated with the apices of the mandibular first molar. (Courtesy of Dr. Garth Bobrowski.)

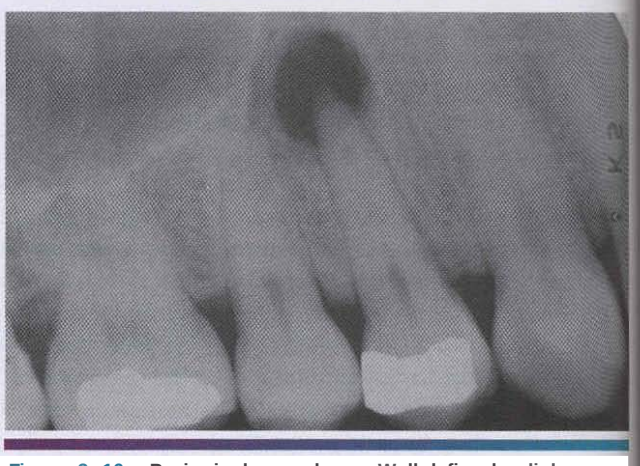


Figure 3-16 • Periapical granuloma. Well-defined radiolucency associated with the apex of the maxillary first bicuspid. (Courtesy of Dr. Frank Beylotte.)

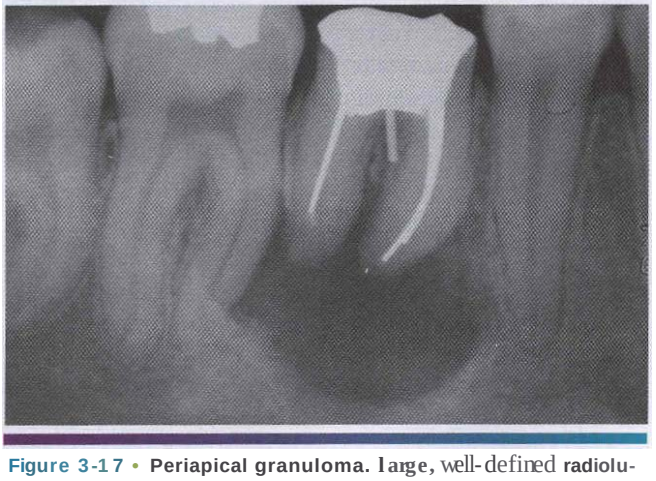


Figure 3-17 • Periapical granuloma. Large, well-defined radiolucency associated with the apices of the mandibular first molar. (Courtesy of D, Robert E. Loy.)

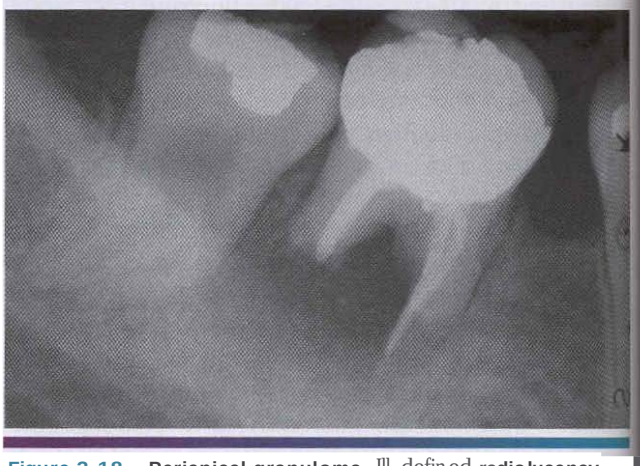


Figure 3-18 • Periapical granuloma. Ill-defined radiolucency associated with the mandibular first molar, which exhibits significant root resorption.

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 bacteria **or their toxic products in the root canal. the** apical tissues. or both . Successful treatment depends on the reduction and elimination of the offending organisms. If the tooth can be maintained. root canal therapy can be performed. Nonrestorable teeth must be extracted. followed by curettage of all apical soft tissue.

Unless they are symptomatic . 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.

Lesions may fail to heal for several reasons:

- Cyst formation
- Inadequate endodontics (e.g.. poor access design, missed canals, perforated canals, inadequate aseptic technique or instrumentation. leaking fillings)
- **Vertical root fractures**
- Periapical foreign material
- Associated periodontal disease
- Penetration of the adjacent maxillary sinus

If initial conventional therapy is unsuccessful, endodontic retreatrnent represents the best approach for total elimination of bacteria 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 em 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 arc mandatory. The primary motivation for this examination is not to dis**cover whether the lesion represents a periapical granuloma or cyst but to eliminate the possibility of a more serious process unrelated to periapical inflammatory disease. In an active oral and maxillofacial pathology service, discovery **of unexpected neoplasms within specimens removed** during periapical surgery is not rare.

On occasion, the defect created by periapical inflammatory lesions may fill with dense collagenous tissue rather than normal bone (Figure 3-20). These fibrous (periapical) scars occur most frequently when both the facial and lingual cortical plates have been lost (Figure 3-21); however, they occasionally arise in areas with intact cortical plates. If during surgery both plates are discovered to be missing, the patient should be informed of the possibility of scar formation. The devel**opment of a periapical scar is not an indication for** future surgery.

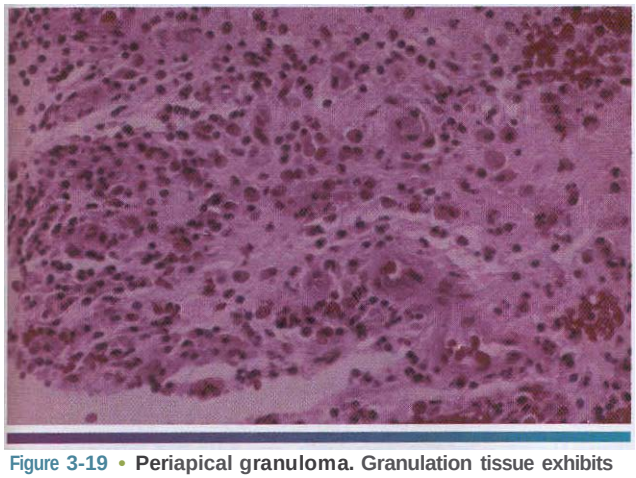


Figure 3-19 • **Periapical granuloma.** Granulation tissue exhibits mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and histiocytes.

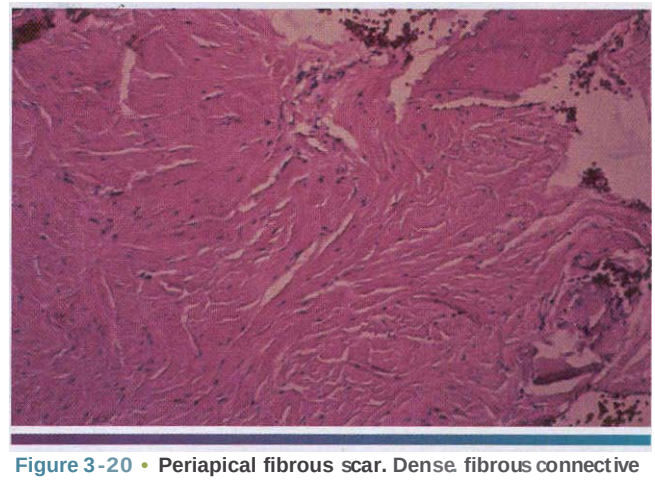


Figure 3-20 • **Periapical fibrous scar.** Dense. fibrous connective tissue with vital bone and no significant inflammatory infiltrate.

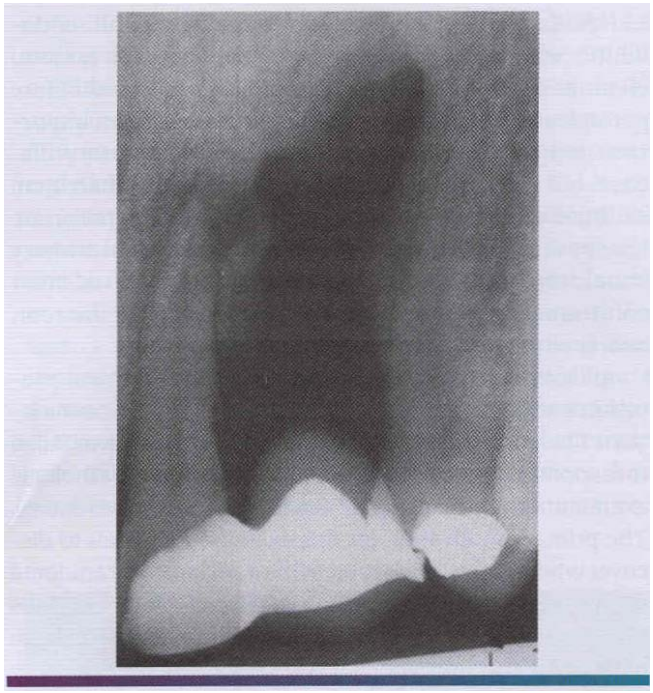


Figure 3-21 • Periapical fibrous scar. Periapical radiolucency of maxilla at the previous site of extraction in which both cortical plates were lost. The site was filled with dense collagenous tissue. (Courtesy of Dr. James Tankersley.)

PERIAPICAL CYST (RADICULAR CYST; APICAL PERIODONTAL CYST)

Epithelium at the apex of a nonvital tooth can be presumably stimulated by inflammation to form a true epithelium-lined cyst, or periapical cyst. The inflammatory response appears to increase the production of keratinocyte growth factor by periodontal stroma cells, leading to increased proliferation of normally quiescent epithelium in the area. 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 fistulous tracts. Cyst development is common; the reported frequency varies from 7% to 54% of periapical radiolucencies.

The wide disparity of prevalence most is likely related to the stringency of the diagnostic criteria used in a particular study. *Several* investigators believe the diagnosis of a periapical cyst can be made only after a lesion has been examined *in toto* with serial or step sectioning of the specimen. Review of random sections of a fragmented and epithelialized periapical granuloma could appear to be an epithelium-lined *cavity* that did not exist in reality. When strict criteria are used, the *prevalence* of periapical cysts appears to be approximately 15%. Because the distinction between an epithelialized periapical granuloma and a periapical cyst has little postsurgical implications, such laborious histopathologic examination is 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 602). 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** cysts*. Typically, patients with periapical cysts have no symptoms unless there is an acute inflammatory exacerbation. In addition, if the cyst reaches a large size, 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 (Figures 3-22 and 3-23). There is a loss of the lamina dura along the adjacent root, and a rounded radiolucency encircles the affected tooth apex (Figure 3-24). Root resorption is common (Figure 3-25). 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 (Figure 3-26). 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. 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 (Figure 3-27).

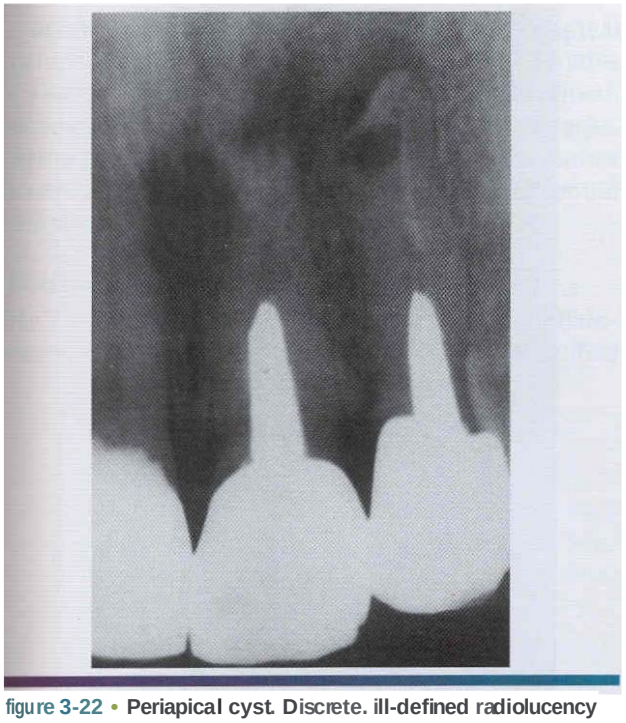


figure 3-22 • Periapical cyst. Discrete, ill-defined radiolucency associated with the maxillary left central incisor.

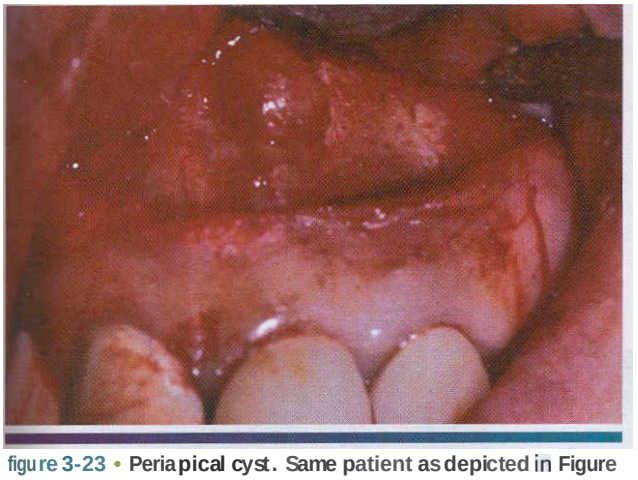


figure 3-23 • Periapical cyst. Same patient as depicted in Figure 3-22. Note the clinically significant cyst, which was not appreciated fully on the radiograph. (Courtesy of Dr. Brian Blocher.)

Lateral radicular *cysts.* lateral radicular cysts appear as discrete radiolucencies along the lateral aspect of the root (Figures 3-28 and 3-29). 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.

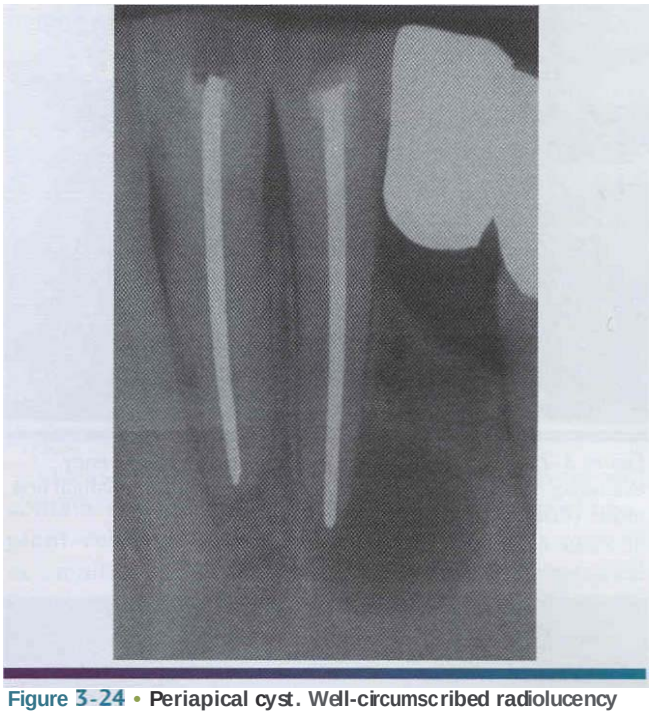


Figure 3-24 • Periapical cyst. Well-circumscribed radiolucency intimately associated with the apex of the mandibular central incisor. Note the loss of lamina dura in the area of the lesion.

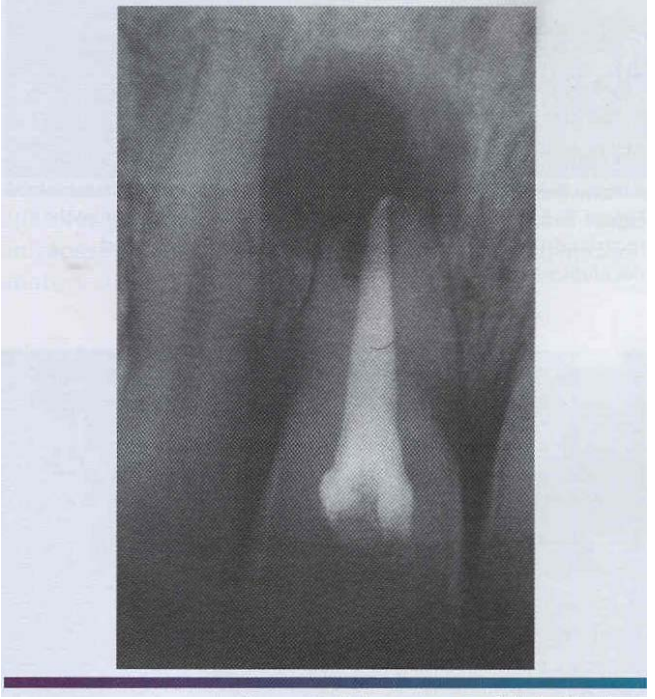


Figure 3-25 • Periapical cyst. Radiolucency associated with the maxillary central incisor, which exhibits significant root resorption.

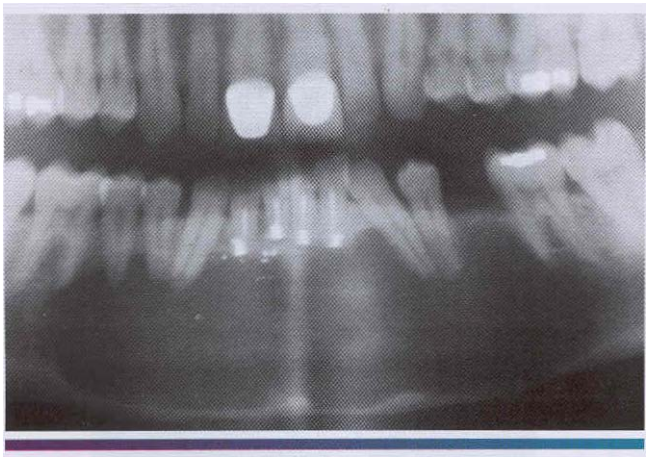


Figure 3·26. Periapical cyst. Large unilocular radiolucency extending from the mandibular first molar to the contralateral first molar. (Courtesy of Dr. John R. Cramer.)

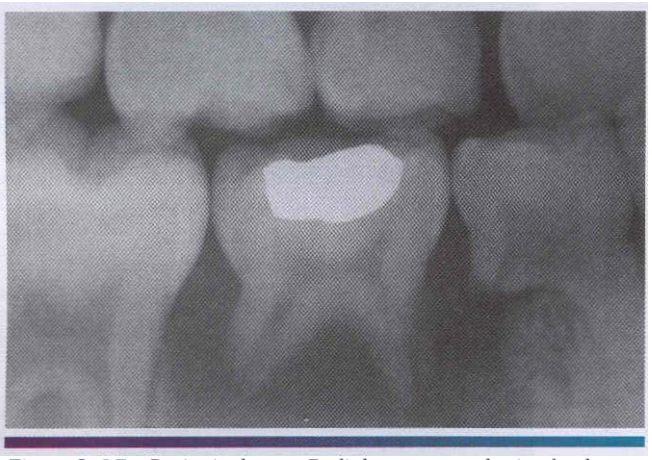


Figure 3·27 • Periapical cyst. Radiolucency enveloping both roots and the bifurcation of the right mandibular second deciduous molar.

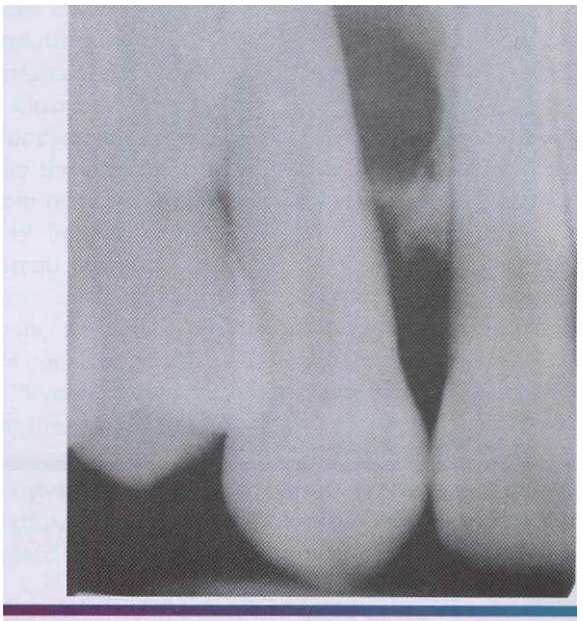


Figure 3-28 • lateral radicular cyst. An interradicular radiolucency has developed as a result of periodontal inflammation alon the mesial surface of the right maxillary cuspid. (Courtesy of Dr. Richard Young.)

A

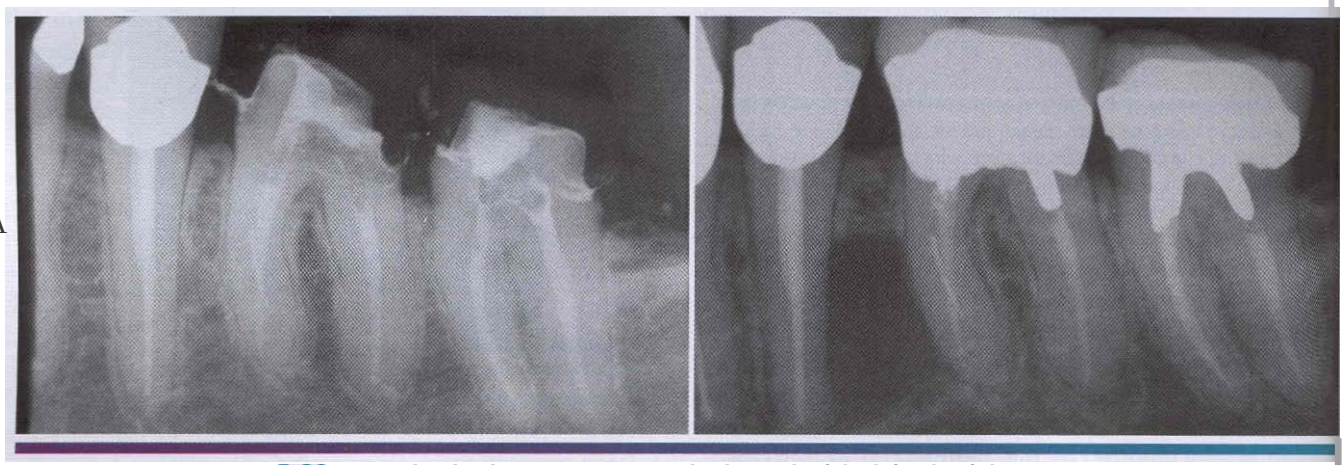


Figure 3-29 • Lateral radicular cyst. A, Periapical radiograph of the left side of the posterior mandible taken at time of completion of endodontic therapy of the bicuspid and molars. B. Subsequent radiograph taken 27 months later. Note radiolucency between bicuspid and first molar extending laterally from the mesial root of the first molar. (Courtesy of Dr. Carroll Gallagher.)

Residual ***periapical*** eysts. 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 (Figures 3-30 and 3-31). As the cyst ages, degeneration of the cellular contents within the lumen occasionally leads to dystrophic calcification and central luminal radiopacity (Figure 3-32).

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 (Figure 3-33). The lumen will be filled with fluid and cellular debris. On occasion, the lining epithelium may demonstrate linear **or** arch-shaped **calcifications known as Rushton bodies** (Figure 3-34). 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 (see Figure 3-33). 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 (see Figure 3-33).

Occasionally. the walls of Inflammatory cysts will contain scattered hyaline bodies (pulse granuloma, giant-cell hyaline angiopathyl.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 (Figure 3-35). The eosinophilic mate**rial may be uniform or contain a variable mixture of** lymphocytes, plasma cells, multinucleated giant cells, neutrophils, necrotic debris, and dystrophic calcification. 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.

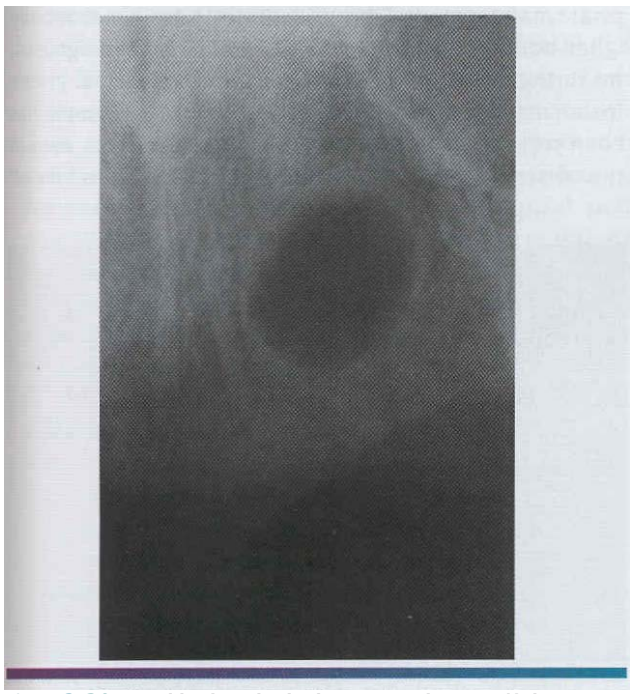
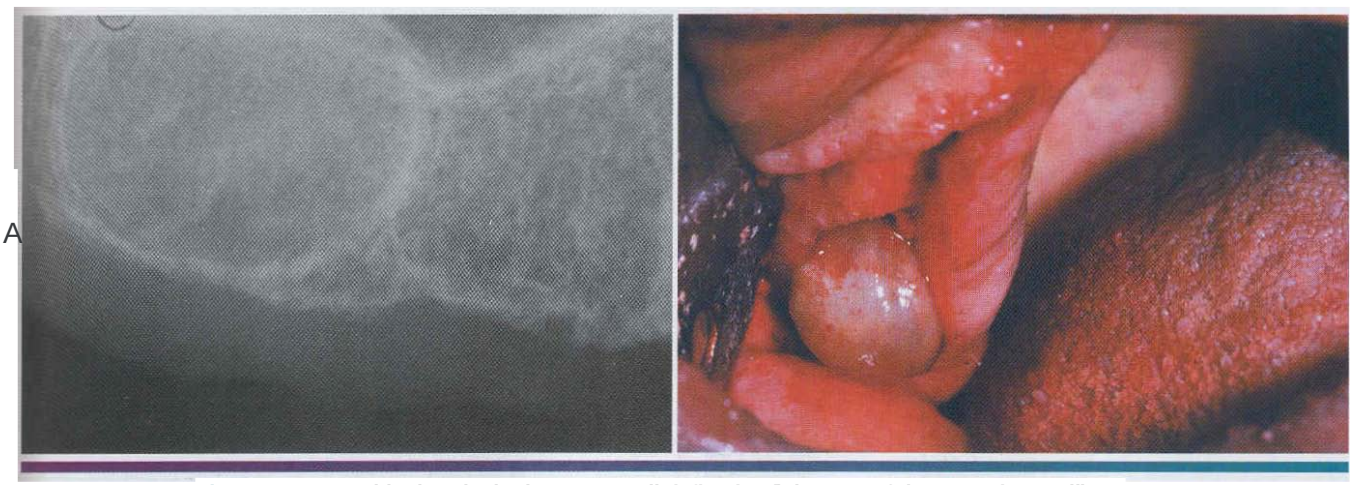


Figure 3·30. **Residual periapical cyst. Persistent radiolucency ofthe mandibular body at site of previous tooth extraction.**



A B

Figure 3-31 • Residual periapical cyst. A. Well-defined radiolucency of the posterior maxilla. B, Clinical photograph exhibiting soft-tissue cyst extruding from the maxillary alveolar ridge after surgical exposure of the site. (Courtesy of Dr. Denise E. Clarke.)

Treatment and Prognosis

A periapical cyst is treated in the same manner as a periapical granuloma. When clinical and radiographic features point to a periapical inflammatory lesion, extraction or conservative nonsurgical endodontic therapy is performed. Larger lesions associated with restorable teeth **have been treated successfully with conservative endo**dontic therapy when combined with biopsy and marsu**pialization, decompression. or fenestration. As with any** suspected periapical inflammatory lesion, minimal follow-up at I and 2 years is advised strongly.

If the radloluc ency fails to resolve, the lesion often can be managed successfully by nonsurgical endodontic retrearrnent. As previously mentioned (see page 115), periapicai surgery is indicated for lesions exceeding 2 em and those associated with teeth that are not suitabie for conventional endodontics. Biopsy is indicated to rule out other possible pathologic processes.

Because any number of odontogenic and nonodonto**genic 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 diag**nosis is made, a thorough evaluation for an inflammatory source is mandatory.**

Cysts of inflammatory origin do not recur after appro**priate management. Fibrous scars are possible, especially** when both cortical plates have been lost; once diagnosed, no further therapy for fibrous scars is indicated. In rare **instances, development of squamous cell carcinoma has** been reported within periapical cysts; therefore, even in the absence of symptoms, treatment is required for all

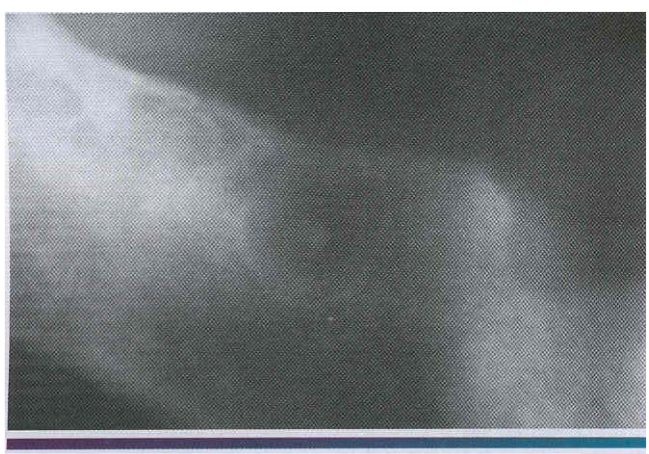


Figure 3-32 • Residual periapical cyst. Radiolucency with central radiopacity of the right mandibular body.

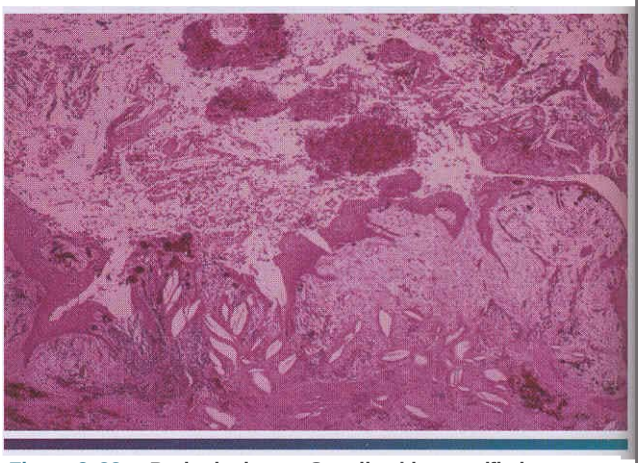


Figure 3-33 • Periapical cyst. Cyst lined by stratified squamous epithelium. Note connective tissue wall, which contains a chronic inflammatory infiltrate and scattered cholesterol clefts with associated multinucleated giant cells.

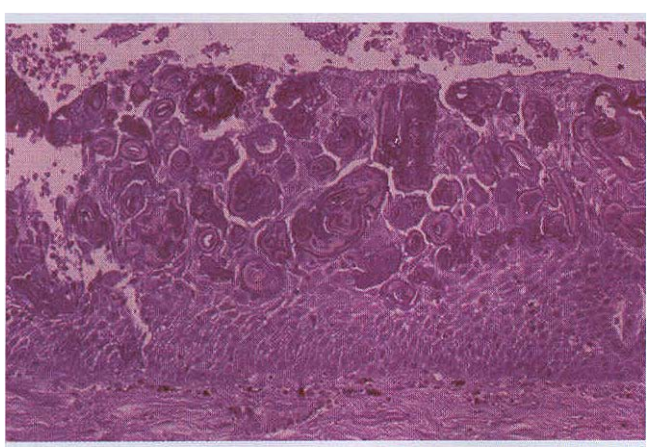


Figure 3-34 • Periapical cyst. Squamous epithelial cyst lining exhibits numerous linear and arch-shaped Rushton bodies.

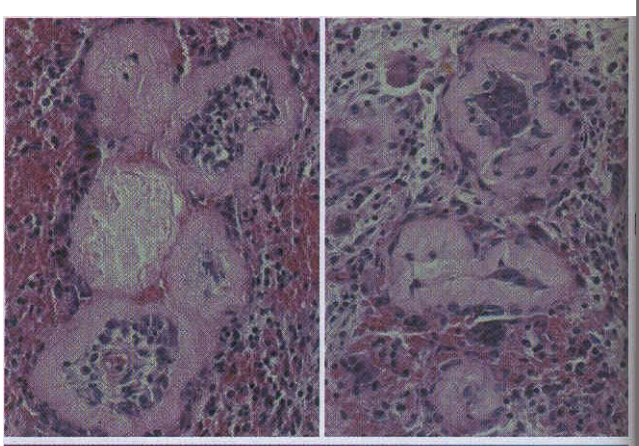


Figure 3-35 • Hyaline bodies. A, Multiple hyaline bodies appearing as corrugated collagenous rings surrounding lymphocytes and plasma cells; note early hyaline body filled with serum. B, Multiple hyaline bodies with numerous multinucleated giant cells within and around the corrugated collagenous rings.

persistent intrabony pathoses that have not been diagnosed definitively by histopathologic examination.

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 exac**erbation (phoenix abscess) of a chronic periapical inflammatory lesion. 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, the periapical periodontal ligament 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 peri**odontitis may present 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 clin**ical 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 there has been insufficient **time 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 (Figures 3-36 and 3-37). At the intraoral opening of a sinus tract, there often is a mass of subacutely inflamed granulation tissue known as a parulis

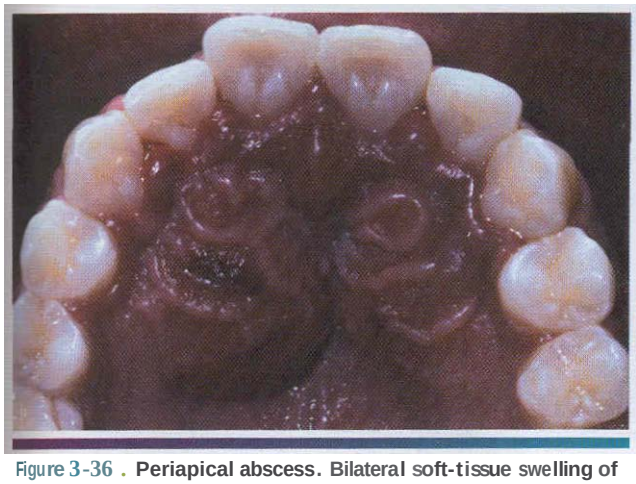


Figure 3-36. **Periapical abscess. Bilateral soft-tissue swelling of the anterior palate**

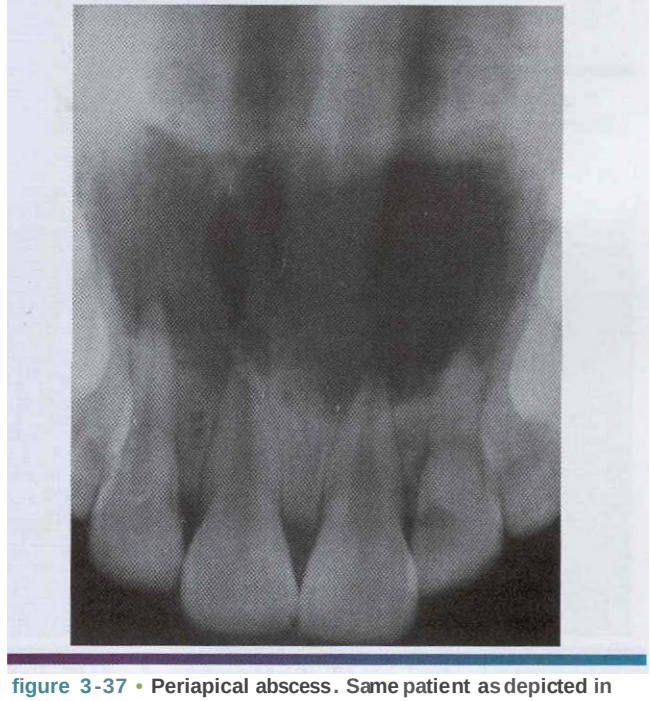


figure 3-37 • **Periapical abscess. Same patient as depicted in Figure 3-36. Multiple, overlapping radiolucencies of the anterior maxilla are present. All four maxillary incisors exhibit pulpal necrosis.**

(gum boil) (Figures 3-38 and 3-39). 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 (Figure 3-40). Dental abscesses also may channelize through the overlying skin and drain *via* a cutaneous sinus (Figure 3-41).

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. Occasionally. such infections are discovered during a routine oral examination after detection of a parulis or drainage through a large cartons defect (Figures 3-42 and 3-43). If the drainage site becomes blocked, signs and symptoms of the abscess frequently become evident in a short period of time.

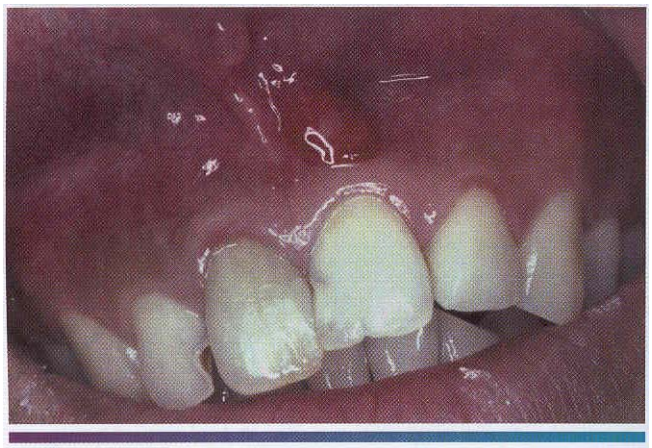


Figure 3-38 • Parulis. Erythematous mass of granulation tissue overlying the left maxillary central incisor. Note discoloration of the maxillary right central incisor.

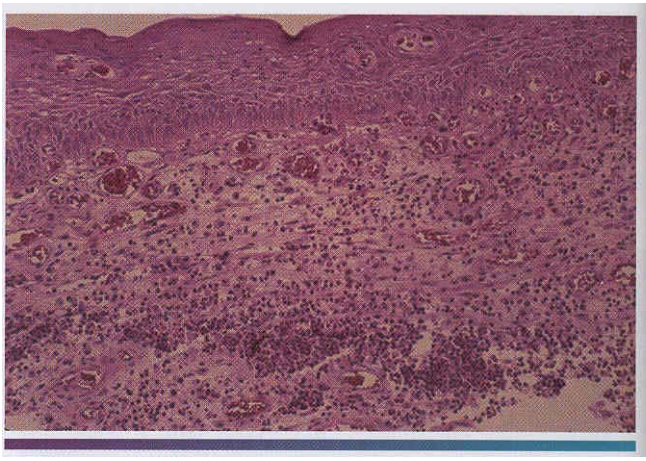


Figure 3-39 • Parulis. Normal connective tissue has been replaced by acutely inflamed granulation tissue. which exhibits focal areas of neutrophilic abscess formation. Note the central sinus tract, which courses from the base of the specimen toward the surface epithelium.

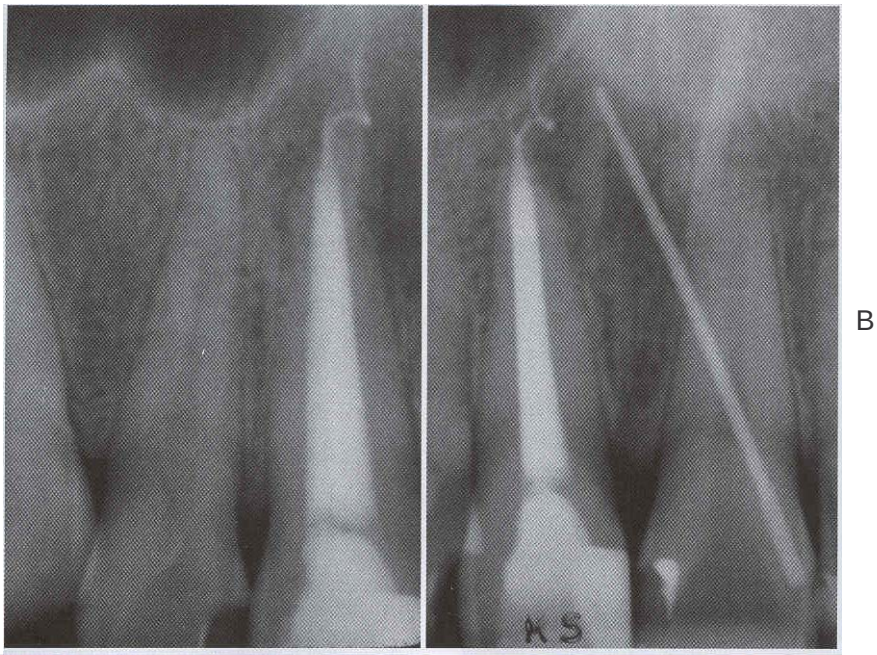


Figure 3-40 • Periapical abscess. A, Same patient as depicted in Figure 3-38. None of the incisors demonstrates an obvious periapical radiolucency. (The large radiolucency at the top is the anterior portion of the maxillary sinus.) B, Gutta-percha point revealed that the right maxillary incisor was the source of the infection.

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** (Figure 3-44). 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 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. If the affected **tooth is extruded. reduction of the occlusion is recommended. Analgesics are administered in more severe** cases. Typicaliy, use of antibiotics 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 fever or diffuse swelling. Once the infection has

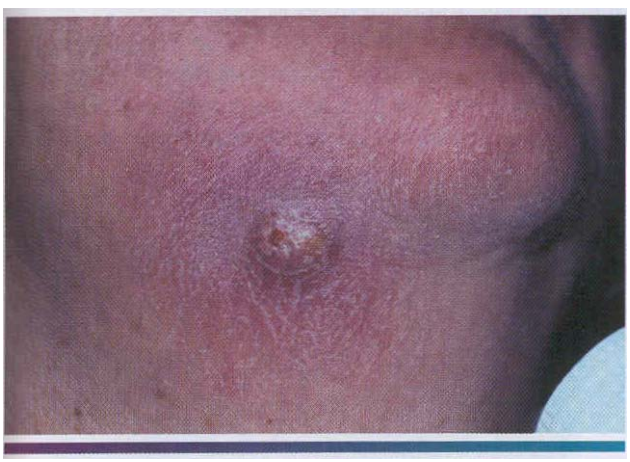


Figure 3-41 • **Cutaneous sinus.** Erythematous, firm, and sensitive enlargement of the skin inferior to the right body of the mandible.

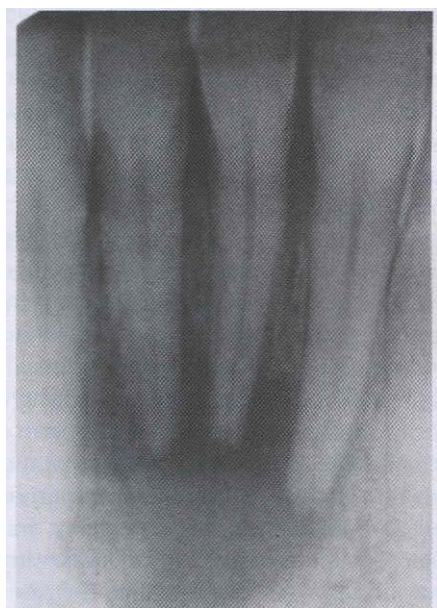


figure 3-43 • **Periapical abscess.** Same patient as depicted in Figure 3-42. Periapical radiolucency associated with the nonvltal mandibular lateral incisor.

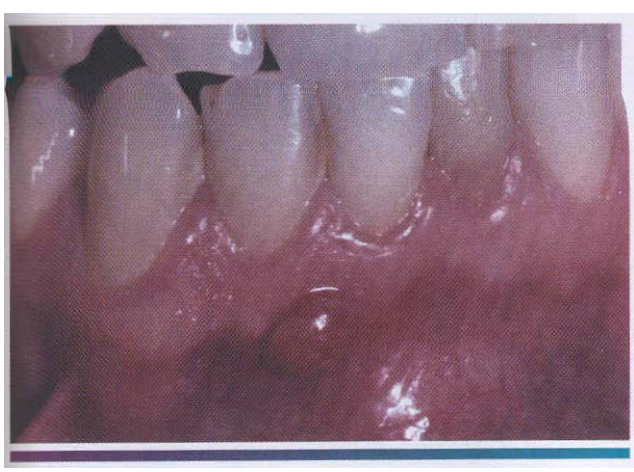


Figure 3-42 • **Parulis.** Asymptomatic yellowish nodule of the anterior mandibular alveolar ridge. Adjacent teeth were normal clinically and also asymptomatic.

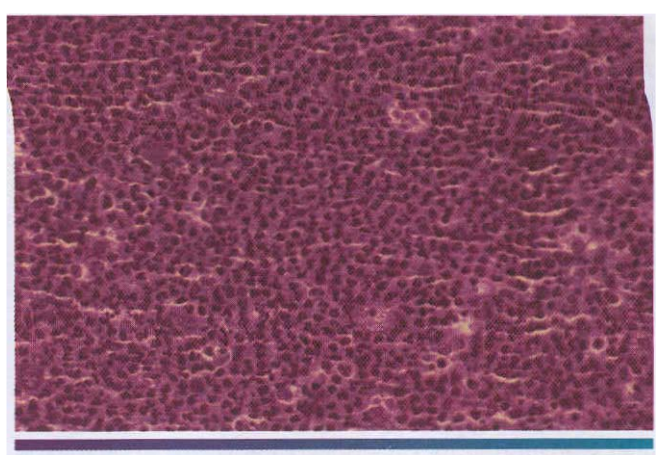


figure 3-44 • **Periapical abscess.** Sheet of polymorphonuclear leukocytes intermixed with scattered histiocytes.

been *resolved* by extraction or appropriate endodontic therapy. the affected bone typically heals.

Usually, a parulis resolves spontaneously after the offending tooth is extracted or endodontically treated. Parulides 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.

CEILULITIS

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 numerous patterns of cellulitis can be seen from the spread of dental infections. two especially dangerous forms warrant further discussion: (I) Ludwig's angina and (2) *cavernous* **sinus thrombosis.**

Ludwig's 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). Ludwig's angina develops from spread of an acute infection from the lower molar teeth in about 70% of cases. Other situations associated with this clinical presentation are peritonsillar or parapharyngeal abscesses. oral lacerations, fractures of the mandible. or submandibular sialadenitis. Although the **process may occur in otherwise healthy individuals. there is an increased prevalence in patients immunocompro**mised secondary to disorders such as diabetes mellitus. organ transplantation, AIDS, and aplastic anemia.

The cavernous sinus is a major dural sinus that is encased between the meningeal and periosteal layers of the dura. The meningeal layer contains the trochlear and oculomotor nerves and the maxillary and ophthalmic branches of the trigeminal nerve. 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 when infection from maxillary premolar or molar teeth perforates the buccal cortical plate and extends into the maxillary sinus, the pterygopalatine space, or the infratemporal fossa, reaching the orbit *via* the inferior orbital fissure. In addi**tion to affecting periorbital structures. the infection then can spread into the cavernous sinus at the cranial vault and result in cavernous sinus thrombosis. Similar involvement also can occur from maxillary anterior teeth,** in which the infection perforates the facial maxillary bone and affects the canine space with spread to the cavernous **sinus via veins of the face. Overall. cavernous** sinus thrombosis is relatively uncommon. and orodental infections are responsible in approximately 10% of the cases.

Clinical Features

Ludwig's angina. Ludwig's **angina is an aggressive** and rapidly spreading cellulitis that *involves* the sublingual. submandibular. and submental spaces. 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.**

Ludwig's angina creates *massive* swelling of the neck that often extends close to the clavicles (Figure 3-45). Involvement of the sublingual space results in *elevation.* posterior enlargement, and protrusion of the tongue (woody tongue). 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,

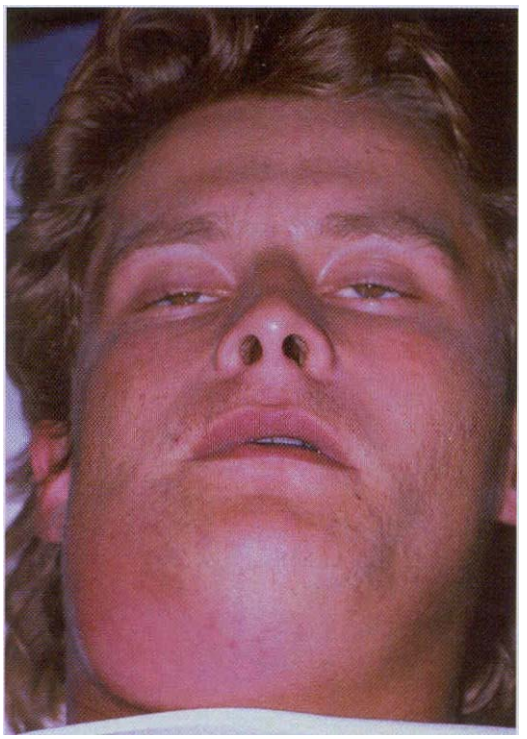


Figure 3-45 • Ludwig's angina. Soft-tissue swelling of the right submandibular region. (Courtesy of Dr. Brian Blocher.)

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 cascs 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 (Figure 3-46). 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 are 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.

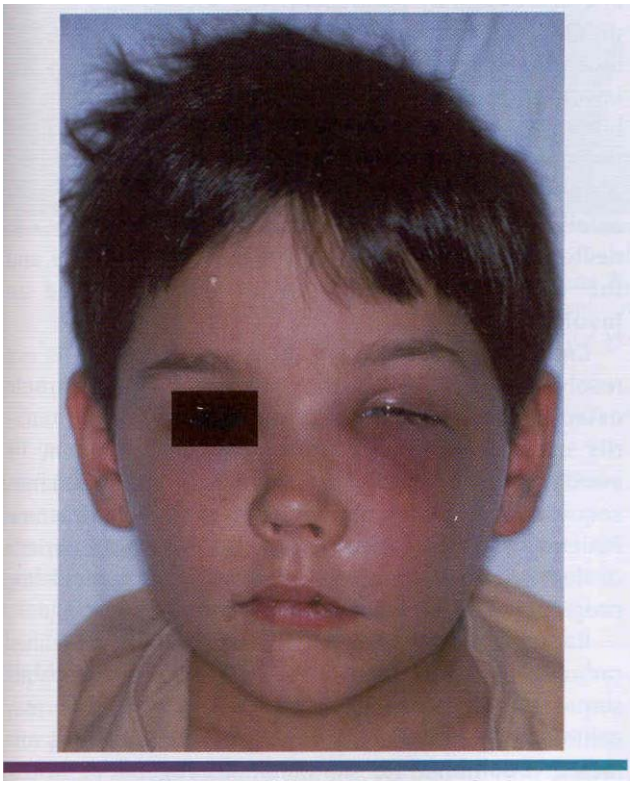


Figure 3-46 • **Cellulitis involving canine space. Erythematous and edematous enlargement of the left side of the face with involvement of the eyelids and conjunctiva. Patients with odontogenic infections involving the canine space are at risk for cavernous sinus thrombosis. (Courtesy of Dr. Richard Ziegler.)**

Fever, chills, headache, sweating, tachycardia. nausea, **and vomiting can occur. With progression, signs of central nervous system 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's **angina**.* **Treatment of Ludwig'S angina centers around four activities:**

1. Maintenance of the airway
2. Incision and drainage
3. Antibiotic therapy
4. Elimination of original focus of infection

Of primary importance is management of an intact airway. On initial observation, many clinicians administer systemic corticosteroids, such as intravenous dexamethasone, in an attempt to reduce the cellulitis. This procedure often protects the airway and allows more rapid penetration of antibiotics in the infected fasciai spaces. Such therapy significantly reduces the need for an artificial airway; in the majority of the cases, tracheotomy or intubation is not required.

If signs or symptoms of impending airway obstruction develop, endotracheal intubation or tracheostomy should be performed. Because intubation is difficult in patients with such massive neck enlargement and may cause laryngospasm or discharge of pus into the bronchial tree. tracheostomy is preferred if there is any chance of significant intubation complications. On occasion. cricothyroidotomy is performed instead of a tracheostomy because of a perceived lower risk of spreading the infection to the mediastinum.

High-dose penicillin is the antibiotic of choice. Amino**glycosides are given for resistant organisms, and** clindamycin or chloramphenicol is used in penicillin-sensitive patients. The antibiotic therapy is adjusted according to the patient's response and culture results from aspirates of fluid from the enlargements.

Although large accumulations of purulent material are rare. decompression of the sublingual. submental. and submandibular spaces should be performed when fluctuance is present. If the infection remains diffuse. indurated, and brawny. surgical intervention is at the discretion of the clinician and often is governed by the patient's response to noninvasive therapy.

Before modern antibiotics. the mortality from Ludwig's angina often exceeded 50%. Although this rate has been reduced to less than 10%. deaths still occur because of **complications such as 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 antibiotics similar to those administered for patients with Ludwig'S angina. The offending tooth should be extracted. and drainage is required if fluctu**ance is present. Administration of systemic cortico**steroids is indicated only in patients who have developed **pituitary insufficiency in advanced cases of cavernous sinus thrombosis. Some investigators also prescribe anti**coagulants to prevent thrombosis and septic emboli; conversely. others believe that thrombosis limits the infection and that the use of anticoagulants may promote hemorrhagic lesions in the orbit and brain.

In older series the mortality rate approached 75%. **Even with current medical advances and modern antibi**otics. the mortality rate remains at approximately 30%. with fewer than 40% of patients achieving full recovery.

OSTEOMYELITIS

Osteomyelitis can be an acute or chronic inflammatory process in the medullary spaces or cortical surfaces of bone that extends away from the initial site of involvement (usually a bacterial infection). Osteoradionecrosis **is excluded from this discussion because this is prima**rily a problem of hypoxia. hypocellularity. and hypovas**cularity. in which the presence of bacteria represents a** secondary colonization of nonhealing bone rather than a primary bacterial infection (see page 263). Several patterns of inflammatory bone disease (e.g.. focal and dif**fuse sclerosing osteomyelitis, proliferative periostitis, alveolar osteitis) are unique and are covered separately** later in the chapter.

True progressive osteomyelitis of the jaws is uncom**mon 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 odon**togenic infections or traumatic fracture of the jaws. In** addition. many cases reported in Africa occur in the presence of acute necrotizing ulcerative gingivitis (ANUG) 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. intravenous drug abuse. diabetes mellitus. exanthematous fevers. malaria. **anemia, malnutrition, malignancy, and** acquired **immuno**deficiency syndrome (AIDS) have been associated with an increased frequency of osteomyelitis. In addition to radiation. several diseases (e.g.. osteopetrosis. dysosteosclerosts, **late Paget's disease. end-stage** cementoosseous dysplasia) may result in hypovascularized bone that is predisposed to necrosis and inflammation.

Acute osteomyelitis exists when an acute inflammatory process spreads through the medullary spaces of the bone and there has been insufficient time for the body to react to the presence of the inflammatory infiltrate. **Chronic 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 antibiotics have** great difficulty reaching the site. This process results in a smoldering infection that is difficult to manage unless the problem is approached aggressively.

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. Max**i1larydisease becomes important primarily in pediatric patients and in cases that arise from ANUG or noma lin African populations).

Acute osteomyelitis. **Patients with acute osteo**myelitis have signs and symptoms of an acute inflammatory process that has typically been less than I month in duration, Fever. leukocytosis. lymphadenopathy, significant sensitivity. and soft-tissue swelling of the affected area may be present. The radiographs may be unremarkable or may demonstrate an ill-defined radiolucency (Figure 3-47). 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 (Figure 3-481. On occasion. fragments of necrotic bone may become surrounded by vital bone. and the mass of encased nonvital bone is called an **involucrum.**

Chronic ***osteomyelitis.*** **If acute osteomyelitis is not** resolved expeditiously. the entrenchment of chronic **osteomyelitis occurs, or the process may arise prima**rily without a previous acute episode. There may be swelling. pain. sinus formation. purulent discharge. sequestrum formation. tooth loss. or pathologic fracture, **Patients may experience acute exacerbations or periods** of decreased pain associated with chronic smoldering progresston (Figure 3-49l.

Radiographs reveal a patchy. ragged. and ill-defined radiolucency that often contains central radiopaque sequestra, Occasionally. the surrounding bone may **exhibit an increased radiodensity, and the cortical sur**face can demonstrate significant osteogenic periosteal hyperplasia.

Because of an anatomic peculiarity. large portions of each jawbone receive their blood supply through multiple

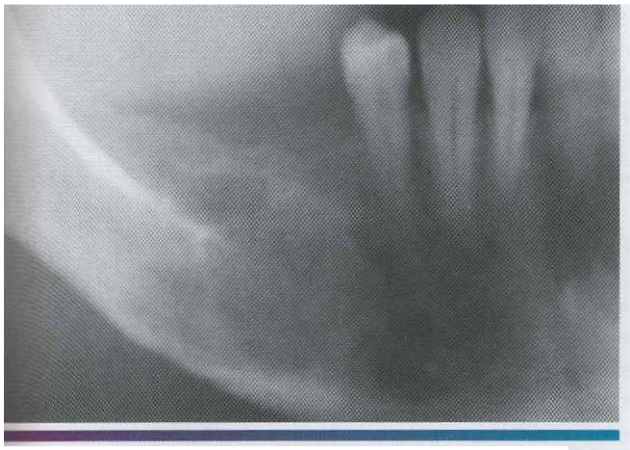


Figure 3-47 • **Acute osteomyelitis. Ill-defined area of radiolucency of the right body of the mandible.**

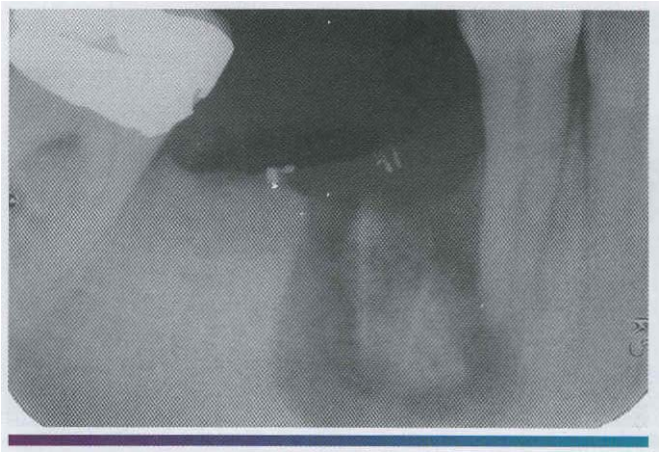


Figure 3-48 • **Acute osteomyelitis with sequestrum. Radiolucency of the right body of the mandible with central radiopaque mass of necrotic bone. (Courtesy of Dr. Michael Meyrowitz.)**

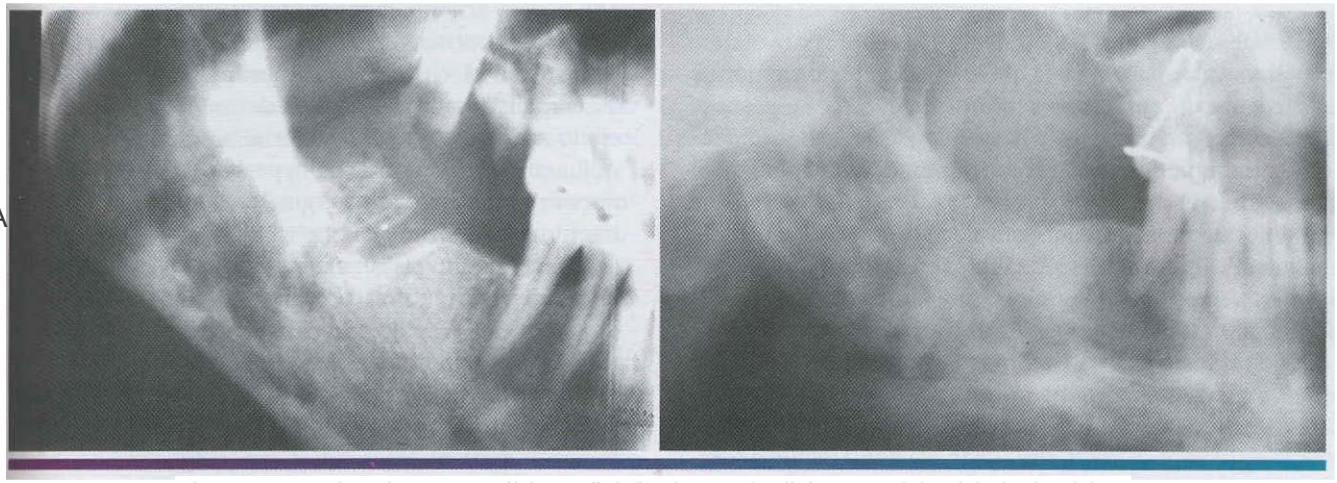


Figure 3-49 • **Chronic osteomyelitis. A, Ill-defined area of radiolucency of the right body of the mandible adjacent to a recent extraction site. B, After the initial intervention. the patient failed to return for follow-up because of lack of significant pain. An enlarged, ill-defined radiolucency of the right body of the mandible was discovered 2 years after the initial surgery. (Courtesy of Dr. Charles Waldron.)**

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** 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 ostcocytes from their lacunae. peripheral resorption. and bacterial colonization (Figure 3-50). The periphery of the bone and the haversian canals contain necrotic debris and an acute inflammatory infiltrate consisting of polymorph onuclear leukocytes. The submitted material will be diagnosed as a sequestrum unless a good clinicopathologic correlation points to the appropriate diagnosis of acute osteomyelitis.

Chronic 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 (Figure 3-51). Scattered sequestra and pockets of abscess formation are common.

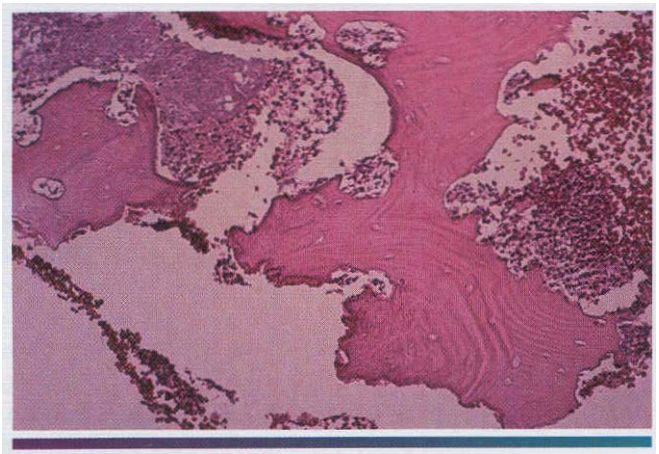


Figure 3-50 . Acute osteomyelitis. Nonvital bone exhibits loss of the osteocytes from the lacunae. Peripheral resorption. bacterial colonization. and surrounding inflammatory response also can be seen .

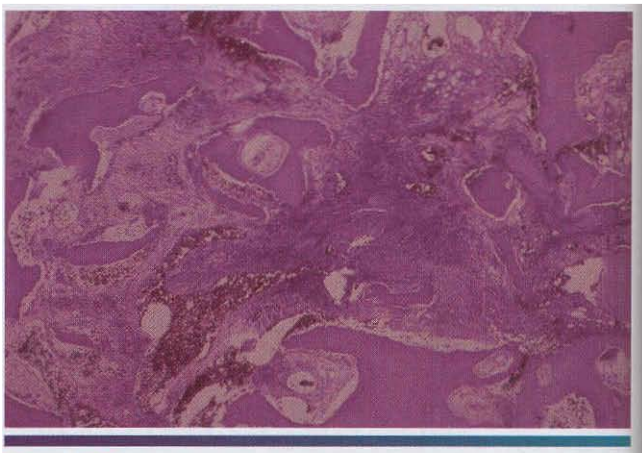


Figure 3-51 • Chronic osteomyelitis. Chronically inflamed and reactive fibrous connective tissue filling the intertrabecular spaces.

Treatment and Prognosis

***Acute osteomyelitis*. If obvious abscess formation is noted. the treatment of acute osteomyelitis consists of** antibiotics and drainage. Microbiologic study of the infectious material typically reveals a polymicrobial infection of organisms normally present in the oral cavity. The antibiotics most frequently selected include penicillin. clindamycin. cephalexin. cefotaxlmc, tobramycin, and **gentamicin.**

In most patients, a sufficient and appropriate antibiotic regimen aborts the infection and averts the need **for surgical intervention. Several investigators** have suggested that antibiotic therapy can bring about sterilization of the sequestra; therefore, these nonvital bone fragments should be allowed to remain in place as a scaffolding for the future development of new bone.

Chronic osteomyelitis. Chronic osteomyelitis is difficult to manage medically, presumably because pockets of dead bone and organisms are protected from antibiotics by the surrounding wall of fibrous connective tissue. **Surgical intervention is mandatory. The antibiotics 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 due to incomplete removal of diseased tissue. Upon successful elimination of all infected material, resolution is expected. Adjunctive procedures (c.g.. hyperbaric oxygen) are rarely necessary if thorough surgical curettage and sequestrectomy have been accomplished.

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 primarily recommended for the rare patient who does not respond to standard therapy or for disease arising in hypovascularized bone (e.g., osteoradionecrosis, osteopetrosis, Paget's disease cemento-osseous dysplasia).

DIFFUSE SCIEROSING 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. On occasion, diffuse sclerosing osteomyelitis can be confused with secondarily inflamed intraosseous pathoses (florid cernento-osseous dysplasia) (see page 558) or Paget's disease of bone (see page 542). In spite of the clinical and radiographic similarities, these processes can be separated from diffuse sclerosing osteomyelitis because of various clinical. radiographic. and histopathologic differences.

The remaining pathoses can be grouped under three major categories: (1) diffuse sclerosing osteomyelitis,

(2) chronic tendoperiostitis, and (3) SAPHO syndrome. Whether these represent variations of a single disorder or different pathologic processes is highly debated with no clear answer expected within the near future. Until that time, it appears prudent for clinicians to consider all possibilities in an effort to ensure the most appropriate care for patients affected with these conditions.

In the purist's view, diffuse sclerosing osteomyelitis should be used only when an infectious process directly is responsible for sclerosis of bone. In these cases, **chronic intraosseous bacterial infection creates a smoldering** mass of chronically inflamed granulation tissue that incites sclerosis of the surrounding bone.

Although initially thought to be an obscure infectious process, chronic tendoperiostitis is thought 10represent a reactive hyperplasia 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, 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.

SAPHO syndrome is an eponym for a complex clinical presentation that includes synovitis, acne, pustulosis, hyperostosis, and osteitis. The cause is unknown, but it is thought to arise in genetically predisposed individuals who develop an autoimmune disturbance secondary to exposure to dermatologic bacteria. Although not found consistently, an increased prevalence of HLA 27 in patients with SAPHO has been noted by several investigators. It is theorized that an abnormal immune **response to the microorganism cross-reacts with normal** bone or joint structures, leading to the variety of clinical **manifestations.**

Clinical and Radiographic Features

Diff"se sclerosing osteomyelitis. Diffuse sclerosing osteomyelitis is similar to the localized variant (condensing osteitis) (see page 131); however, it is also very different. The disorder arises almost exclusively in adulthood and does not exhibit a sex predominance. It primarily occurs in the mandible. An increased radiodensity develops around sites of chronic infection (e.g., periodontitis, pericoronitis, 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 docs not appear to orlginate in the areas of attachment of the masseter or digastric muscle (Figure 3-52). The radiodensities do not develop from previously radiolucent fibro-osseous lesions and do not exhibit the predifection for black females, as is found in those patients with florid ccrnento-osseous dyspiasia. Pain and swelling are not typical.

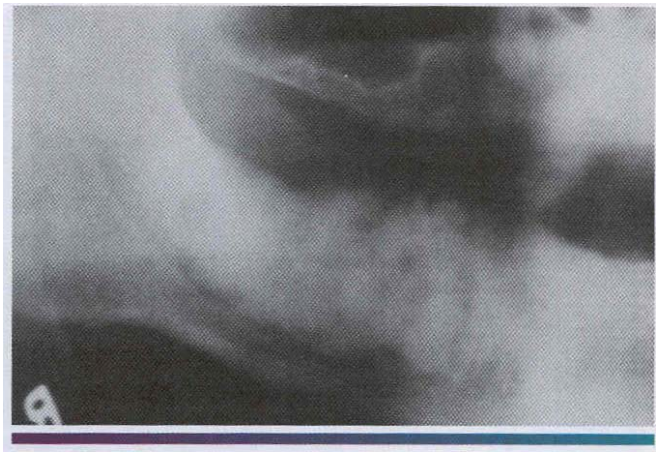


Figure 3-52 • Diffuse sclerosing osteomyeliti s. Diffuse area of increased radiodensity of the right body of the mandible in the tooth-bearing area. No other quadrants were involved. (Courtesy of Dr. louis M. Beto.}

Classically, diffuse sclerosing osteomyelitis definitively caused by bacteria spreads through cancellous bone, with eventual perforation of the cortex. At this site the periosteum is elevated from the cortical surface with localized deposition of periosteal new bone. In the cancellous bone, significant bone apposition and sclerosis **occur around the central zone of infection and bone** resorption. On plain films, the sclerosis often obscures the central lytic area.

To make a definitive diagnosis of diffuse sclerosing osteomyelitis, microbiologic cultures should be positive, with the infected sites typically responding to appropriate antibiotics and surgical debridement. Many investigators **believe those cases exhibiting negative cultures and nonresponsiveness to antibiotics do not represent sclerosing** osteomyelitis, and they should be evaluated for features of chronic tendoperiostitis or SAPHO syndrome. Other authorities suggest the negative cultures may be caused by inappropriate microbiologic techniques. When adhering to strict protocols, unusual organisms (e.g., *Eikenella corrodens)* often are detected within areas of sclerosing osteomyelitis.

Chronic tendoperiostitis. Although the mean age of **occurrence is 40, chronic tendopcriostitis may occur in** people of all ages. There is no sex predilection. Recurrent pain, swelling of the check, 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 antibiotics. 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. there may be involvement in the cuspid and premolar region and the anterior mandible (i.e.. attachment of the digastric muscle). 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.

SAPHO syndrome. Patients affected with SAPHO syndrome arc usually under the age of 60 years and suffer from chronic multifocal osteomyelitis that is typically associated with negative microbiologic cultures and is nonresponsive to antibiotic therapy. 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. The most frequently involved location is the anterior chest wall. with the sternum. clavicles. and ribs being affected individually or together. Other bones occasionally involved include the spine. pelvis. and long bones.

In early gnathic lesions. diffuse osteolytic zones are more prominent than sclerosis; the affected bone is enlarged because of significant production of periosteal new bone. \Vith time. the bone decreases in size because of diminished periosteal apposition. and the osteolytic zones become smaller and fewer. External bone resorption and deformity of the mandible are characteristic in older lesions.

In some instances. bone lesions are present without associated skin involvement. In these cases the osseous abnormalities have been termed chronic recurrent rnultifocal osteomyelitis. Dermatologic involvement may be absent. appear after some delay, or be so subtle as to escape detection. The interval between initial recognition of bone lesions and ultimate development of skin alterations has been as long as 20 years. Commonly associated skin lesions include palmoplantar pustulosis. pustular or plain psoriasis, acne conglobata or ulcerans, and hidrosadenitis suppurativa.

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 soh tissue component. If the adjacent inflammatory process extends into the sclerotic bone, 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.

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. they are located in cortical resorption defects and the subcortical bone adjacent to sites of muscle insertion.

SAPHO syndrome. Histopathologic studies reveal active bone remodeling rather than signs of infection. such as abscess formation and bone necrosis. Typically, biopsy of altered areas reveals interconnecting trabeculae of vital reactive bone intermixed with fibrous connective tissue that contains a mixture of chronic inflammatory cells.

Treatment and Prognosis

Diffllse 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 i26),

Chronic tendoperiostitis. Treatment of chronic tendoperiostitis as a form of osteomyelitis has been most unsatisfactory. Large series of patients have been treated with antibiotics, explorations, intraoral decortication, implantation of gentamicin beads, hyperbaric oxygen. and corticosteroids 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;

- Muscular relaxation instructions (soft diet. avoidance of parafunctional habits)

- **Rotation exercises**
- Occlusal splint therapy
- Myofeedback
- Muscle relaxant drugs (e.g., diazepam, rnefenoxalon)

SAPHO syndrome, Most treatments directed toward **elimination of infection have been proven ineffective.** long-term antibiotic therapy has produced no noticeable results. Surgical decortication has decreased the intensity and frequency of symptoms but has failed to resolve the process totally. Steroidal and nonsteroidal anli-inflammatory medications are reported to be the most effective agents to relieve symptoms, but they are **usually associated with incomplete resolution. Even** with significant surgical and medical interventions, the course is characterized by flares separated by partial **remissions.**

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 people. 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 space or an apical inflammatory lesion (Figure)-53). 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 557), 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 osteo-**sclerosis (see page 540).

Treatment and Prognosis

Treatment of the patient with condensing osteitis con**sists of resolution of the odontogenic focus of infection.** Afterextraction 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, 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 *bonescar* (Figure 3-54).

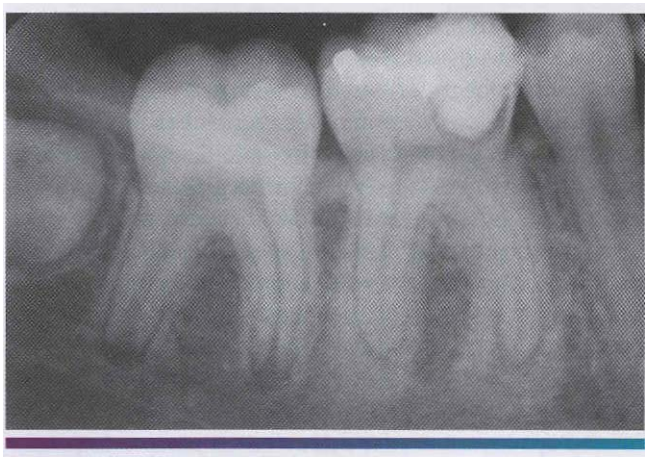


Figure 3-53 • Condensing osteitis. Increased areas of radio**density surrounding the apices of the** nonvital **mandibular first molar.**

Figure 3-54. Bone scar. Residual area of increased radiodensity in the area of extraction of the mandibular first molar. (Courtesy of Dr. Walter Blevins.]

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. Common causes of **periosteal new bone formation arc osteomyelitis,** trauma, cysts, and neoplasms. Of these, osteomyelitis and malignant neoplasms are associated most frequently **with formation of bone within a periosteal reaction.**

In 1893 a German physician. C. Garrc, reported on patterns of acute osteomyelitis. Since that time. numerous articles have been written that associate Carre's report with a form of inflammatory periosteal hyperplasia demonstrating an onion skin- like reduplication of the cortical plate. (In these subsequent articles. Garre's name was misspelled consistently as Garre. with an improper accent.) However. Garre did not have any pathologic specimens for microscopic examination. and Roentgen did not discover x-rays until two years after Garres publication. Nowhere in the original publication is there any mention of periostitis. periosteal duplication. or "onion skinning." Therefore, although the term "Garre's 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 nonodontogcnic 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 umfocal, although multiple quadrants may be affected.

Appropriate radiographs demonstrate radiopaque laminations of bone that roughly parallel each other and the underlying cortical surface (Figure 3-55). The laminations vary from I 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.

Because of difficulty in proper angulation and problems related to superimposition of the underlying bone. computed tomography 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. The latter type often is favored because of finer detail of the final image. If lateral oblique radiographs fail to demonstrate the lesion, occlusal views and. less frequently, posteroanterior radiographs may be successful.

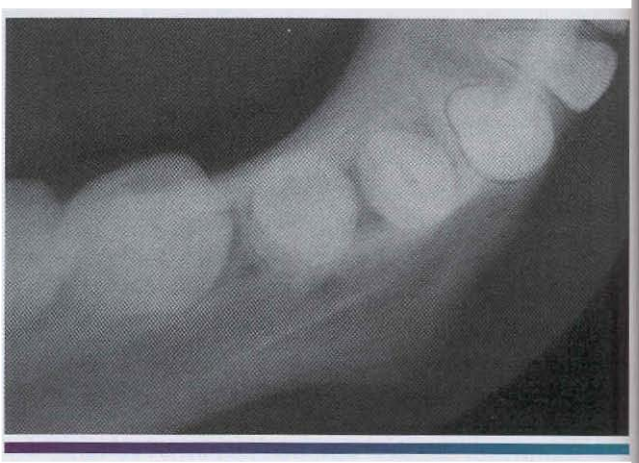


Figure 3-55 • Proliferative periostitis. Radiopaque laminations of cortical bone parallel the cortex adjacent to inflammatory process of the mandibular bicuspid. (Courtesy of Dr. William Bechtold.)

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 (Figure 3-56). The trabeculae sometimes form an interconnecting meshwork of bone or are scattered more widely. resembling the pattern seen in immature fibrous dysplasia. Between the cellular trabeculae. relatively uninflamed fibrous connective tissue is evident. Sequestra. if included, demonstrate the typical features of bone necrosis (see "Osteomyelitis." page 126).

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 ellminating 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. On occasion. periosteal hyperplasia has been found in patients without any detectable cause except for the close proximity of an unerupted tooth surrounded by ils dental follicle. The cause for the periosteal hyperplasia in these instances is unclear.

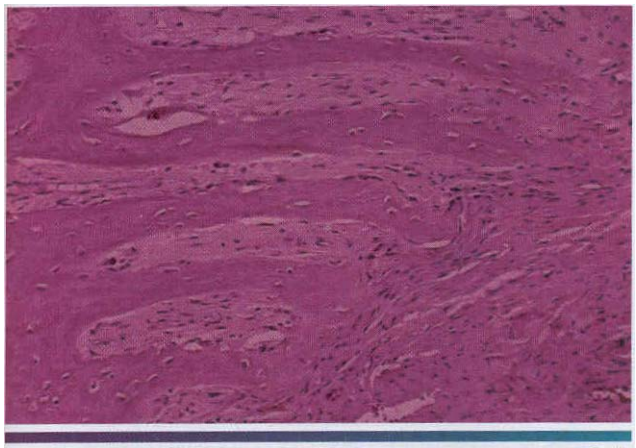


Figure 3-56 . Proliferative periostitis. Cellular and reactive vital bone with individual trabeculae oriented perpendicular to the surface.

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. Destruction of the initial clot prevents appropriate healing and causes **theclinical syndrome known as alveolar osteitis.**

Extensive investigations *have* shown that the clot is lost secondary to transformation of plasminogen to plasmin, with subsequent lysis of fibrin and formation of kinins (fibrinolytic alveolitis): these are potent pain mediators. Local trauma, estrogens, and bacterial pyrogens are known to stimulate fibrinolysins. This knowledge correlates well with the increased frequency of alveolar osteitis in association with inexperienced surgeons. traumatic extractions. oral contraceptive use. and presurgical infections. In addition. inadequate irrigation at surgery and the use of tobacco products have been related to the development of the problem.

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 docs not appear to be a significant sex predilection. The prevalence is between I% 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 prophylactically removed rather than for therapeutic reasons after development of chronic inflammation of pericoronal tissues. 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. 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. The socket is irrigated with warm szfine, 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. Finally, the socket is packed with an obtundent and antiseptic dressing, such as iodoform gauze containing eugenol. Typically, the dressing is changed every 24 hours for the first 3 days, then every 2 to 3 days **until granulation tissue covers the exposed bone.** Because it acts as a foreign material. the dressing should **be discontinued as soon as the patient is out of pain.** After that time the patient should be given a plastic **syringe with instructions for home irrigation. The irrigation** should be continued until the socket no longer collects any debris (usually 3 to 4 weeks).

Many investigators have studied preventive measures for alveolar osteitis and have found several that offer **promise. For female patients using oral contraceptives.** the extractions should be scheduled on days without estrogen supplementation (typically days 23 to 28 of the menstrual cycle). Topical antibiotics, systemic antibiotics, **systemic or topical antifibrinolytics. antimicrobial rinses. and intraoperative irrigation** have **been used. The best results have** been **obtained with** intraoperative **irrigation** combined with placement of antibiotics into the socket, or chlorhexidine rinsing both before and after the surgical procedure. Tetracycline is the most frequently chosen antibiotic, but lincomycin, c1indamycin, and metronidazole also show favorable results. The antibiotic should not **be in an ointment form. because such use has resulted in** chronic foreign body reactions (e.g.. myospherulosis) (see page 281). Many surgeons are hesitant to place a medicament into an extraction socket. Those who do often restrict its use to those patients who are considered "high risk," such as those who:

- **Take oral contraceptives**
- Smoke
- **Have existing signs of pericoronitis**
- **Have traumatic extractions**
- **Have a history of alveolar osteitis**

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CHAPTER 4

Periodontal Diseases

CHAPTER OUTLINE

In this textbook of oral and maxillofacial pathology, the discussion of periodontal diseases is limited appropriately in scope. However, there are several fine textbooks available on periodontology that 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. 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, human immunodeficiency virus [HIV]) is discussed in Chapters 5 and 7. The gingiva is a frequent site of involvement in several of the dermatologic vesiculocrosive 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, but its true prevalence is difficult to determine because of the lack of a standardized method of measurement. 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 (Figure 4-11). 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. Progesterone appears to increase the permeability of gingival blood vessels. thereby rendering the area more sensitive to bacterial, physical, and chemical irritants.

Other factors shown to relate directly to the frequency of gingivitis are smoking. stress. poor nutrition. medications. diabetes mellitus (see page 728). metal poisontng (see page 272), trauma. tooth crowding with overlapping. and mouth breathing. 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. If the trauma follows a chronic pattern, however. 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 (Figure 4-2),

After such factors as age, sex. family income, education. and race are considered. numerous studies have shown that smoking correlates with a higher frequency of gingivitis and related periodontal diseases in every age group. Inflammation of the gingiva also can be enhanced by a poor nutritional status. Although the lack of vitamin C and its relationship to scorbutic gingivitis is well known (see page 713), indirect evidence also demonstrates a correlation between gingival health and the intake of protein, folic acid, and zinc.

Inflammation of the gingiva may be localized or generalized. The involved area may be diffuse or confined to the free gingival margins (marginal gingivitis) (Figure 4-3) 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 margins that may be blunted. receded, or hyperplastic (Figure 4-4). When chronic inflammation causes

Box 4-1 *Types of Gingivitis*

1. Plaque-related gingivitis
2. Necrotizing ulcerative gingivitis (NUG)
3. Medication-influenced gingivitis
4. Allergic gingivitis
5. Specific infection-related gingivitis
6. Dermatosis-related gingivitis

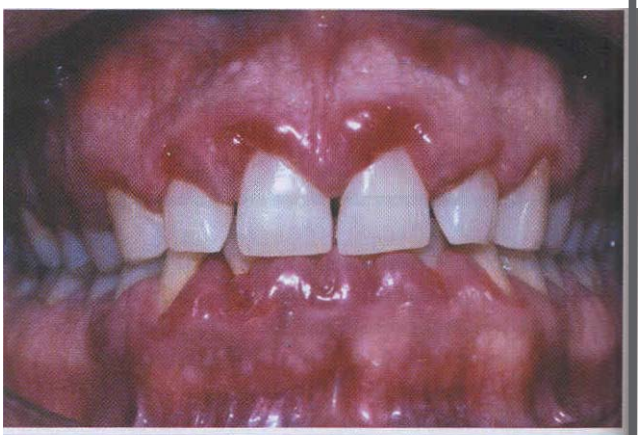

Figure 4-2 • Mouth breathing-related gingivitis. Slick, swollen, and red gingivitis of the anterior facial gingiva secondary to chronic mouth breathing.

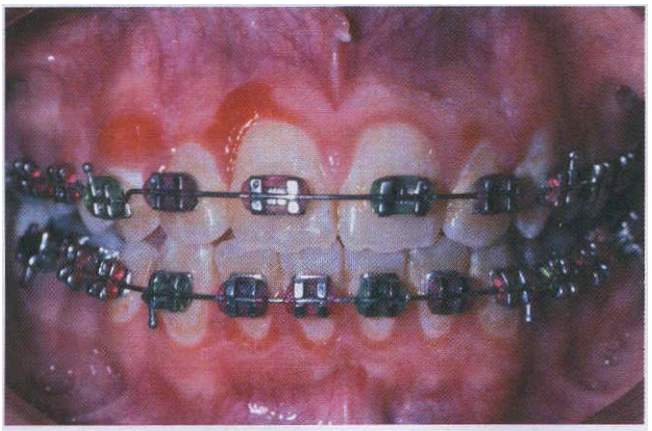

Figure 4-1 • Puberty gingivitis. Erythematous gingivitis that arose at time of initial menses and was slow to respond to local therapy.

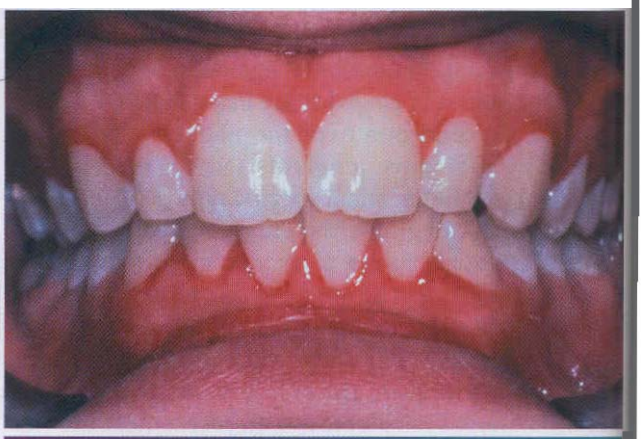

Figure 4-3 • Marginal gingivitis. Diffuse erythematous alteration of the free gingival margins.

significant enlargement because of edema or fibrosis. the process is termed chronic hyperplastic gingivitis (Figure 4-5). 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 447), can develop on the gingiva of patients with severe gingivitis (Figure 4-6).

Histopathologic Features

Incipient gingivitis demonstrates a light inflammatory infiltrate consisting of polymorphonuclear leukocytes that accumulate in the connective tissue adjacent to the sulcular epithelium. With progression. the infiltrate becomes more intense and demonstrates a mixture of lymphocytes. plasma cells. and acute inflammatory cells (Figure 4-7). 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. 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. Most self-administered plaque control programs are ineffective unless periodic professional reinforcement also is provided. A further discussion of dental plaque and its relationship to gingival inflammation is presented in the discussion of periodontitis (see page 150). Mechanical removal of dental plaque can be aided by the use of numerous chemical agents. such as chlorhexidine. essential oils (such as those contained in Listerinel. or triclosan-containing products. Typically. these chemopreventive

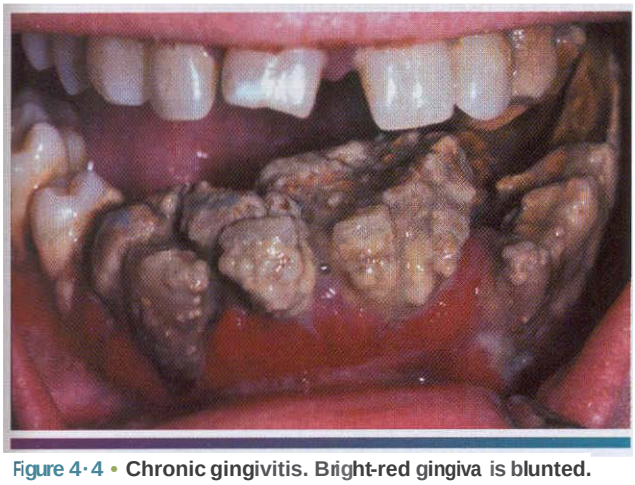

Figure 4-4 • Chronic gingivitis. Bright-red gingiva is blunted. receded. and hyperplastic secondary to a total lack of oral hygiene. Note the extensive calculus build-up.

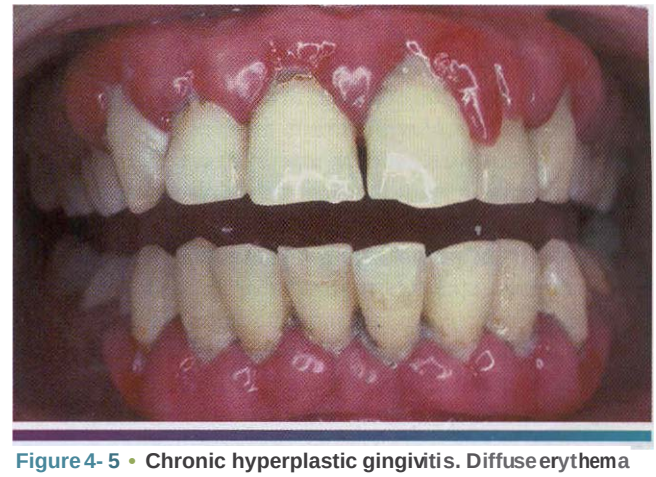

Figure 4-5 • Chronic hyperplastic gingivitis. Diffuse erythema and enlargement of marginal and papillary gingiva.

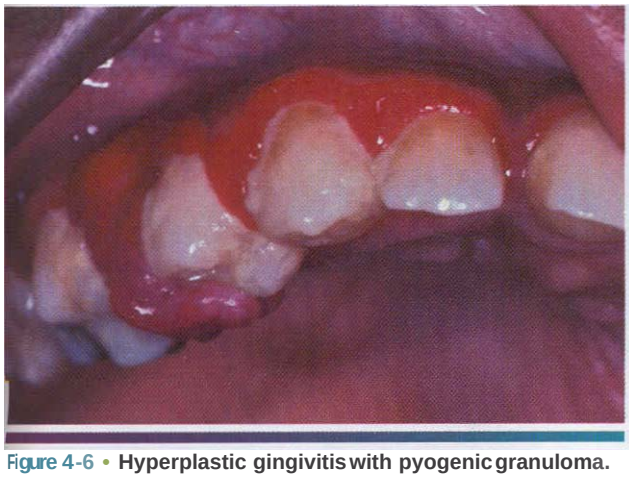

Figure 4-6 • Hyperplastic gingivitis with pyogenic granuloma. Diffuse erythematous enlargement of marginal and papillary gingiva with hemorrhagic. tumorlike proliferation (which arose during pregnancy) between the maxillary bicuspid and first molar.

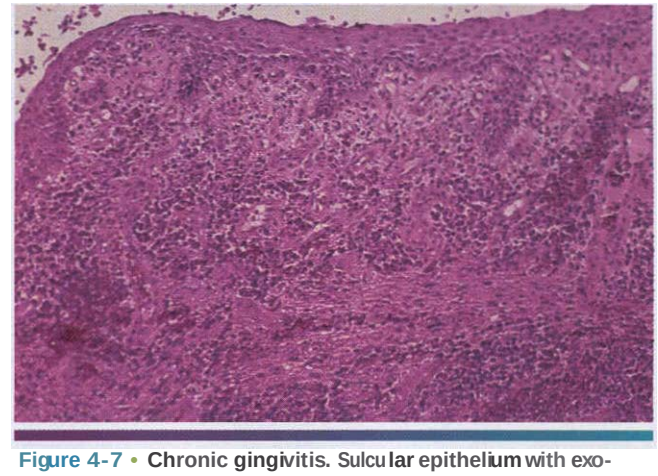

Figure 4-7 • Chronic gingivitis. Sulcular epithelium with exocytosis overlying connective tissue that contains inflammatory infiltrate consisting of lymphocytes, plasma cells. and polymorphonuclear leukocytes.

agents are reserved for those patients who do not respond appropriately to the augmented oral hygiene efforts. On occasion. hyperplastic and fibrotic *gingiva* may *have* to be recontoured surgically to allow total resolution of the pathosis after improvements in hygiene *have* been made. If the gingivitis does not *resolve* after improved plaque control and elimination of *obvious* contributing factors. the patient should be evaluated for underlying systemic disorders that could be contributing to the process.

NECROTIZING ULCERATIVE GINGIVITIS (VINCENT'S 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" (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*** *vincentit*, 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 species of ***Treponema,*** *Seienomonas*, and ***Fusobacterium.*** in addition to *Prevotella intetmedta*.

The mfectlon 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. Stress-related corticosteroids are thought to alter T4/T8 lymphocyte ratios and may cause the decreased neutrophilic chemotaxis and phagocytic response seen in patients with NUG. Stress-related epinephrine may result in localized ischemia. which predisposes the gingiva to NUG.

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

Immunocompromised status, especially that seen in association with acquired immunodeficiency syndrome (AIDS) (sec page 239) and infectious mononucleosis (see page 224). 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 (Figure 4-8). 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 arc usually noted. 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)** (Figure 4-9). If the necrotizing infection extends through the mucosa to the skin of the face, it is typically termed noma (cancrum oris) (sec page 178).

Several investigators *have* suggested that NUG. necrotizing ulcerative periodontitis. and necrotizing stomatitis are one disease process termed necrotizing gingivo-

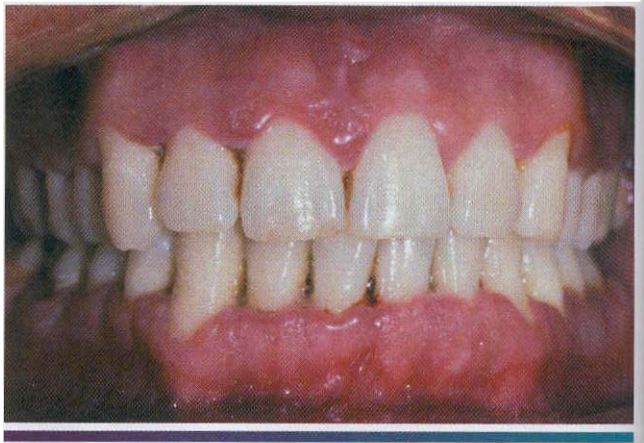

Figure 4-8 • Necrotizing ulcerative gingivitis. Gingiva demonstrates blunted interdental papillae that exhibit early mucosal necrosis.

stomatitis. Evidence presented by numerous authors has shown the diseases to be similar clinically. histopathologically, and bacteriologically, with the oniy differences being underlying systemic factors and anatomic extension of the necrosis.

Histopathologic Features

The histopathoiogic features of NUG are not specific. Typicaily, 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, there often is a loss of the typical surface keratinization. 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 debridement 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 debride the tissues adequately. Frequent rinses with chlorhexldine, warm saltwater, or diluted hydrogen peroxide are beneficial in increasing the therapeutic response. Antibiotics (e.g., metronidazole. tetracycline, penicillin, erythromycin) 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; soft, nutritious diet) often improves the ciinical 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 ciinician 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 241) 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 arc resistant to normal therapy,

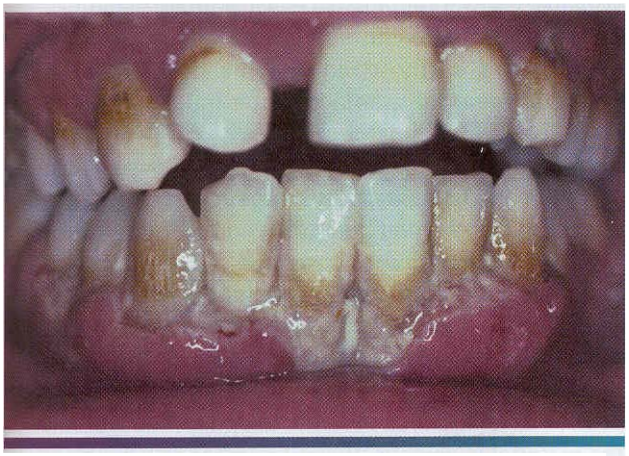

Figure 4·9 • Necrotizing ulcerative mucositis. Gingiva exhibits epithelial necrosis that has extended between the adjacent interdental papillae and apically to the alveolar mucosa junction.

PLASMA CEII GINGIVITIS (ATYPICAL GINGIVOSTOMATITIS)

A distinctive pattern of gingival alteration, 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 occasionaily reported,

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 (Figure 4-10). Extension onto the palate can occur, and edentulous areas typically exhibit less intense changes.

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 19705, 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.

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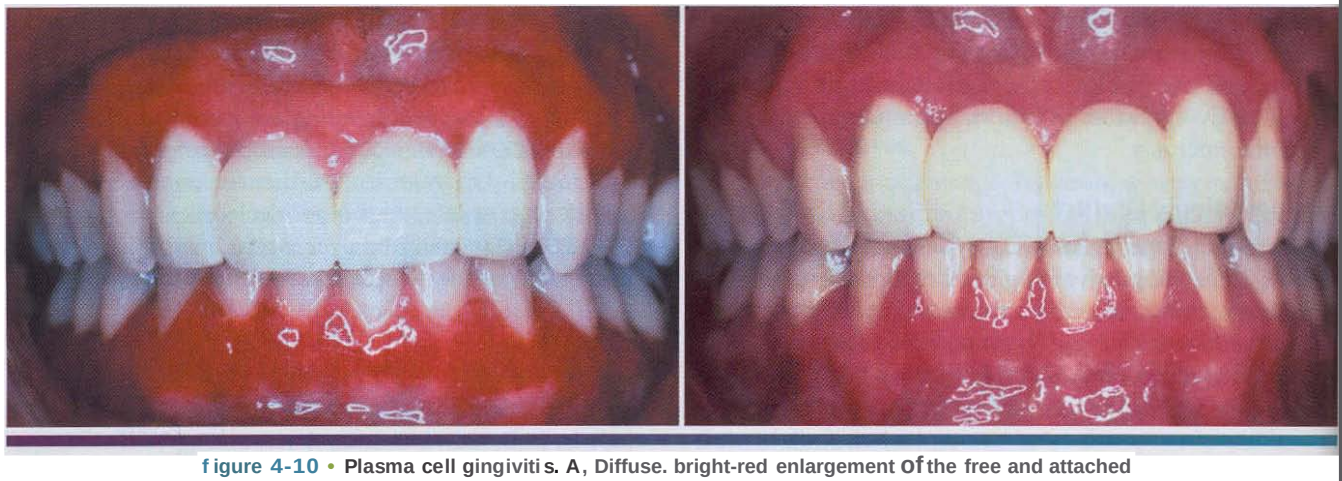

figure 4-10 • Plasma cell gingivitis. A, Diffuse. bright-red enlargement of the free and attached gingiva. B, Same patient as depicted in *A* after elimination of the inciting allergen.

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 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 (Figure 4-11). 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.

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, medications). Possible allergens should be eliminated in an attempt to discover the underlying cause. If an easy answer is not apparent. 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 discovery of unexplained granulomatous inflammation in a gingival biopsy specimen is termed granulomatous gingivitis and represents a diagnostic challenge for the pathologist, referring clinician. and patient. The pathologist must rule out histologically distinctive granulomatous diseases and specific granulomatous infectious processes (e.g.. foreign material. deep fungal infections. acid-fast bacteria) (see Chapters 5 and 6). The clinician must search for signs and symptoms of local and systemic granulomatous diseases (e.g.. Crohri's disease, sarcoidosis. chronic granulomatous disease, Wegener's granulomatosis) (see Chapters 9 and 17). and the patient must endure and pay for these evaluations. Even after a costly workup. some patients who have localized areas of granulomatous inflammation of the gingiva have no signs or symptoms of any of the previously mentioned disorders.

One group presented data that suggested some granulomatous or lichenoid gingival lesions may be caused by the introduction of dental materials into the connective tissue deep to the suleular epithelium. These lesions have been termed foreign-body gingivitis and are thought to arise when damage to the suleular epithelium during restorative or oral hygiene procedures allows the introduction of foreign material into the gingival tissues. When the material is obvious on light microscopy, the areas can be diagnosed easily as foreign-body reactions. in the majority of cases. the material was smaller than 1 um in diameter and was so fine that it could be overlooked easily.

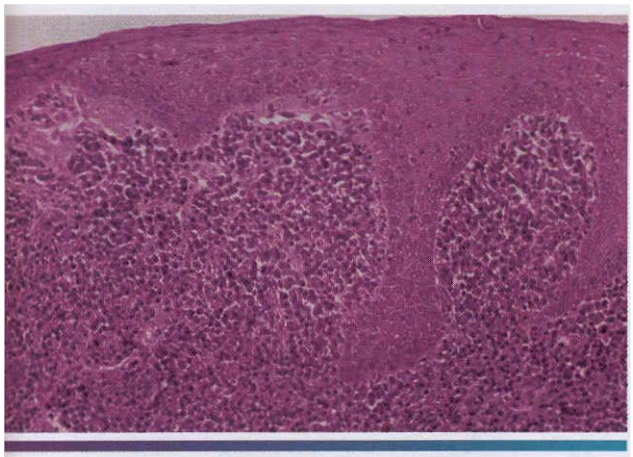

Figure 4-11 • Plasma cell gingivitis. Hyperplastic squamous epithelium exhibiting exocytosis and dense plasmacytic infiltrate of the underlying lamina propria.

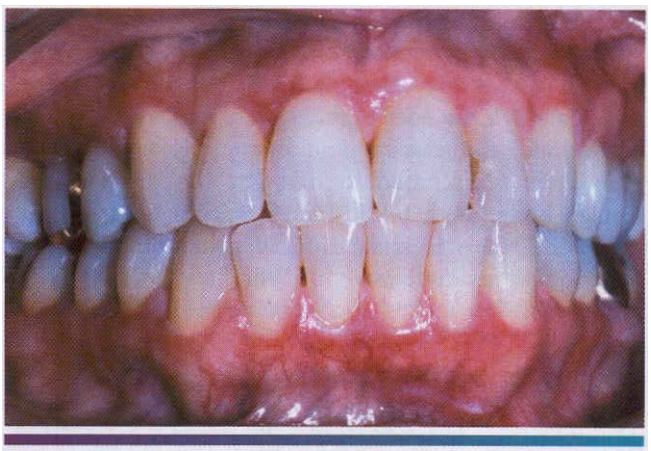

Figure 4-12 • Foreign-body gingivitis. Patient developed multifocal areas of tender erythematous gingiva that arose shortly after periodontal curettage and coronal polishing.

Energy-dispersive radiographic microanalysis revealed the most frequently discovered materials were silicon, aluminum, iron, and titanium, Less frequently discovered materials included nickel. silver, chromium, zinc, copper, lin, manganese, zirconium, gold, and mercury. Rarely, nondental foreign material was detected.

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 diameterless than 2 cm (Figure 4-12). The affected areas appear as red or red-and-white rnacules, which most frequently involve the interdental papillae. Extension may occur along the marginal gingiva or onto the attached gingiva (Figure 4-13). Pain or sensitivity is a common finding, and the lesions persist despite conventional therapy and rigorous oral hygiene. The process can be seen adjacent to clinically normal teeth or next to teeth with restorations.

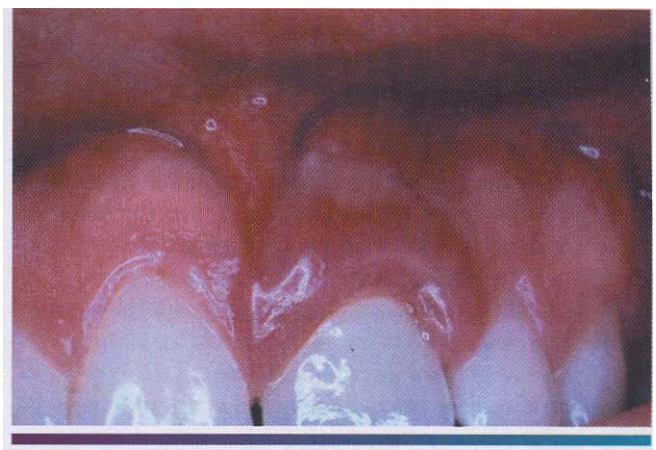

Figure 4-13 • Granulomatous gingivitis. localized enlarged and erythematous gingiva associated with the maxillary left central incisor. The alterations developed shortly after placement of a porcelain-fused-to-metal full crown and were not responsive to conservative local therapy. (Courtesy of Dr. Timothy L. Gutierrez.)

Hlstopathologtc Features

A biopsy specimen of granulomatous gingivitis demonstrates focal collections of histiocytes intermixed with an intense lymphocytic infiltrate (Figure 4-14). On occasion, well-formed histiocytic granulomas with multinucleated giant cells are seen, Special stains for organisms should be negative. If foreign material is detected, the clinician can render a diagnosis of a foreign-body reaction (rather than the more nonspecific term, granulomatous gingivitis). In some cases, however, the foreign material may be 100 fine to be detected.

In almost half of the reported cases of foreign-body gingivitis, granulomatous inflammation has not been present. Instead, a lichen planus-like reaction has been

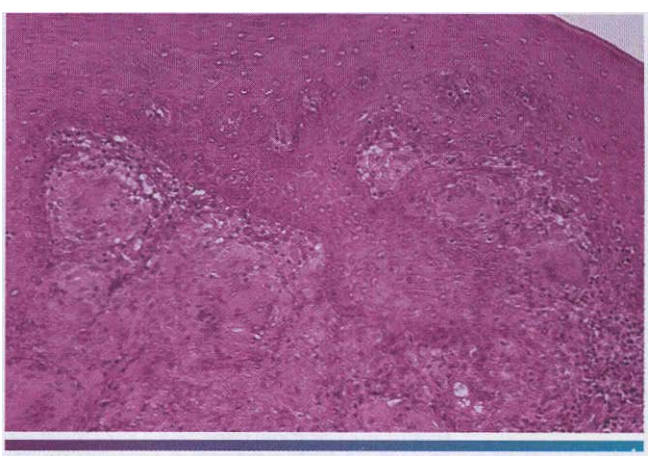

Figure 4-14 • Granulomatous gingivitis. Focal collection of histiocytes, lymphocytes, and multinucleated giant cells within the superficial lamina propria of the gingiva.

noted, with degeneration of the basal cell layer of the epithelium and a superficial bandlike infiltrate of lymphocytes (Figure 4-15). When lichenoid lesions are limited to the gingiva, do not migrate, and do not respond well to therapy, the clinical and histopathologic features should be reevaluated to rule out the possibility of foreign-body gingivitis. In many cases of foreign-body gingivitis, there is a mixture of granulomatous and lichenoid inflammation.

Treatment and Prognosis

When all the histopathologic and clinical investigations *have* been performed, the final differential diagnosis of granulomatous gingivitis is usually narrowed down to a localized form of orofacial granulomatosis (see page 294) or a foreign-body reaction. Without definitive demonstration of foreign material, a complete physical evaluation for diseases known to be associated with orofacial granulomatosis is mandatory.

Surgical excision of the affected tissue is the therapy of choice for those cases related to foreign material. There is strong evidence that the dental materials present in foreign-body gingivitis represent components of prophylaxis paste, other *abrasives,* or dental *restorative* materials. In an attempt to prevent future introduction of iatrogenic foreign material, it appears appropriate to follow the guidelines listed below:

- The clinician should use extreme care when trimming restorations or using abrasive instruments close to gingival margins.
- Air abrasion (i.e., sandblasting) should be used cautiously.
- 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 despite cautious dental care should be classified as having orofacial granulomatosis and managed accordingly.

DESQUAMATIVE GINGIVITIS

Most clinicians use the term desquamative gingivitis to describe gingival epithelium that spontaneously sloughs or can be removed with minor manipulation. The process most likely represents a manifestation of one of several different *vesiculoerosive* diseases. Histopathologic and immunologic investigations of this condition *reveal* that most patients exhibit features that are diagnostic of pemphigoid or lichen planus. Other diagnoses that are made less frequently include linear IgA disease, pemphigus vulgaris, epidermolysis bullosa acquisita, systemic lupus erythematosus, chronic ulcerative stomatitis, and paraneoplastic pemphigus. (For a complete discussion of these entities, see Chapter 16.)

In some cases, the process demonstrates a subepithelial separation, but the immunofluorescent assay *gives negative* results and does not support any of the dermatologic disorders previously discussed. The negative results may be caused by improper sampling, laboratory error, or low *levels* of tissue-bound autoantibodies that are below the *level* of testing sensitivity. *Several* investigators *believe* this process may represent a hormone-mediated desquamative gingivitis. Interestingly, human gingiva has been shown to metabolize estrogens and to contain specific high-affinity estrogen receptors.

Another group has suggested that desquamative lesions localized to the *gingiva* may represent an abnormal local immune response to certain plaque substances. Frequently, the lesions are related topographically to plaque;

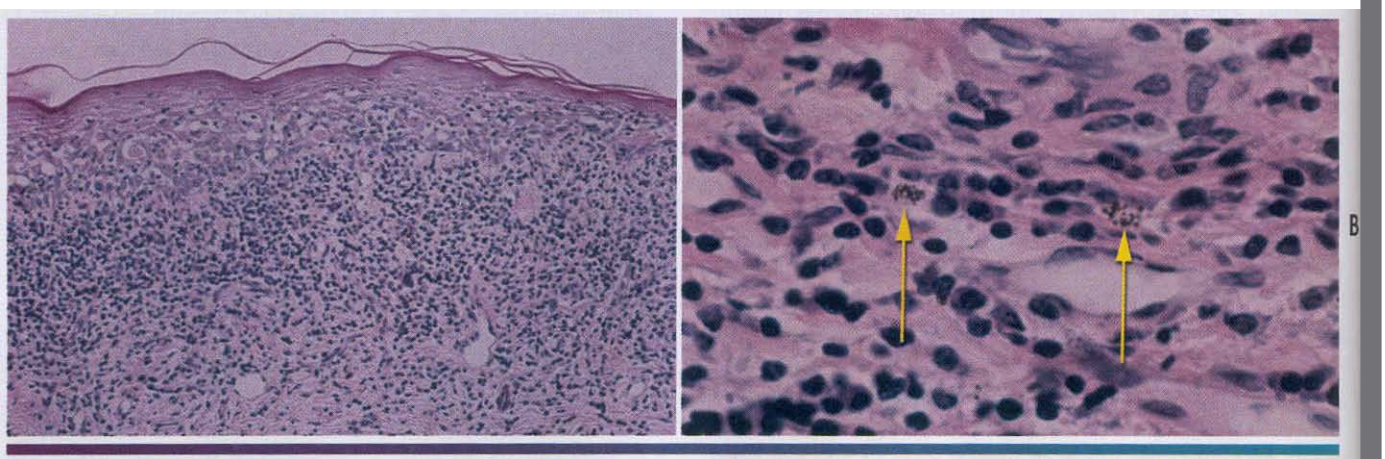

Figure 4-15 • Foreign-body gingivitis. A, Lichen planus-like reaction with exocytosis, degeneration of the basal cell layer, and a superficial bandlike infiltrate of lymphocytes. B, High-power image demonstrating focal clusters of foreign material *(arrows)*. This biopsy was obtained from the patient depicted in Figure 4-12.

Ihis group's investigation revealed a statistically significant improvement when affected patients were treated wlthdoxycychne monohydrate. Wh ether this is due to the antibacterial or antii nflammatory activity of tetracyclines has not been determined. Regardless of the mechanism. ithas been shown that improved oral hygiene can decrease the severity of the lesions in patients with desquamative gingivitis.

In conclusion. there is a form of chronic mucosal desquamation that is limited to the gingiva. Wh ether this represents **a separate entity. a *forme fruste* variation of one of the chronic dermatologic vesiculoerosive processes, or a mixture of several different diseases has yet** to be definitively determined. Until the controversy has been resolved. the term desquamative gingivitis should be used only as a clinical description and not as a definitive diagnosis. With rare exceptions. almost all cases will be able 10 be diagnosed definitively as one of the known vesiculoeroslve **diseases.**

Clinical Features

Most people who are affected with desquamative gingivitis are older than age 40, with a significant female predominance (up to 80% in those with negative immunofluorescent findings). The process demonstrates **a gradual onset in which the involvement is limited initially;** however. with time. it spreads to affect large portions of the gingiva. By definition. the process is limited 10 the gingiva. The facial surface is involved more frequently than the lingual gingiva. Involvement may be multifocal or may demonstrate a generalized pattern.

Affected sites present as areas of smooth erythema in which there is a loss of normal stippling (Figure 4-16). Withprogression, blister formation. spontaneous desquamation. **or zones of erosion can be found. If blisters are present,** they are filled with clear fluid or can be contaminated with blood. Manipulation of the affected erythematous surface epithelium with a cotton swab, gauze pad. **or compressed air often can cause desquamation. Yellowish fibrinopurulent membranes cover areas of frank** erosion. and significant pain is usually present.

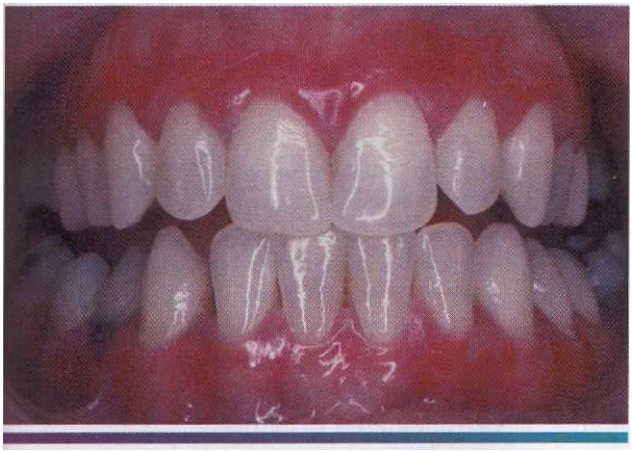

figure 4-16 • **Desquamative gingivitis. Diffuse, smooth. red and painful gingiva.**

Histopathologic Features

The histopathologic features and immunofluorescent findings of desquamative gingivitis are variable, although most patients report features diagnostic of lichen planus or pemphigoid (see Chapter 16).

Treatment and Prognosis

An incisional biopsy specimen should be submitted for routine histopathologic examination, often followed by a specimen for immunofluorescent studies. The biopsy incision should extend from the adjacent normal epithelium into the area of separation. The type of immuno**fluorescent investigation necessary for definitive diag**nosis is guided by the light microscopic findings. A thorough evaluation of all dermatologic and mucosal surfaces should be performed to rule out the possibility of other occult sites of involvement. Before definitive therapy. the dentition should be cleaned thoroughly (and the patient should be taught to maintain excellent oral hygiene). A course of doxycycline monohydrate can be prescribed in an attempt to reduce the degree of mucosal **inflammation before immunosuppressive therapy.**

Currently. definitive therapy is guided by the histopathologic and immunologic diagnoses. As described in Chapter 16, many patients respond well to topical cor**ticosteroids. Patients whose conditions are resistant to** corticosteroids often respond to dapsone or sulfapyridine. In cases that demonstrate negative immunofluorescent findings and are not diagnostic for any of the specific dermatologic erosive disorders, therapy with estrogens has been attempted with equivocal results.

DRUG-RELATED GINGIVAL HYPERPLASIA

Drug-related gingival hyperplasia refers to an abnormal growth of the gingival tissues secondary to use of a sys**temic medication. The term is a misnomer because nei**ther the epithelium nor the cells within the connective tissue exhibit either hyperplasia or hypertrophy. The increased gingival size is due to the production of an increased amount of extracellular matrix, predominantly collagen. Therefore, several authors designate the alter**ation as medication-associated gingival enlargement or** gingival overgrowth.

A list of medications reported to be associated with gingival hyperplasia is provided in Box 4-2. *at* these **medications, a strong association has been noted only** with cyclosportnc (Figure 4-17). phenytoin, and nifedipine (Figure 4-18). In the remainder, the prevalence is

80x 4·2 *Medications Reported to be Associated with Gingival Hyperplasia*

1. Anticonvulsants
   - Carbamazepine
   - Ethosuximide
   - Ethotoin
   - Felbamate
   - Mephenytoin
   - Methsuximide
   - Phenobarbital
   - Phensuximide
   - Phenytoin
   - Primidone
   - Sodium valproate
2. Calcium channel blockers
   - Amlodipine
   - Bepridil
   - Diltiazem
   - Felodipine
   - Nicardipine
   - Nifedipine
   - Nimodipine
   - Nitrendipine
   - Verapamil
3. Cyclosporine
4. Erythromycin
5. Oral contraceptives

much lower or the association is weak or anecdotal. As new drugs have been developed. the list of offending medications has grown. When two drugs known to cause gingival hyperplasia are used concurrently. the severity of of the hyperplasia often is increased (Figure 4-19).

The prevalence of these hyperplasias varies widely: however, as reported in a critical review of the literature, the prevalence related to use of phenytoin is approximately 50%. Cyclosporine and nifedipine produce significant changes in about 25% of patients treated. Whether there is a relationship between the dose and the risk or severity of the hyperplasia is controversial.

The degree of gingival enlargement appears to be related to the patient's susceptibility and the level of oral hygiene. The correlation between gingival hyperplasia and poor oral hygiene is positive and significant. In observations of patients with excellent oral hygiene. gingival overgrowth (as ascertained by pseudopocket formarten) 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 arc 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.

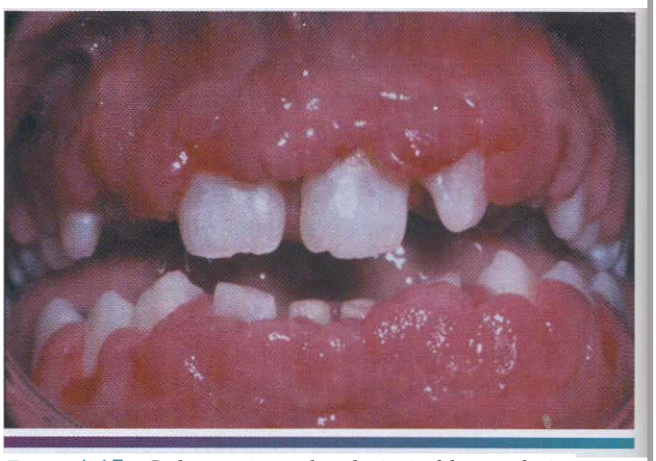

Figure 4-17 . Cyclosporine-related gingival hyperplasia. Diffuse. erythematous, and fibrotic gingival hyperplasia.

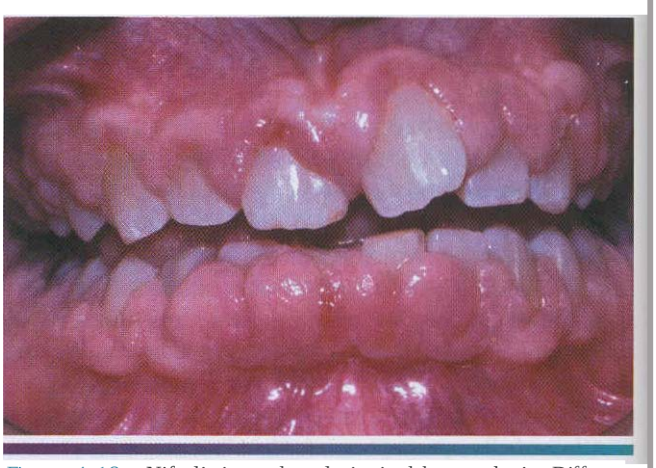

Figure 4-18 • Nifedipine-related gingival hyperplasia. Diffuse, fibrotic gingival hyperplasia after 1 month of intensive oral hygiene. Significant erythema. edema. and increased enlargement were present before intervention.

Clinical Features

Because phenytoin is used most often by young patients. 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,

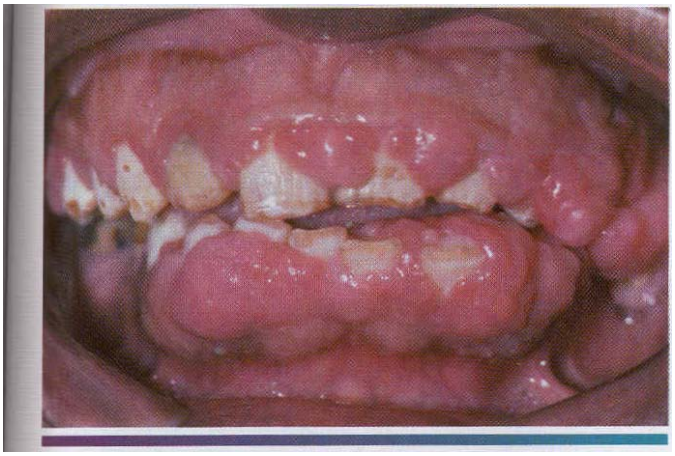

figure 4-19 • Cyclosporine- and nifedipine-related gingival hyperplasia. Dramatic gingival hyperplasia in a patient using two drugs associated with gingival enlargement.

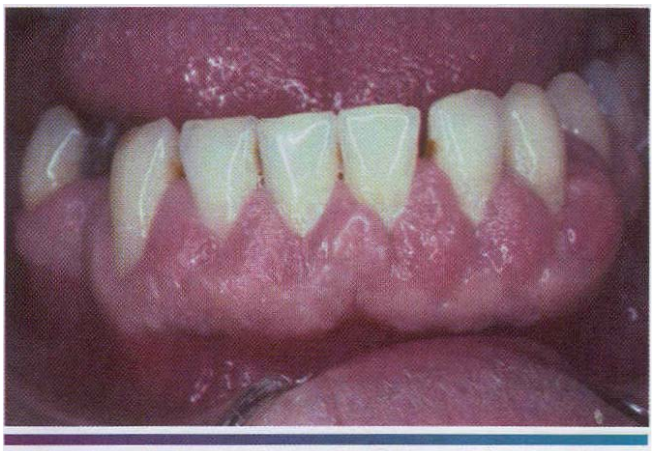

Figure 4-20 • Mild phenytoin-related gingival hyperplasia. Gingival enlargement present predominantly in the interdental papillae.

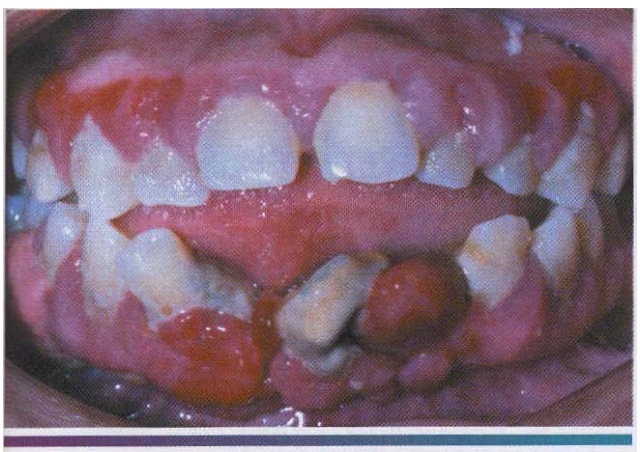

Figure 4-21 • Phenytoin-related gingival hyperplasia. Significant erythematous gingival hyperplasia is covering portions of the crowns of numerous teeth.

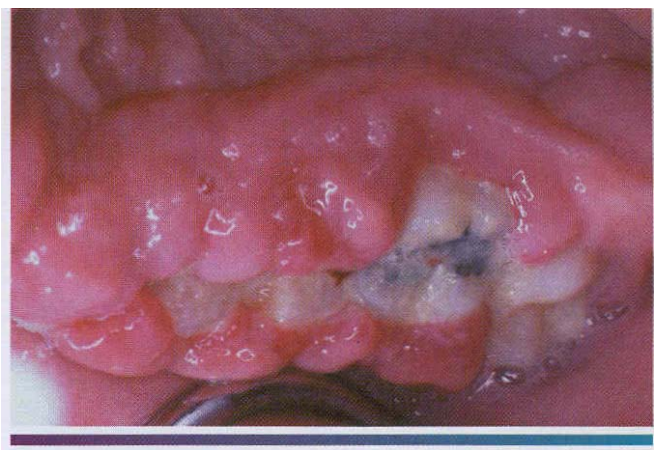

Figure 4-22 • Phenytoin-related gingival hyperplasia. Significant gingival hyperplasia almost totally covers the crowns of the posterior maxillary dentition. (Courtesy of Dr. Ann Drummond and Dr. Timothy Johnson.)

After 1 to 3 months of drug use, the enlargements originate in the interdental papillae and spread across the tooth surfaces (Figure 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 (Figures 4-21 and 4-22). Extension lingually and occlusally can interfere with speech and mastication. In one report, significant lingual expansion of the gingiva resulted in tongue displacement and respiratory distress. Edentulous areas are generally not affected, but significant hyperplasia under poorly maintained dentures and around implants has been noted (Figure 4-23).

Nongingival soft-tissue growths that resemble pyogenic granulomas have been reported in allogenic bone marrow transplant recipients who are receiving cyclosporine for graft-versus-host disease (Figure 4-24). It is thought that cyclosporine triggers the proliferations in areas chronically inflamed by graft-versus-host disease.

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 affected gingiva often becomes dark-red and edematous, with a surface that is friable, bleeds easily, and is occasionally ulcerated. Pyogenic granuloma-like enlargements are occasionally seen in the presence of heavy inflammation.

Histopathologic Features

The exact histopathologic changes that occur in people with drug-induced gingival hyperplasia are difficult to ascertain because of *variations* in the techniques of

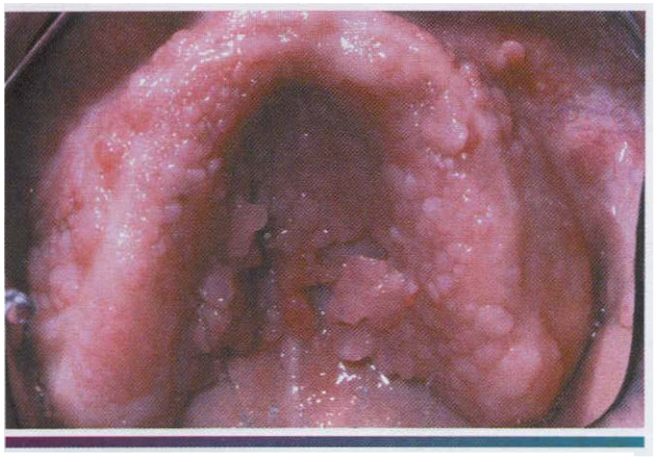

Figure 4-23 • Phenytoin-related palatal hyperplasia. Extensive hyperplasia of palatal mucosa in an edentulous patient with poor denture hygiene.

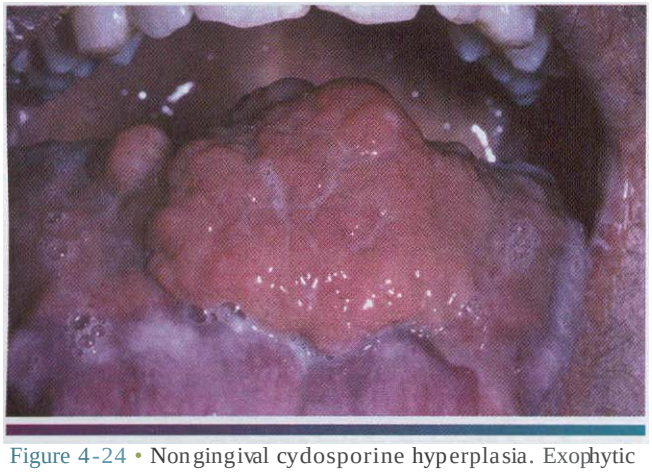

Figure 4-24 • Nongingival cydosporine hyperplasia. Exophytic and granulomatous-appearing mass of the dorsal surface of the tongue that arose in a bone marrow transplant patient who was receiving cyclosporine for graft-versus-host disease.

investigation. In spite of this, most controlled microscopic examinations of hyperplastic gingival tissues removed from lesions caused by phenytoin or the dihydropyridines reveal redundant tissue of apparently normal composition. Those cases related to cyclosporinc use demonstrate an increased amount of collagen per unit volume, with a normal density of fibroblasts.

The overlying surface epithelium may demonstrate elongation of the rete ridges. with long extensions into the underlying iamina propria. 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 may be beneficial.If the patient's response allows drug substitution, cyclosporine can been replaced with tacrolimus. phenytoin with carbamazepine or valproic acid, and nifedipine with one of many dihydropyridines not associated strongly with gingival hyperplasia. If the drug use is mandatory. professional cleaning, frequent reevaluations. and home plaque control are important. Antiplaque agents. such as chlorhcxidtne, 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 cyclosporinc-rclatcd gingival hyperplasia after a short course of metronidazole or azithromycin. Although the mechanism is not clear, it appears these antibiotics can inhibit proliferation of collagen fibers along with their antimicrobial abilities. It is thought azithromycin aiso may be beneficial in resolving gingival hyperplasia related to nifedipine and phenytoin.

if all other interventions fail to achieve significant resolution, eradication of the excess gingival tissues remains the treatment of choice. This can be achieved by gin*givectomy,* by chemosurgical techniques. by means of electrosurgery. or by use of a carbon dioxide laser. Histopathologic examination of all excised tissue is mandatory to confirm the diagnosis. With subsequent rigorous oral hygiene, recurrence typically is not a problem.

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 444 and 573).

Clinical Features

Gingival fibromatosis may be familial or idiopathic. The familial variations may occur as an isolated finding or in association with one of several hereditary syndromes (e.g., Zimmermann-Laband, Murray-Purctic-Drescher, Rutherfurd, multiple hamartoma [sec page 6591. Cross syndrome). Other findings sometimes seen in conjunction with gingival fibromatosis include hypertrichosis (Figure 4-25). epilepsy, mental retardation, sensorineural deafness, hypothyroidism, chondrodystrophia, and growth hormone deficiency.

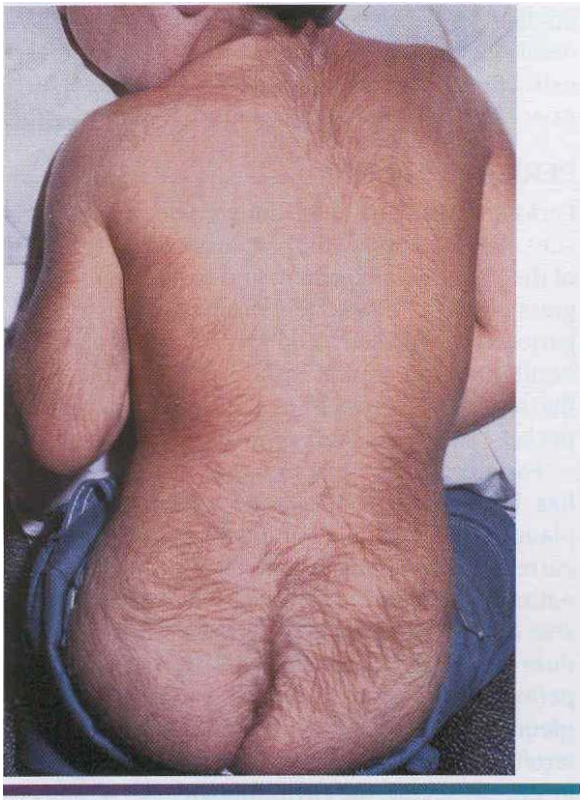

Figure 4-25 • **Hypertrichosis in association with gingival fibromatosis.** Dramatically increased body hair of the back and buttocks in a patient with gingival fibromatosis. (Courtesy of Dr. George Blozis.)

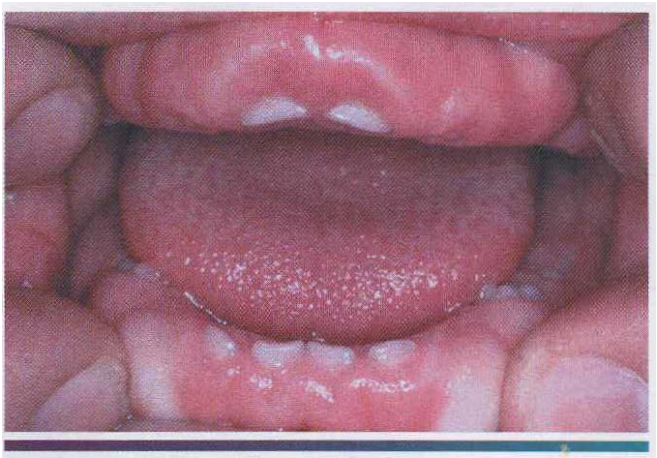

figure 4-26 • **Gingival fibromatosis. A young child with cheeks retracted by the parent. Note erythematous gingival hyperplasia arising in association with erupting deciduous dentition. (Courtesy of Dr. George Blozis.)**

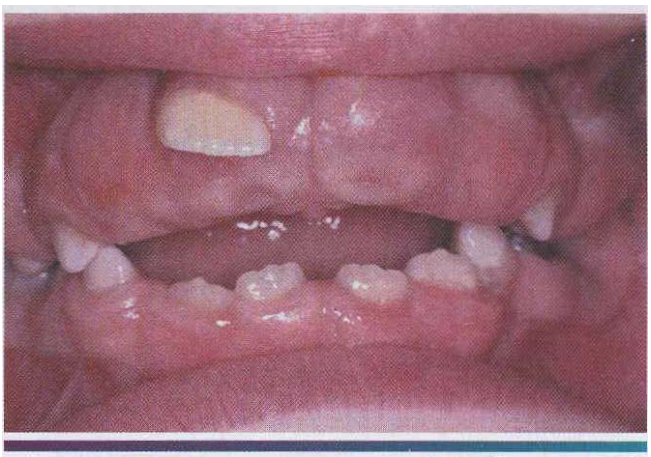

figure 4-27 . **Gingival fibromatosis. Significant fibrotic gingival hyperplasia with resultant delayed eruption of numerous teeth. (From Neville BW, Damm DD, White OK, Waldron CA: *Color atlas of clinical oral pathology.* Philadelphia, 1991, Lea & Febiger.)**

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. Even in cases with similar patterns of inheritance, genetic heterogeneity of gingival fibromatosis has been noted and confirms that this alteration represents a group of clinically similar disorders.

In most instances, the enlargement begins before age 20 and often is correlated with the eruption of the deciduous or permanent teeth (Figure 4-26). Most investigators believe that the presence of teeth probably is necessary for the condition to occur. After the process has begun, it can overgrow the associated teeth and even interfere with lip closure. Failure or delay in eruption of subsequent teeth may be evident (Figure 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 bilaterally symmetric enlargements that extend posteriorly and palatally from the posterior alveolar ridges (Figure 4-28).

The gingiva is firm, normal in color, and *covered* by a surface that is smooth or finely stippled. In older patients, the surface may develop numerous papillary projections.

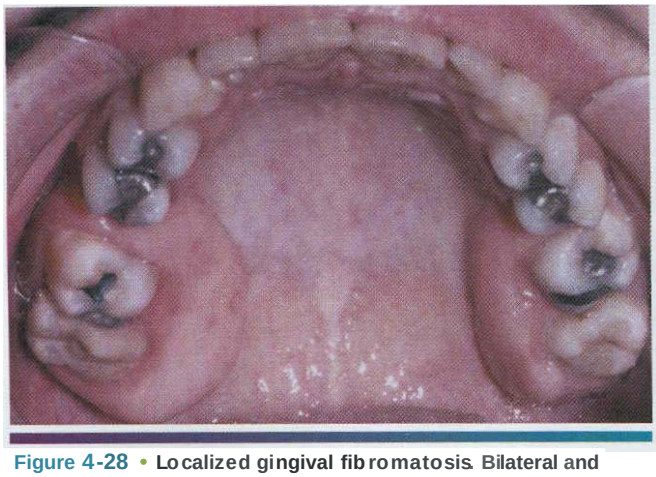

Figure 4-28 • Localized gingival fibromatosis. Bilateral and symmetric fibrotic enlargements of the palatal surfaces of the posterior maxillary alveolar ridges.

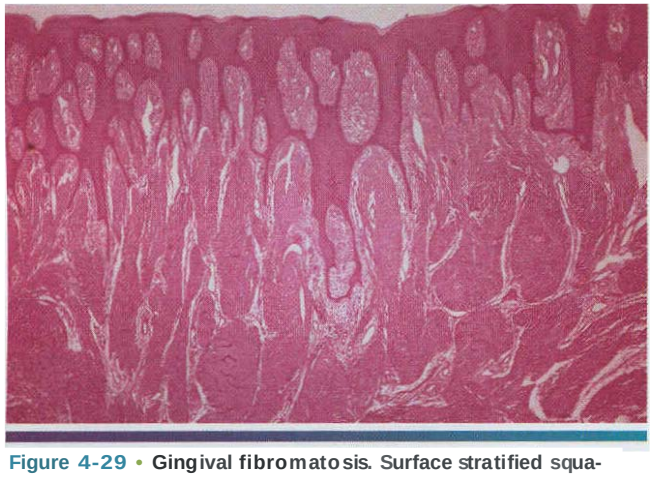

Figure 4-29 • Gingival fibromatosis. Surface stratified squamous epithelium exhibiting long, thin rete ridges and underlying dense, fibrous connective tissue.

The frenular attachments may appear to divide the gingival tissues of the alveolar ridge into lobules.

Histopathologic Features

The enlargements of gingival fibromatosis consist of dense hypocellular, hypovascular collagenous tissue, which forms numerous interlacing bundles that appear to run in all directions. The surface epithelium often exhibits long, thin rete ridges that extend deeply into the underlying fibrous connective tissue (Figure 4-29). Inflammation is absent to mild, and dystrophic calcification sometimes is seen. Electron microscopic examination demonstrates a mixture of both fibroblasts and myofibroblast-like cells.

Treatment and Prognosis

Conservative treatment consists of gingivectomy in conjunction with a rigorous program of oral hygiene. Follow-up is recommended because there is a tendency for recurrence within a few years. In severe cases, selective extraction of teeth (and gingivectomy) often is 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, current *evidence* suggests that dental plaque is part of the natural human microflora. In some patients with extensive dental plaque, destructive lesions of the periodontium do not develop. Many investigators now believe that periodontitis occurs not from the mere presence of dental plaque but as a result of shifts in the proportions of bacterial species in the plaque, possibly related to changes in the *dentogingival environment* (e.g., a soft diet or a highly fermentable carbohydrate content diet).

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, such as actinomycetes and streptococci; plaque within areas of active periodontitis contains anaerobic and microaerophilic gram-negative flora. Of the more than 300 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 predominantly with *Actinobacillus actinomycetemcomitans*, *Bacteroides [otsythus*, *Porphyromonas gingivalis*, and *Prevotella intermcdia*, in addition to a handful of other organisms that occasionally can be involved in active periodontitis.

The pathogenic organisms exist in an organized community termed a biofHm. Bacteria growing in biofilms relatively are protected from normal host defenses and exhibit an increased resistance to locally or systemically administered antibiotics. Lipopolysaccharides released from the biofilms are thought to trigger release of catabolic inflammatory mediators that lead to the loss of attachment.

The presence of pathogenic bacteria is essential but insufficient to produce periodontitis. Other host factors such as smoking, diabetes, and hereditary predisposition are important determinants of the presence and *severity* of significant periodontal disease. Although

Box 4-3 elllSsifimlioll of Periodontltls

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
5. Abscesses of the periodontium
   - Gingival abscess
   - Periodontal abscess
   - Pericoronal abscess
6. Periodontitis associated with endodontic lesions

Box 4-4 Systemic Disorders with Premature Attachment Loss

1. Acatalasia
2. Acrodynia
3. Acquired immunodeficiency syndrome
4. Blood dyscrasias
   + leukemia
   + Agranulocytosis
   + Cyclic neutropenia
5. Crohn's disease
6. Diabetes mellitus
7. Dyskeratosis congenita
8. Ehlers-Danlos syndrome, types IV and VIII
9. Glycogen storage disease
10. Hemochromatosis
11. Hypophosphatasia
12. langerhans cell disease
13. leukocyte dysfunctions with associated extraoral infections
14. Oxalosis
15. Papllion-Lefevre syndrome
16. Sarcoidosis
17. Trisomy 21

mild-to-moderate periodontitis is present in the majority of adults, only 5% to 20% of the population develops severe, generalized disease.

The classification of periodontitis, as delineated by the American Academy of Periodontology, is listed in Box 4-3. 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 4-4 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 t40). This form has been correlated with aggressive invasion by a number of spirochetes and P. *intetmedia.*

Clinical and Radiographic Features

Chronic periodontitis. wtth the decline in caries, chronic periodontitis has become the primary cause of tooth loss in patients older than 35 years of age. A national survey found that 44% of adults in the United States had attachment loss of 3 rnrn or more in at least one site. The disorder demonstrates an increased prevalence in males, although much of this effect is thought to be related to poorer oral hygiene and dental-visit behavior. In addition, there Is an increased prevalence associated with:

- Advancing age
- Smoking
- Diabetes mellitus
- Lower socioeconomic level

Conversely, it appears the presence of significant periodontitis may place patients at risk for an increased prevalence or greater severity of certain medical disorders. Some evidence links periodontitis with an increased risk for coronary artery disease, stroke, progressive diabetes mellitus, and delivery of low-birth weight babies.

In chronic periodontitis, no abnormalities of the immune system 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 the elderly reflects a lifetime 01 disease accumulation rather than an age-specific disease.

In patients with periodontitis, gingivitis is present and precedes the development of significant periodontal lesions. Blunting and apical positioning of the gingival margins are typically present (Figure 4-30). Periodontal disease is present when a loss of attachment can be demonstrated through the use of a periodontal probe. In

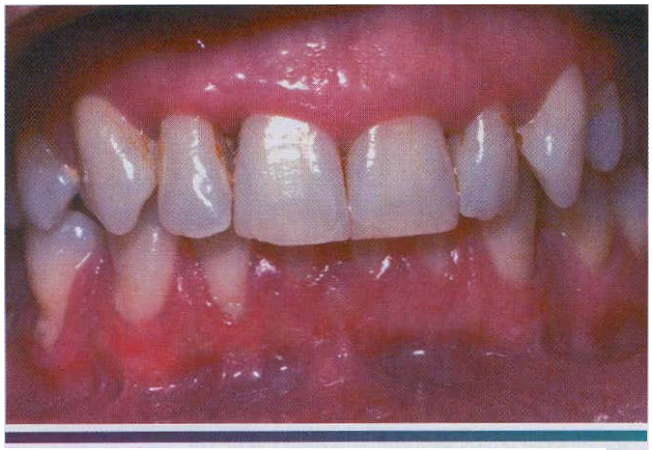

Figure 4-30 • **Adult periodontitis. Diffuse gingival erythema with blunting and apical positioning of the gingival margins.** (Courtesy of D, Samuel Jasper.)

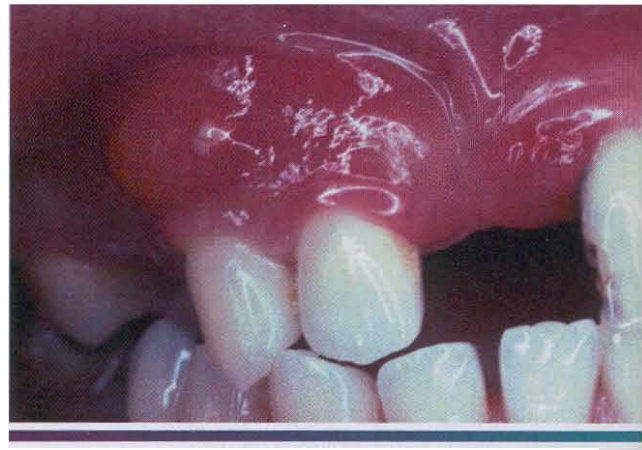

Figure 4-32 • **Periodontal abscess. Localized erythematous gingival enlargement with central purulent drainage.**

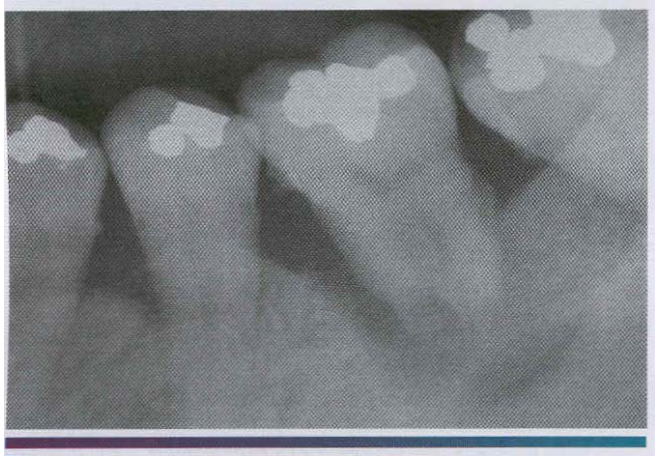

Figure 4-31 • **Advanced adult periodontitis. Extensive loss of bone support of the posterior mandibular dentition. Significant mobility of the first molar was noted.**

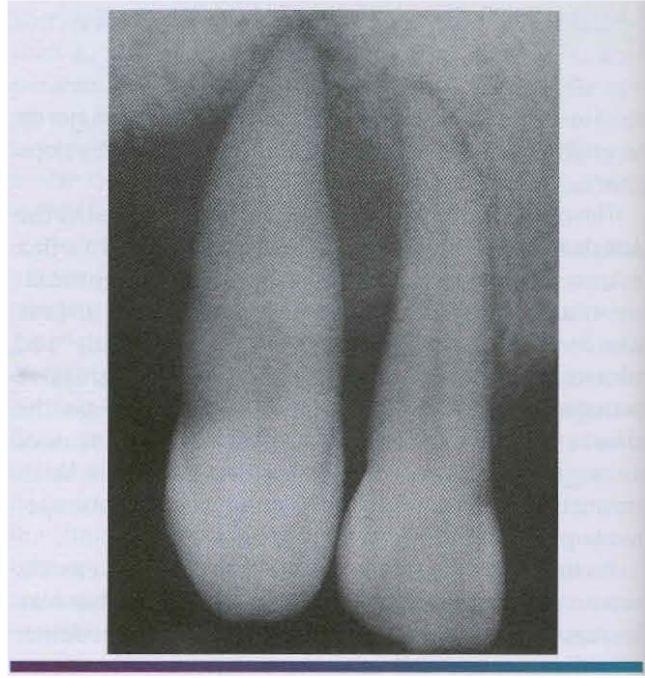

Figure 4-33 • **Periodontal abscess. Same patient as depicted in Figure 4-32. Note extensive loss of bone support associated with the maxillary cuspid.**

the absence of significant gingival hyperplasia. a measurement of pockets greater than 3 to 4 mm indicates destruction of the periodontal ligament and resorption of adjacent alveolar bone. High-quality dental radiographs exhibit a decreased vertical height of the bone surrounding the affected teeth. With advanced bone loss. tooth mobility is present (Figure 4-311.

Necrotizing** ulcerative **periodontitis. **Necrotizing** ulcerative periodontitis presents similarly to NUG (see page 140). 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. 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 (Figures 4-32 and 4-33) often arises in a preexisting periodontal lesion and is usually precipitated by alterations in the subgingival flora, host resistance. or both. Factors frequcntly **associated with abscess formation are closure of the entrance into a periodontal pocket. furcation involvement. or diabetes. In addition. systemic antibiotics** given for non-oral infections can lead to superinfection by opportunistic organisms. resulting in development of a periodontal abscess. Other factors involved less fre-

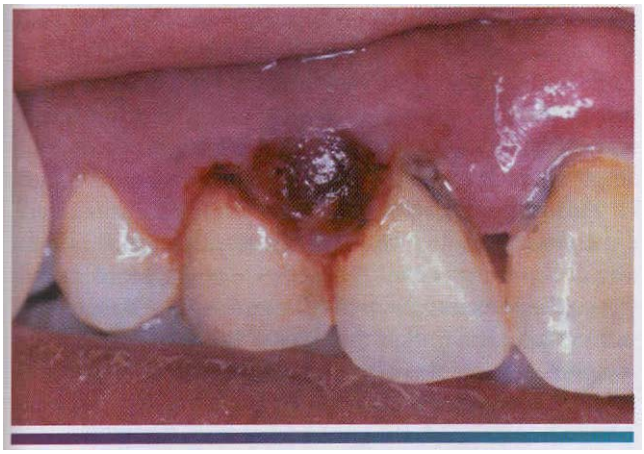

Figure 4-34 • **Periodontal abscess. Dark-red and hemorrhagic enlargement of the interdental papilla between the maxillary right lateral incisor and cuspid.**

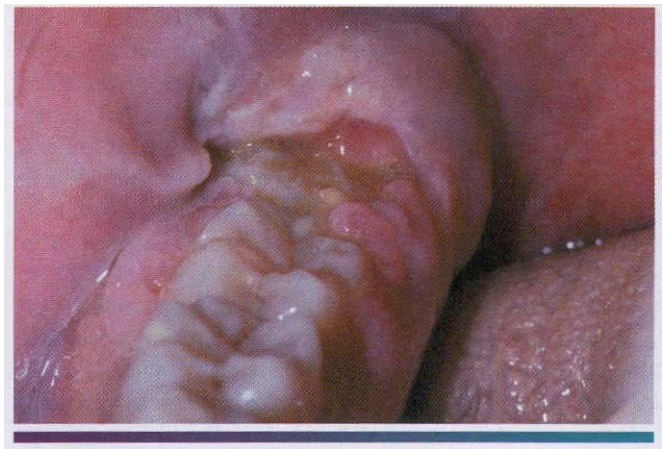

figure 4-35 • **Pericoronitis. Painful erythematous enlargement of the soft tissues overlying the crown of the partially erupted right mandibular third molar.**

quently arc trauma and anatomic dental anomalies, such as enamel pearls (see page 82) and dens invaginatus (see page 80). Most cases arise In adults: periodontal abscesses in children 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 (Figure 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)

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.**

Pericoronitis. **A similar inflammatory lesion known as** pericoronitis can develop around impacted or partially erupted teeth when food debris and bacteria are present beneath the gingival flap overlying the crown. These gingival flaps *can* exhibit long periods of chronic inflammation without symptoms. **If** the debris and bacteria become entrapped deep within the gingival flap. 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 (Figure 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

PeriodoJltitis. Initial **attention must be directed toward** elimination of any existing risk factors. Even with appropriate treatment and improved oral hygiene. many patients fail to respond to therapy unless certain factors (e.g.. smoking. inadequately controlled diabetes) are eliminated. 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 debridement. 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, antibiotics are not generally used except in patients who do not respond to conventional therapy. Inappropriate use of antibiotics can lead to overgrowth of potentially pathogenic organisms and development of bacterial drug resistance. When required, tetracycline or metronidazole are used most frequently. The choice of antibiotic always should be guided by microbiologic analysis with susceptibility testing. Several studies also suggest that nonsteroidal antiinflammatory drugs (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 antibiotics are placed directly into sites of refractory periodontitis and consist of gels, ointments, nonresorbable fibers, and resorbable polymers. These antibiotics represent an adjunct to scaling and root planing and should be limited to sites that are resistant to conventional therapy alone. Although short-term benefits have been demonstrated, many investigations *have* revealed limited long-term positive effects when compared with scaling and root planing without antibiotics.

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. Professional scaling and root planing modify the composition of the plaque microflora so that pathogenic plaques are converted to those with bacterial types normally found in healthy mouths. 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.

Investigators are beginning to discover genetic markers for those patients that are at risk for developing severe, progressive periodontitis. Many envision a future in which patients are evaluated for the presence of these markers, with susceptible individuals monitored closely for early colonization by periodontal pathogens. If colonization is detected, it could be eliminated easily and inexpensively.

Necrotizing ***ulcerative*** *periodontitis,* Once any underlying influence (e.g., immunosuppression, malnutrition) has been resolved, necrotizing ulcerative periodontitis often responds well to effective oral hygiene measures and administration of systemic antibiotics (e.g., metronidazole).

Periodontal *abscess.* A periodontal abscess is treated by drainage through the sulcus or by an incision through the overlying mucosa. Penicillin or other antibiotics are prescribed when a fever is present. Analgesics 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 the 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 antibiotics 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, the overlying gingival flap is removed surgically, 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. Many argued that this pattern of periodontitis can occur at any age and is not restricted to patients under the age of 35 years. It was agreed that an appropriate classification system should not be based on age but should consider primarily the clinical, radiographic, historical, and laboratory findings.

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 syndrome. This disease cur-

rently 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 4-4) should be ruled out before the definitive diagnosis is made.

In contrast to chronic disease, aggressive periodontitis appears to be correlated with one or more deficiencies in the immune response, rather than with inappropriate accumulations of plaque and calculus. In addition, a genetic predisposition is suggested in many cases. A review of numerous investigations into the immunology and genetics of these diseases revealed conflicting results, which may be due to the multifactorial nature of aggressive periodontitis. In addition, it is believed that aggressive periodontitis represents a number of different pathoses that have been grouped together because of similar clinical presentations. Suspected pathogens that are commonly found in these diseases include *A. actinamycetemcomitans*, *P. intermedia*, *P. gingivalis*, and a variety of other less common organisms. The response to therapy often hinges on the successful elimination of these organisms.

The majority of patients with aggressive periodontitis have a demonstrable neutrophil dysfunction but without systemic manifestations. In the localized variant, a number of affected patients demonstrate a specific defect of bactericidal activity toward *A. actinomycetemcomitans*. 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.

Clinical and Radiographic Features

Localized aggressive periodontitis. As previously stated, aggressive periodontitis can be localized or generalized. One large study of children aged 5 to 17 years in the United States demonstrated a prevalence of 0.53% for the localized form and 0.13% for the generalized variant. 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 of time (Figure 4-36). Typically, there is a lack of gingival inflammation, with minimal plaque and calculus; however, subgingival plaque is present on every affected root. The rate of bone destruction is 3 to 5 times faster than that seen in chronic periodontitis.

In the first molar regions, radiographs reveal vertical bone resorption that often is bilateral and symmetric. In classic cases an arc-shaped zone of bone loss extends from the distal aspect of the second bicuspid to the mesial aspect of the second molar. Similar involvement is apparent around the anterior teeth. Tooth migration and

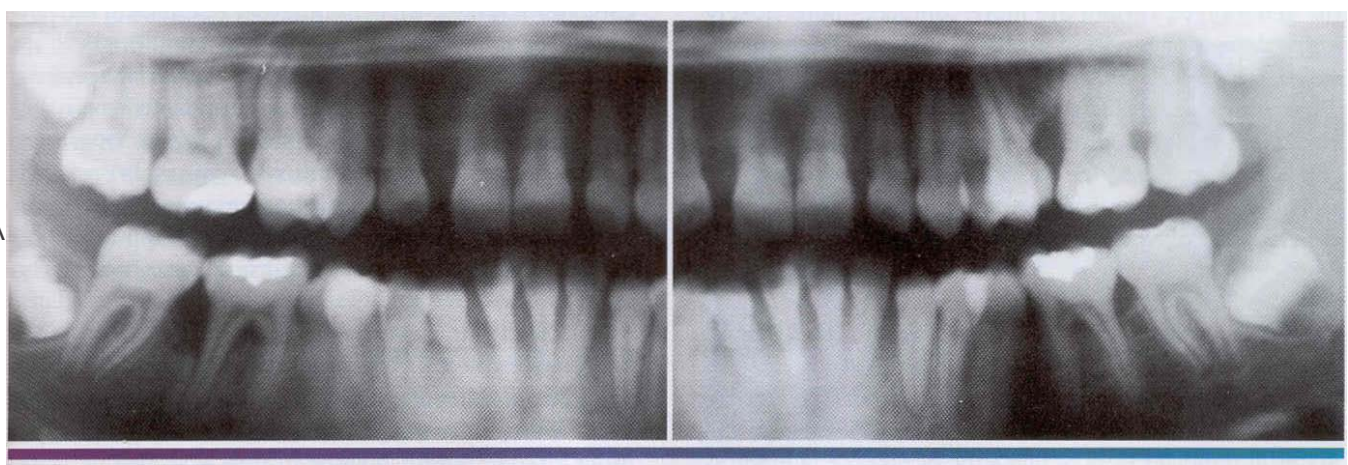

Figure 4-36 • localized aggressive periodontitis. A. Loss of bone support in the area of the first molars and incisors of both maxillary and mandibular right quadrants in a 11-year-old patient. **B,** left quadrants of the same patient depicted in A. Note the similar pattern of bone loss in the area of the first molars and incisors.

mobility are common. If untreated. 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 the 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 be 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. The American Academy of Periodontology recognizes the following features:

- Usually diagnosed in patients under the age of 30 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 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. *acttnomycetemcomitans,* the pathogens active in the generalized variant are more complex, more closely aligned to chronic periodontitis, and also involve organisms such as P. *tntetmedia.* P. *gingivalis,* B. *[otsythus,* F. *nucleatum, Campyiobactet rectus,* and various spirochetes. In patients who progress 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 is not different dramatically from that seen in chronic periodontitis. In spite of this, initial histopathologic examination of the material removed from active sites of disease is mandatory to rule out the possibility of other disease processes, such as Langerhans cell disease (see page 513). Even when the attachment loss presents in a classic localized pattern, systemic disease cannot be eliminated without an examination of tissue. 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. Tetracycline. amoxicillin and c1avulanate potassium. and a combination of amoxicillin and metronidazole are the medications of choice (although minocycline and erythromycin also are used). 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.

Antibiotics are prescribed. and surgery is performed 2 days after the initiation of the antimicrobial therapy. Surgery is approached in a manner similar to thai described for chronic periodontitis. Chlorhexidine rinses are used for 2 weeks after surgery. 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. Dental practitioners should alert proband patients with aggressive periodontitis of the possibie 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.

PAPILLON-LEFEVRE SYNDROME

Papillon and Lefèvre initially described the syndrome that bears their names in 1924. This autosomal recessive disorder predominantly demonstrates oral and derrnatologic manifestations; similar dermatologic changes can be seen in the absence of oral findings (keratoderma

palmoplantar of tInna-Thost and Meleda disease). **Because of the autosomal recessive inheritance pattern.** the parents are not typically affected; consanguinity is noted in approximately one third of the cases. The predominant oral finding is accelerated periodontitis that appears to be caused by defects in neutrophil function and multiple immune mediated mechanisms.

Genetic studies of patients with Papillon-Lefevre syndrome mapped the major gene locus to an interval on chromosome IIq14 and revealed mutation 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. Loss of appropriate function of the cathepsin Cgene is thought to result 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. Haim-Munk syndrome also exhibits mutation of the cathepsin C gene and has been shown to represent an allelic variant of Papillon-Lcfevre syndrome.

Clinical and Radiographic Features

Papillon-Lefevre syndrome exhibits a prevalence of I to 4 per million people in the population. and carriers are thought to be present in 2 to 4 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 sales and then spreads to the dorsa of the hands and feet) palmarplantar keratosis develops. with occasional reports of diffuse follicular hyperkeratosis and keratosis on the elbows and knees (Figure 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 iesions typically present as white. light yellow. brown. or red plaques and patches that develop crusts. cracks, or deep fissures. Some patients describe worsening In the winter. and others describe keratotic desquamation. which may be confused with psoriasis.

The oral manifestations consist of dramatically advanced periodontitis that is seen in both the deciduous and permanent dentitions and develops soon after the eruption of the teeth. Extensive hyperplastic and hemorrhagic gingivitis is seen (Figure 4-38). A rapid loss of attachment occurs. with the teeth soon lacking osseous support and radiographically appearing to float in the soft tissue (Figure 4-39). Without aggressive therapy. the loss of the dentition is inevitable. Mobility and migration of the teeth are observed consistently. and mastication often is painful because of the lack of support. The teeth spontaneously exfoliate or are removed because of sensitivity during function. This process prematurely eliminates the deciduous dentition; with eruption of the permanent teeth. the destructive pattern is duplicated, When the teeth are absent. the alveolar mucosa is normal in appearance.

Although other pathogenic bacteria have been isolated from sites of active disease. A. *actinomycetemcomt-*

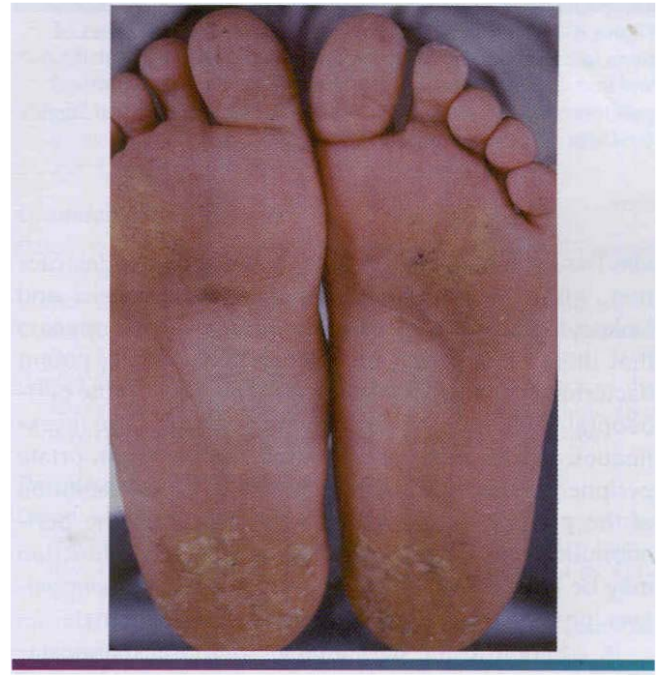

Figure 4-37 • Papillon-Lefevre **syndrome. Plantar keratosis of the soles of both feet. (Courtesy of Dr. *James* L Dickson.)**

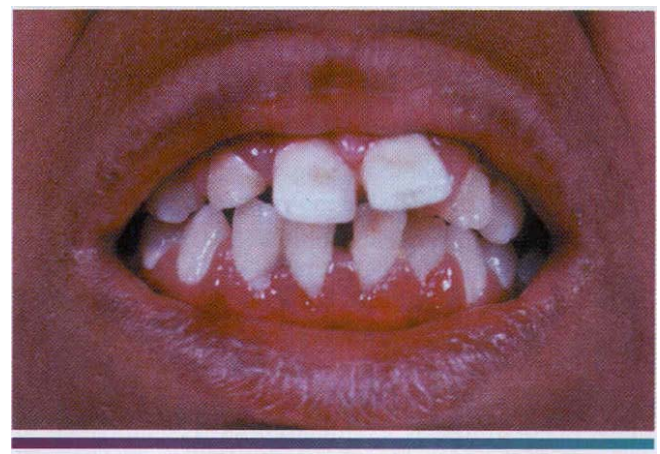

Figure 4-38 • Papillon-Lefevre **syndrome. Diffuse erythematous and hyperplastic gingivitis. (Courtesy of Dr. *James* L.** Dlckson.)

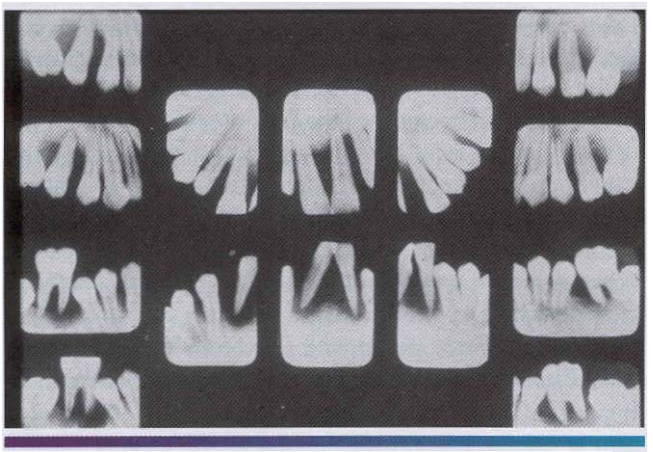

Figure 4-39 • Papillcn-Lefevre syndrome. Multlfocal sites of bone Joss in all four quadrants. (From Giansanti JS, Hrabak RP. Waldron CA: Palmoplantar hyperkeratosis and concomitant periodontal destruction [Papillon-Lefevre syndrome], *Oral Surg Oral Med Oral Patho/36:40. 1973.)*

tans has been related directly to the periodontal destruction. Although there is a hereditary component and leukocyte dysfunctions can be demonstrated. it appears that there must be an infection with a specific, potent bacterium, such as A. *acunomycetemcomnans.* for the periodontal component to develop. Interestingly. one investigation documented the development of appropriate peripheral leukocyte function after successful resolution of the pathogenic organisms responsible for the periodontitis. This indicates that the leukocyte dysfunction may be induced by infection with *A. actinomycetemcomitans* (possibly secondary to generated leukotoxinsl.

In addition to the dermatologic and oral manifestations, numerous investigators have documented less frequent findings. Ectopic calcifications of the falx ccrebrt 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.

Htstopathologlc Features

Once again. the histopathologic features of Papillon-Lefèvre syndrome resemble those seen in chronic periodontitis and are not specific. Submitted tissue often contains hyperplastic crevicular epithelium with exocytosls. The underlying connective tissue exhibits increased vascularity and a mixed inflammatory cellular infiltrate consisting predominantly of polymorphonuclear leukocytes, lymphocytes. histiocytcs. and plasma cells. Initially. histopathologic examination is recommended to rule out other pathologic causes of the periodontal destruction.

Treatment and Prognosis

The most successful treatment of the skin lesions has been administration of retinoids (e.g.. etretinate). which has resulted in remarkable Irnprovcrnent with complete clearance in the majority of patients. Surprisingly. a few authors have reported improvement of the associated periodontal disease during periods of retinoid administration. Possible adverse reactions of the retinoids include angular cheilitis. dry lips. hair loss. arthralgia. tendinous and ligamentous calcifications. and teratogenicity.

Attempts at resolution of the periodontal disease often have been frustrating. In spite of extensive periodontal therapy and antibiotics. in many patients the disease progresses until all teeth are lost. However, several investigators have reported a cessation of attachment Joss, and two different treatment approaches have been used.

Despite the usc of numerous antibiotics, several reports document a difficulty in resolution of the infection associated with teeth that already exhibit attachment loss. In some of the cases, all of the periodontally involved deciduous teeth were extracted and followed by a period of edentulousness with antibiotic treatment in an attempt to remove the causative pathogens. Tetracycline was successful in preventing the redevelopment of periodontitis in the permanent teeth after the extractions and the resolution of the infection in the deciduous dentition. However. penicillin. erythromycin, metronidazole. and tetracyclinewere all unsuccessful in resolving active sites of periodontitis.

The second approach revolves around direct attack against A. *acunomycetemcomttans.* In one investigation, culture and sensitivity testing revealed that the most effective antibiotic regimen was amoxicillin and clavulanatc potassium. Ceftriaxone and erythromycin were moderately effective; penicillin. tetracycline. and chloramphenicol were less effective. Metronidazole and ornidazole were ineffective. In another report. sensitivity testing suggested use of erythromycin and tetracycline: however. inadequate clearance of A. *l1ctinomycetemcomitans* was seen after use of rninocycline followed by erythromycin. Ultimately. clearance was achieved through mechanical removal combined with ofloxacin. It appears clear that clearance of *A. acunomycetemcomttans* is mandatory. but the antibiotic best suited for this task is variable.

Through the use of mechanical plaque control and appropriate antibiotics directed toward A. *actinomycetemcomitans*, the course of the disease may be altered. The progression of attachment loss is slowed dramatically, and the teeth that erupt after the initiation of therapy do not develop periodontal destruction. Rigorous oral hygiene. chlorhexidine mouth rinses. frequent professional prophylaxis. and periodic appropriate antibiotic therapy arc necessary *tor* long-term maintenance.

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CHAPTER 5

Bacterial Infections

CHAPTER OUTLINE

IMPETIGO

Impetigo is a superficial infection of the skin that is caused by *Streptococcus pyogenes* and *Staphylococcus aureus*, either separately or together. This infection is endemic in young children and can occur in epidemics. Intact epithelium is normally protective against infection; therefore, most cases arise in areas of dermatitis or previous trauma, such as cuts, abrasions, or insect bites. Individuals harboring the organisms can transmit them through skin contact, and outbreaks are associated with poor hygiene, crowded living conditions, and hot, humid climates.

Clinical Features

Impetigo most commonly occurs on the skin of the face or the extremities. Two clinical patterns are seen. The infection may produce fragile *vesicles* that quickly rupture and are replaced by thick, adherent, amber crusts; in other instances, longer-lasting flaccid bullous lesions develop (Figure 5-1). After the bullae rupture, thin, light-brown (honey-colored) crusts *develop*. Pruritus and regional lymphadenopathy may be seen, but systemic manifestations, such as fever, are not normally present. Some cases appear like exfoliative cheilitis (see page 266) or may resemble recurrent herpes simplex (see page 216).

Diagnosis

A strong presumptive diagnosis can normally be made from the clinical presentation. When the diagnosis is not obvious clinically, the definitive diagnosis requires isolation of S. *pyogenes* or S. *aureus* from cultures of involved skin.

Treatment and Prognosis

For patients with nonbullous impetigo involving only a small area with few lesions, topical mupirocin has been shown to be *effective*. For bullous or more extensive lesions, topical antibiotics 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*. Clindamycin, cephalexin, and dicloxacillin represent good current choices. Erythromycin is also frequently used, but resistance by S. *aureus* has become an increasing problem. If left untreated, 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.

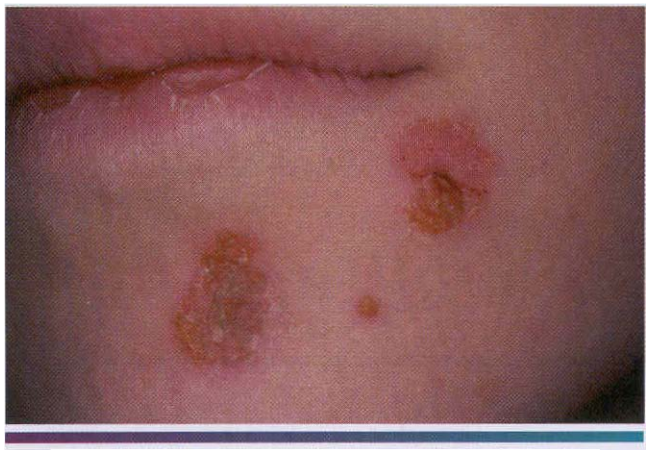

Figure 5-1 • Impetigo. Amber crusts of skin of the chin.

ERYSIPELAS

Erysipelas is a superficial skin infection most commonly associated with β-hemolytic streptococci (usually group A but occasionally other groups such as group G). Other less **common causative organisms include S.** *aureus, Pneumococcus, Klebsiella pneumontae, Yersinia entetocolitica,* and *Haemophilus illfillenzae.* 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 elderly patients or in those who are debilitated or diabetic. The infection may occur anywhere on the skin, especially in **areas of previous trauma. An increased prevalence is** noted in the winter and spring months.

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 689). If the eyelids are involved, they may become edematous and shut, thereby resembling angioedema (see page 308). The affected area is painful, bright red, well circumscribed, swollen, indurated, and warm to the touch (Figure 5-2). Although not frequent, other signs and symptoms (e.g., fever, elevated white blood cell count, nausea, vomiting) may be present. Diagnostic confirmation is difficult because cultures are not usually beneficial.

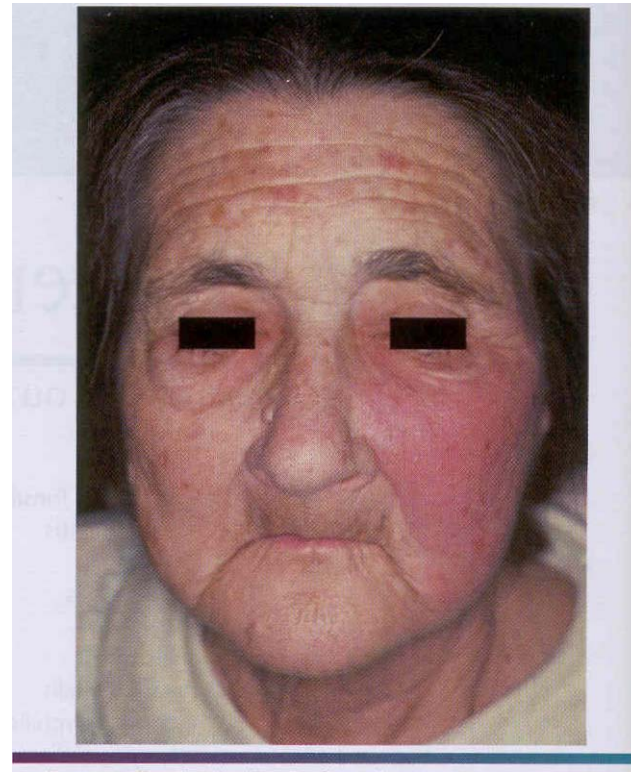

Figure 5-2 • Erysipelas. Red. swollen area of the left cheek.

Treatment and Prognosis

The treatment of choice is penicillin or erythromycin. On **the 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 fascIttls. 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. With repeated recurrences, permanent and disfiguring 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, adcnovtruses, **enteroviruses, influenza, parainfluenza, and Epstein-Barr virus. The streptococcal *variety* is one of the most common bacterial infections in humans and** represents as many as 25% of the cases of pharyngitis. Spreading is typically by person-to-person contact with **infectious nasal or oral secretions.**

Clinical Features

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 (Figure 5-3). Systemic symptoms, **such as headache, malaise, anorexia, abdominal** pain. and vomiting, may be noted. especially in younger children. Rhinitis. laryngitis, and bronchitis are typically associated with the viral infections and normally are not present in streptococcal pharyngotonsillitis.

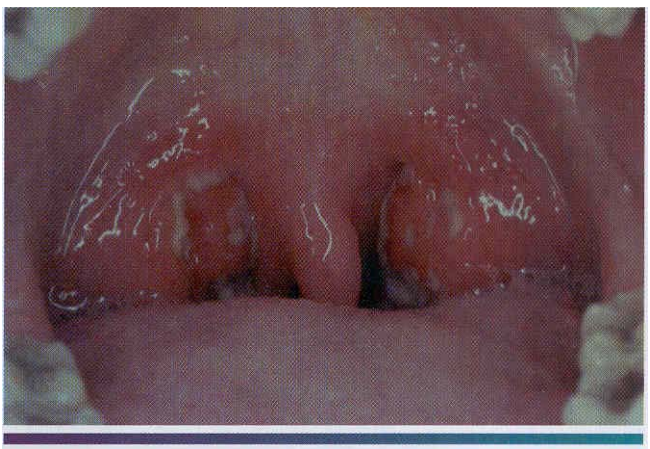

Figure 5-3 • Tonsillitis. Hyperplastic pharyngeal tonsils, with yellowish exudate of crypts.

Diagnosis

A diagnosis of streptococcal pharyngotonsillitis based solely on clinical features is most difficult. but 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. The majority of patients affected with group A. β-hemolytic streptococcal pharyngitis arc between the ages of 5 and 15 years, and the infection occurs most frequently in the latewinter, early spring, or **summer. Certain clinical features** (e.g., **conjunctivitis, cough, hoarseness, coryza, discrete ulcerative lesions,** viral exanthem, diarrheal strongly suggest a viral cause and should lead away from testing for a streptococcal cause. Diagnostic confirmation can be obtained by throat **culture or use of a rapid antigen detection test.**

Treatment and Prognosis

In addition to reducing the localized morbidity of the infection, the main goals of therapy are to prevent development **of acute rheumatic fever and complications such** as acute glomerulonephritis. toxic shock-like syndrome, bacteremia, and deep tissue cellulitis. Initiation of appropriate therapy within the first 9 days after development of the pharyngitis will prevent rheumatic fever.

Group A streptococci are uniformly sensitive to penicillin. Cephalosporins (e.g., cephalexin, cefadroxill also **are effective but more expensive. Erythromycin is used only in patients who have a known sensitivity to penicillin. Newer macrolides (e.g., cJarithromycin,** azithromycin) *have* similar effectiveness but cause less gastrointestinal distress when compared with erythromycin.

No single regimen eliminates pharyngeal pathogenic **streptococci in 100% of treated patients. Post-therapeutic laboratory testing is recommended in** patients with a family history of rheumatic fever, during **outbreaks of acute rheumatic fever or streptococcal** glomeruionephritis, during outbreaks of streptococcal pharyngitis in semiclosed communities, and when "ping pong" spread is occurring within a family. **In** these cases, clindamycin often is able to clear the organism in patients **who continue to demonstrate positive culture after penicillin therapy.**

SCARLET FEVER

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 incubation period ranges from 1to 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 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 166),

Scattered petechiae may be seen on the soft palate. 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 (Figure 5-4). 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.

Classically, in untreated cases, fever develops abruptly around the second day. The patient's temperature peaks around 103° F. and it returns to normal within 6 days. 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**

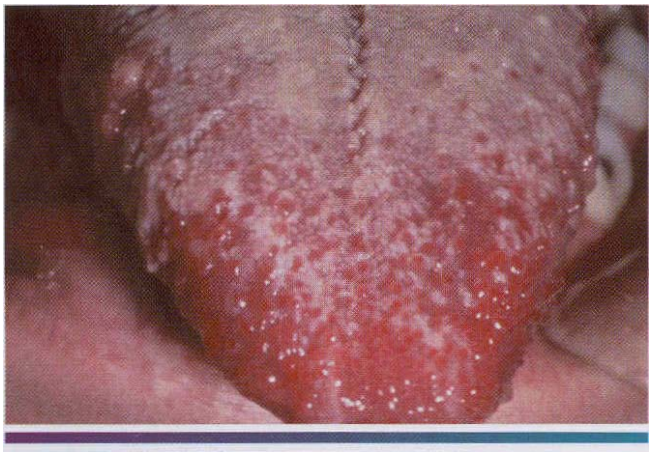

figure 5-4 . Scarlet fever. Dorsal surface of the tongue exhibiting white coating in association with numerous enlarged and erythematous fungiform papillae (white strawberry tongue).

referred to 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. In contrast, the face exhibits a diffuse erythema without punctate zones. The rash is more intense in areas of pressure and skin folds. Often there are transverse red streaks, known as Pastla's lines. which occur in the skin folds secondary to the capillary fragility in these zones of stress. The mouth demonstrates circumoral pallor.

The rash usually clears within I 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 extrernilies 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

A culture of throat secretions may be used to confirm the diagnosis of streptococcal infection. but this has been replaced by several methods of rapid detection of antigens that arc specific for group A. p-hemolytic streptococci. Failure to respond to appropriate antibiotics should alert the clinician that the detected streptococci may represent an intercurrent carrier state and other causes of infection should be investigated.

Treatment and Prognosis

Treatment of scarlet fever is necessary to prevent the possibility of complications. such as rheumatic fever or glomerulonephritis. The treatment of choice is oral penicillin. with erythromycin reserved for patients who are allergic to penicillin. The fever and symptoms show dramatic improvement within 48 hours after the initiatio of treatment. With appropriate therapy. the prognosisi excellent.

TONSILLOIITHIASIS

Tonsilloliths are calcified structures that develop in enlarged tonsillar crypts that arc packed with bacteri and organic debris. The calcifications develop within a mass of desquamated epithelium. serum. food debris. and bacterial colonies. Recurrent tonsiliar inflammation may promote the development of these tonsillar concretions.

Clinical and Radiographic Features

Tonsillolithiasis can develop over a wide age range, from childhood to old age. with a mean patient age in the early 40s. Men and women arc affected equally. These calcifications may 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. Many tonsillohths, especially the smaller examples. are asymptomatic. However. these calcifications can promote recurrent tonsillar infections and may lead to pain. abscess formation. ulceration. dysphagia. and halitosis. In patients with large stones, clinical examination often reveals a hard. yellow submucosal mass of the affected tonsil. In elderly patients. large tonsilloliths can be aspirated and produce significant secondary pulmonary complications. On occasion. tonsilloliths may be discovered on panoramic radiographs as radiopaque objects superimposed on the midportion of the ascending mandibular ramus (Figure 5-5).

Diagnosis

A strong presumptive diagnosis can be made through a combination of the clinical and radiographic features. The definitive diagnosis can be confirmed by the demonstration of the calculi on removal of the affected tonsil.

Treatment and Prognosis

Superficial calculi can be enucleated: deeper tonsilloliths require excision of the affected tonsil. Deep tonsilloliths discovered incidentally during evaluation of a panoramic radiograph often are not treated unless associated with significant tonsillar hyperplasia or clinical symptoms.

DIPHTHERIA

Diphtheria is a life-threatening infection produced by *Corynebacterium diphtheriae*. The disease was first described in 1826. and C. *diphtheriae* (also termed *Kfebs-Löffler bacillus*) was discovered initially by Klebs in 1883 and isolated in pure culture by Loftier 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 nutrients for further growth and leading to peripheral spread. However, an effective antitoxin has been available since 1913, and immunization has been widespread in North America since 1922.

In the first edition of this textbook, it was stated that diphtheria was included mainly for historical interest because the world was on the threshold of virtual eradication of this infection in developed countries. However, a recent epidemic in Russia reveals how rapidly such advances can be reversed in the absence of an effective immunization program. The epidemic began in Moscow and spread to involve all of the newly independent states of the former Soviet Union. During this outbreak, greater than 150,000 cases were reported with approximately 4500 deaths. This one epidemic represented greater than 90% of all cases reported between 1990 and 1995. The process was finally 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.

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 is often accompanied with prolonged mucoid or hemorrhagic discharge. The oropharyngeal exudate begins on one or both tonsils as a patchy, yellowish-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.

During the recent Russian epidemic, patients with lesions isolated to the oral cavity were documented. In these patients, scattered areas of necrosis were noted on the buccal mucosa, upper and lower lips, hard and soft palate, or tongue. Such localization is rare and makes diagnosis more difficult.

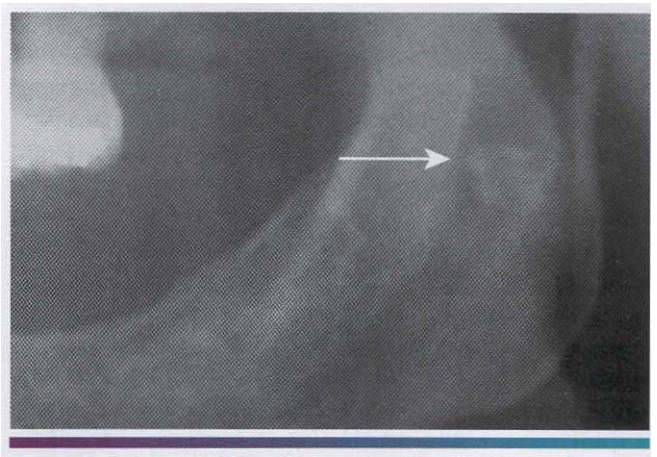

Figure 5-5 • Tonsilloliths. Cluster of radiopacities *(arrow)* in the midportion of the ascending ramus. (Courtesy of Dr. J.R. Cramer.)

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.

Although bacteremia is rare, circulating toxin can result in systemic complications. Myocarditis and neurologic difficulties are seen most frequently and are usually 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-Barre syndrome also may occur.

Diagnosis

Although the clinical presentation can be distinctive in severe cases, laboratory confirmation should be sought in all instances. The specimen for culture should be obtained from underneath the diphtheric membrane, if possible, or from the surface of the membrane. Culture material also should be obtained from the nasal mucosa.

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.

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.

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.** Although the risk of infection from blood transfusion is negligible because of serologic testing of donors. transmission through exposure to infected blood is theoretically possible because the organism may survive up to 5 days in refrigerated blood.

After the advent of penicillin therapy in the 1940s. the incidence of syphilis slowly decreased to a low point in 1956; since that time. the infection rate has peaked and troughed in approximately 10-year cycles. Overall. there **is a trend toward an increasing incidence. The World** Health Organization estimated approximately 12 million new cases of syphilis occurred in adults worldwide in 1995. The prevalence of infection is 50 to 100 times higher in the United States when compared with other **industrialized countries.**

The primary cause for a recent upsurge in cases appears related to crack cocaine abuse and the barter of illegal drugs for sex. Although the data varies from year to year. a significant and prolonged increased prevalence **has been seen in African Americans. In the past, there** was a male predominance that approached 3.5: 1 during certain recording periods. Recently the male-to-female ratio has dropped to approximately I:r. most likely because of elevated rates of syphilis among women **involved in prostitution related to crack cocaine. This** increased incidence in females has ultimately resulted in another increasing problem. congenital syphilis.

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 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. Because of the** morbidity and mortality associated with this infection. it is recommended that all pregnant women be screened for syphilis early in the gestation period.

Oral syphilitic lesions are uncommon but may occur in any stage. Many of the changes are secondary to obliterative endarteritis, **which occurs in areas of infection.**

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. Although multiple lesions may be seen occasionally. the majority of chancres are solitary. The external **genitalia and anus are the most common sites, and the** affected area begins as a papular lesion. which develops **a central ulceration. Less than 2% of chancres occur in** other locations. but the oral cavity is the most common **extragenital site. Oral lesions are seen most commonly** on the lip. but other sites include the tongue. palate. gingiva. and tonsils (Figure 5-6). The oral lesion appears as a painless. clean-based 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. 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 to weeks after the initial infection. The lesions of secondary syphilis may arise before the primary lesion

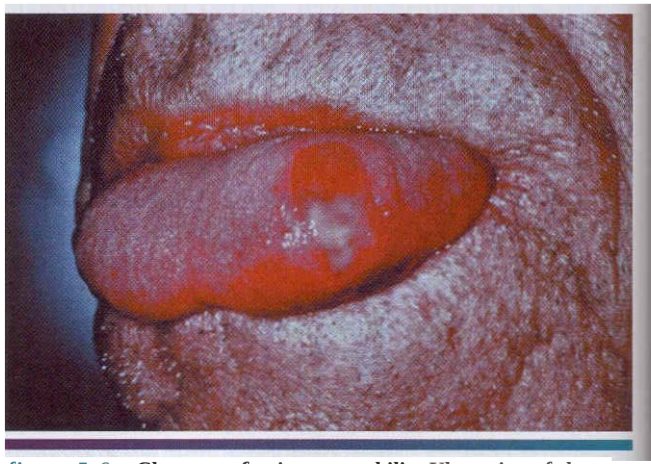

figure 5-6 • Chancre of primary syphilis. Ulceration of the dorsal surface of the tongue on the left side. (From Neville BW, Oamm DO, White OK: *Color atlas of cfinical oralpathology.* ed 2, Philadelphia, 1999. Williams & Wilkins.)

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 (Figure 5-7). 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 (Figure 5-8). Subsequently, superficial epithelial necrosis may occur. ieading 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. Occasionally. papillary lesions that resemble viral papillomas may arise during this time and are known as condylomata lata. In contrast to the isolated chancre noted in the primary stage, multiple lesions are typicai of secondary syphilis. Spontaneous resolution usually occurs within 3 to t2 weeks; however, relapses may occur during the next year.

On occasion, especially in the presence of a compromised immune system. secondary syphilis can exhibit an explosive and widespread form known as lues malign". This form has prodromal symptoms of fever. headache. and myalgia. followed by the formation of necrotic ulcerations. which commonly involve the face and scalp. Oral lesions are present in more than 30% of affected patients. Malaise, pain. and arthralgia are seen occasionally. Several cases of lues maligna have been reported in patients with acquired immunodeficiency syndrome (AIDS) (see page 234), and this possibility should be kept in mind whenever human immunodeficiency virus (HIV) infected patients have atypical ulcerations of the skin or oral mucosa.

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 I to 30 years; then (in approximately 30% of patients) the third stage. which is known as tertiary syphilis. develops. The third stage of syphilis 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. and congestive heart failure may occur. ***Involvement of the central nervous system may result in tabes dorsalis, psychosis, dementia. paresis, and death. 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 (Figure 5-9). 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 (Figure 5-10>' In the past, this form of atrophic glossitis was thought 10 be precancerous. but several more recent publications dispute this concept.

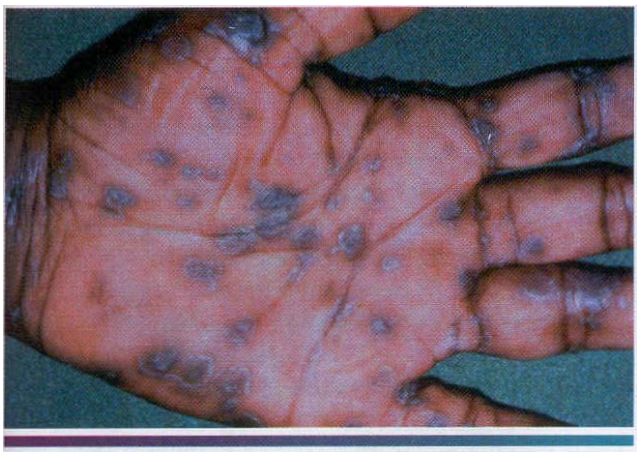

Figure 5-7 • Secondary syphilis. Erythematous rash of secondary syphilis affecting the palms of the hands. (Courtesy of Dr. John Maize.]

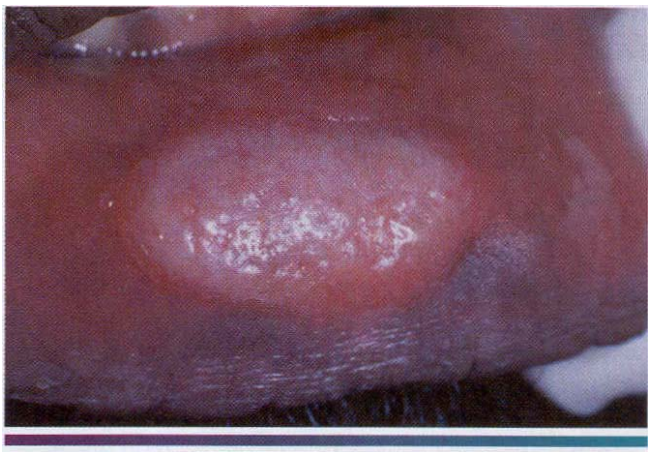

Figure 5-8 • Mucous patch of secondary syphilis. Whitish zone of intense epithelial exocytosis and spongiosis of the lower labial mucosa. (Courtesy of Dr. Pete Edmonds.]

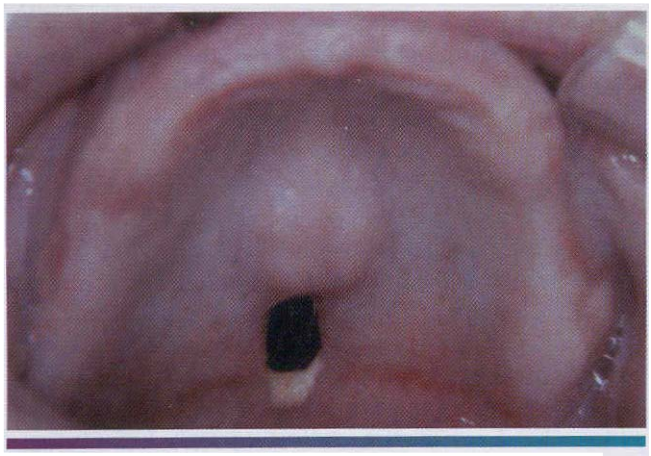

Figure 5-9 • **Tertiary syphilis. Perforation of the hard palate. (Courtesy of Dr. George Blozis.}**

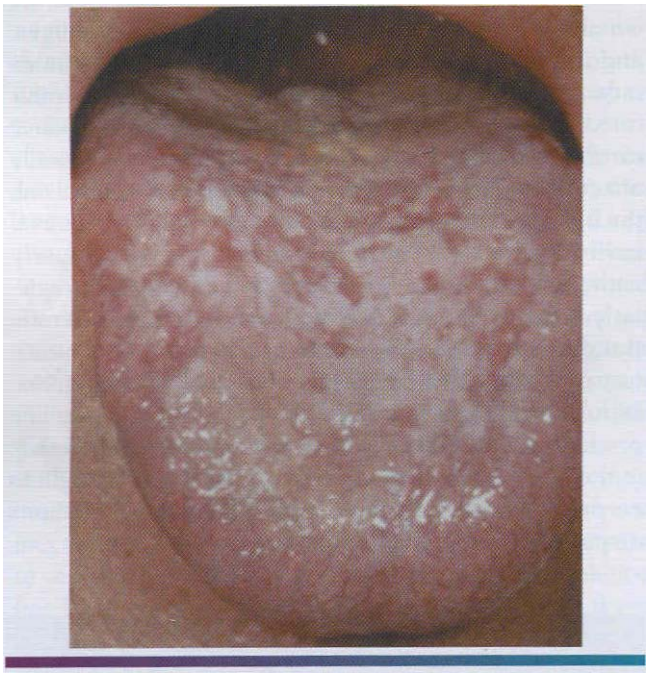

Figure 5-10 • **Atrophic glossitis of tertiary syphilis. Dorsal surface of the tongue exhibiting loss of filiform papillae and areas of epithelial atrophy and hyperkeratosis. (Courtesy of Dr. Robert J** Corlin.)

Congenita! sYl,ili/is.In 1858, Sir Jonathan Hutchinson described the changes found in congenital syphilis and defined the following three pathognomonic diagnostic **features, known as Hutchinson's triad:**

- Hutchinson's teeth
- **Ocular interstitial** keratitis
- Eighth nerve deafness

Like many diagnostic triads, few patients exhibit all three features.

The infection alters the formation of both the anterior teeth (Hutchinson's incisors) and the posterior dcntl-

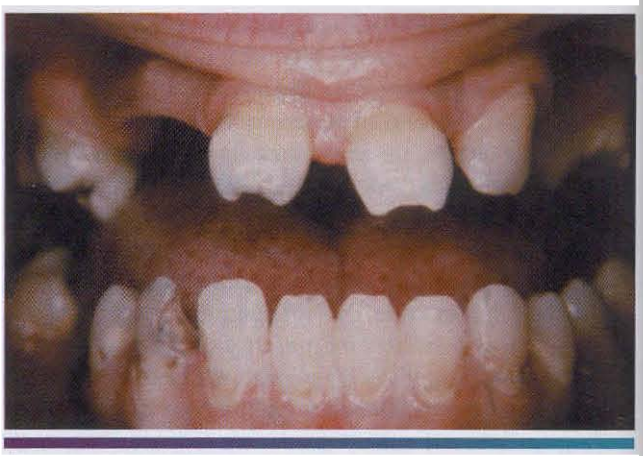

Figure 5-11 • **Hutchinson's incisors of congenital syphilis. Dentition exhibiting crowns tapering toward the incisal edges. (From Halstead** Ct. Blozis **CG, Drinnan AJ, Gier RE:** ***Physical evaluation of the dental patient.*** **5t louis. 1982. Mosby.)**

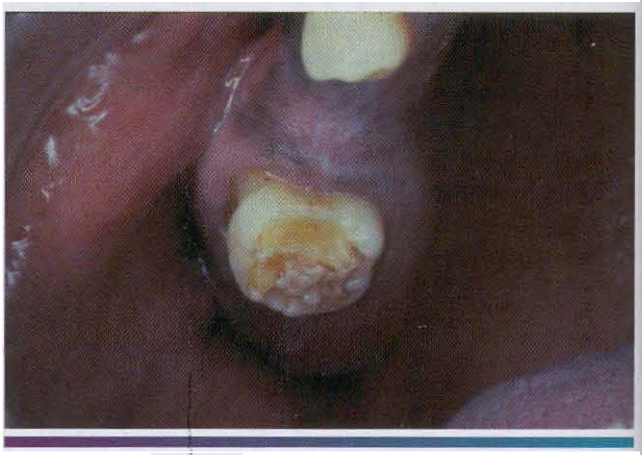

Figure 5-12 • **Mulberry molar of congenital syphilis. Maxillary molar** demonstrating **occlusal surface with numerous globular projections.**

lion (mulberry **molars. Fournier's molars, Moon's** molars). Hutchinson's 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 straightedge screwdriver (Figure 5-11). 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 (Figure 5-12l.

Interstitial keratitis of the eyes is not present at birth but usually develops between the ages of 5 and 25 years. The affected eye has an opacified corneal surface, with a resultant loss of vision. In addition to Hutchinson's triad, a number of other alterations may be seen. Table 5-1 delineates the prevalence rates of the stigmata of congenital syphilis in a cohort of affected patients.

Table 5-1 *Stigmata of COl/gel/it", Syphilis*

STIGMATA OF CONGENITAL SYPHILIS'	NUMBER OF PATIENTS	% 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's incisors	171	63.1
Higoumenaki's sign[1]	107	39.4
Relative prognathism of mandible	70	25.8
Interstitial keratitis	24	8.8
Rhagades[2]	19	7.0
Saber shin[3]	11	4.1
Eighth nerve deafness	9	3.3
Scaphoid scaputae"	2	0.7
Gutton's jointS	1	0.3

'In a cohort of 271 patients.

Modified from Fiumara NJ, i.cssel S: Manifestations of late congenital syphilis: an analysis of 271 patients, *Arch Detmatot 102;78,1970.*

'Enlargement of clavicle adjacent to the sternum.
-Prcmature perioral ftssurtng.
JAnlerior bowing of tibia as a result of periostitis.
'Concavity of vertebral border of the scapulae,
'Painless synovitis and enlargement of joints, usually the knee.

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. The underlying lamina propria may demonstrate an increase in the number of vascular channels, and an intense chronic inflammatory reaction Is present. The infiltrate is composed predominantly of lymphocytes and plasma cells and often demonstrates a perivascular pattern (Figure 5-13). Although the presence of plasma cells within the infiltrate may suggest the diagnosis of syphilis on the skin, their presence in areas of oral ulceration is commonplace and, therefore, not necessarily of diagnostic significance. The use of special silver impregnation techniques, such as Warthin-Starry or Steiner stains, often shows scattered corkscrew-like spirochetal organisms (Figure 5-14). in addition, the organism can be detected in tissue through direct fluorescent antibody 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 histiocytcs and multinucleated giant cells. Even with special stains, the organisms are hard to demonstrate in the third stage, and the inflammatory response is thought to be an immune reaction rather than a direct response to *T. pallidum*.

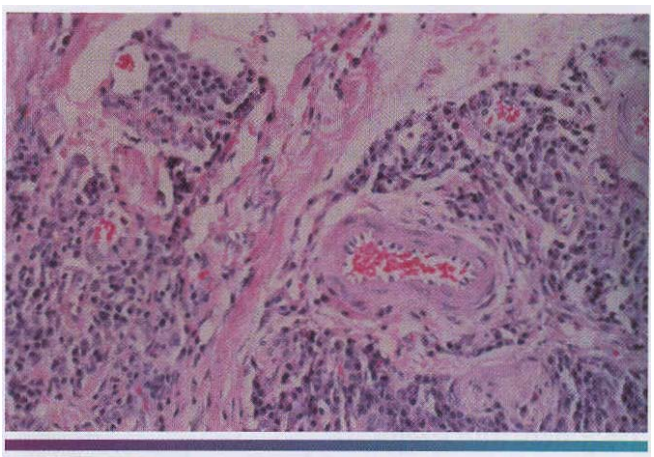

Figure 5-13 • Primary syphilis. A chronic perivascular inflammatory infiltrate of plasma cells and lymphocytes. (Courtesy of Dr. John Metcalf.)

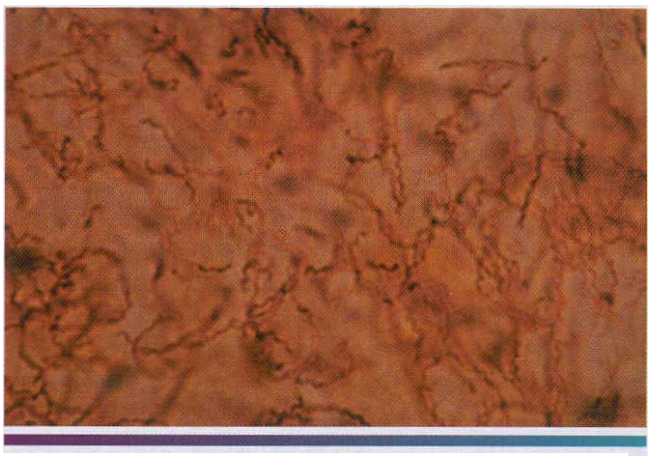

Figure 5-14 • Primary syphilis. Silver stain exhibiting numerous corkscrew-like organisms.

Diagnosis

The diagnosis of syphilis is best confirmed by demonstrating the spiral organism by dark-field examination of a smear of the exudate of an active lesion. False-positive results are possible in the oral cavity because of morphologically similar oral inhabitants, such as T. *microdentium, T. macrodentium.* and *T. mucosum.* Demonstration of the organism on a smear or in biopsy material shouid be confirmed through the use of specific immunofluorescent antibody or serologic tests,

Several nonspecific and not highly sensitive serologic screening tests for syphilis are available. These include the Venereal Disease Research Laboratory (VORL) and the rapid plasma reagin (RPR). After the first 3 weeks of infection, the screening tests arc positive strongly

throughout the first two stages. After the development of latency. the positivity generally subsides with time.

Specific and highly sensitive serologic tests for syphilis are also available. These include the fluorescent treponemal antibody absorption (FTA-ABS) and *T. pallidum* hemagglutination assays (TPHA). These tests become positive at the time of the development of the first lesion of primary syphilis and remain positive for life. This lifelong persistence of positivity limits their usefulness in the diagnosis of a second incidence of infection. In cases of suspected reinfection, therefore. 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. Most patients obtain a clinical cure with penicillin, but it must be remembered that *T. pal/idum* can escape the lethal effects of the antibiotic when the organism is located within the confines of lymph nodes or the central nervous system. 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. Erythromycin or tetracycline is given to patients who are allergic to penicillin.

GONORRHEA

Gonorrhea, a sexually transmitted disease that is produced by *Neisseria gonorthoeae*, represents the most common reportable bacterial infection In the United States. The disease is epidemic, especially in urban areas, and millions of people are infected each year. Although the prevalence of gonorrhea has been declining since a peak in 1975.the rate in the United States remains the highest of any industrialized country. The incidence of gonorrhea between 1981 and i996 has decreased 71.3%; however. certain segments of the population remain at high risk. Groups exhibiting an increased prevalence of infection include those with a low socioeconomic or education level, injecting drug users. prostitutes. homosexual men, and military personnel.

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 50% 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 the most important female complication of gonorrhea- pelvic inflammatory disease (PID). The symptoms of PID include cramps and abnormal bleeding. and they may be severe or mild. The long-term complications of PID include ectopic pregnancies or infertility from tubal obstruction.

Between 0.5% and 3.0% of untreated patients wllh 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 thai 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.

Approximately 20% of patients with gonorrhea will exhibit involvement of the oropharyngeal region. Gonococcal septicemia. kissing. and cunnilingus may transmit the organism to this site, but most cases of oral gonorrhea appear to be a result of fellatio. Therefore, the majority have been reported in women or homosexual men. The most common site of oral involvement is the pharyngeal area along with the tonsils and uvula. A mild-to-moderate sore throat often is accompanied by nonspecific. diffuse oropharyngeal erythema. Involved tonsils typically demonstrate edema and erythema, often with scattered. small punctate pustules. Rarely. lesions have been reported in the anterior portion of the oral cavity. with areas of infection appearing erythematous. pustular, erosive, or ulcerated. 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 blindness.

Diagnosis

To confirm the diagnosis. a Gram stain of the purulent material can be used to demonstrate gram-negative diplococci within the neutrophils. Confirmation of the diagnosis is made through culture and sugar fermentation tests or by a positive fluorescent antibody test.

Treatment and Prognosis

Patients with gonorrhea are at risk for additional sexually transmitted diseases. most commonly *Chlamydia trachomatis*. Isolation of *Chlamydia* is costly and tends to delay therapy. The most cost-effective approach is to cotreat all cases of gonorrhea for possible associated chiamydial infection; the preferred regimen is ceftriaxone and doxycycline. In patients allergic to ccphalosporrns. spectinomycin is used instead of ceftriaxone. 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. Prophylactic ophthalmic erythromycin, tetracycline. or silver nitrate is applied to the newborn's eyes to prevent the occurrence of gonococcal ophthalmia neonatorum.

TUBERCULOSIS

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*. Worldwide. more than I billion people are infected. with 8 million new cases and 3 million deaths *per* year. In the United States. the disease has been declining since the 1800s. especially since the introduction of effective antimicrobials in the I940s. The decline ceased abruptly in the early 1980s and *appears* to be the result of a combination of several factors. The HIV epidemic, increased immigration from countries with endemic tuberculosis. transmission of tuberculosis in crowded or unsanitary environments, and a decline of the health care infrastructure have been implicated in the recent resurgence. Most infections are the result of direct person-to-person spread through airborne droplets from a patient with active disease.

Nontuberculous mycobacterial disease can occur from a variety of organisms. Before the tuberculin testing ofdairy herds. many cases arose from the consumption of milk infected with M. *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 234). M. *avium-intracellutare* is a common cause of opportu nistic infections.

Infection must be distinguished from active disease. Primary tuberculosi s occurs in previously unexposed people and almost always involves the lungs. The organism initially elicits a nonspecific. chronic inflammatory reaction. In most individuals. the primary infection results only in a localized. fibrocalcified 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 tuberculosis progress from infection to active disease. and an existing state of immun osuppression often is responsible. In rare instances, active tuberculosis 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 has been termed miliary tuberculosis. Secondary tuberculosis often is associated with old age. poverty. and crowded living conditions. AIDS represents one of the strongest known risk factors for progression from infection to disease. The prevalence of active tuberculosis in patients with AIDS is approximately 100 times that documented in the general population.

Clinlcal and Radiographic Features

Primary tuberculosis is usually asymptomatic. Occasionally. fever and pleural effusion may occur.

Classically. the lesions of secondary tuberculosis arc 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. welght loss, and night sweats. With pulmonary progression. a productive cough develops. often with hemoptysis or chest pain. Progressive tuberculosis 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 tuberculosis is seen and represents an increasing proportion of the currently diagnosed cases. in patients with AIDS. greater than 50% wili have extrapulmonary lesions. Any organ system may be involved. including the lymphatic system. skin. skeletai system. central nervous system. kidneys. and gastrointestinal tract. Involvement of the skin may develop and has been called lupu s vulgaris.

Head and neck involvement is not rare. 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 tuberculosis arc uncommon, with most cases appearing as a chronic painless ulcer. Less frequent** presentations include nodular. granular. or (rarely) firm leukoplakic areas. Most of the lesions represent secondary infection from the initial pulmonary lesions. It is unclear whether these develop from hematogenous spread or from exposure to infected sputum. The reported **prevalence of clinically evident oral lesions varies from** 0.5% to 1.5%. However. one autopsy study revealed a prevalence of close to 20% when the tongues of those infected were examined microscopically. The discovery of pulmonary tuberculosis as a result of the investigation of oral lesions **occurs but is unusual. Primary oral tuberculosis without pulmonary involvement is rare.**

When present. primary oral tuberculosis usually *involves* the gingiva. mucobuccal fold. and areas of **inflammation adjacent to teeth or in extraction sites; secondary** oral lesions are mostly present on the tongue. palate. and lip (Figures 5-15 and 5-16). Primary oral lesions are usually associated with enlarged regional lymph nodes. Tuberculous osteomyelitis has been reported in the jaws and appears as ill-defined areas01 radiolucency.

Nontuberculous mycobacterial infections from contaminated milk are currently rare in the industrialized world because of pasteurization of milk and rapid elimination of infected cows. **Drinking contaminated milk can result in a form of mycobacterial infection known as** scrofula. Scrofula exhibits enlargement of the oropharyngeal lymphoid tissues and cervical lymph nodes (Figure 5-17). On occasion. the *involved* nodes may **develop significant caseous necrosis and form numerous** fistulas through the overlying skin (Figure 5-18). In addition, areas of nodal involvement may radiographically appear as calcified lymph nodes (Figure 5-19). **Pulmonary involvement is unusual in patients with scrofula.**

Histopathologic Features

The cell-mediated hypersensitivity reaction is responsible for the classic histopathologic presentation of **tuberculosis. Areas of infection demonstrate the forma-**

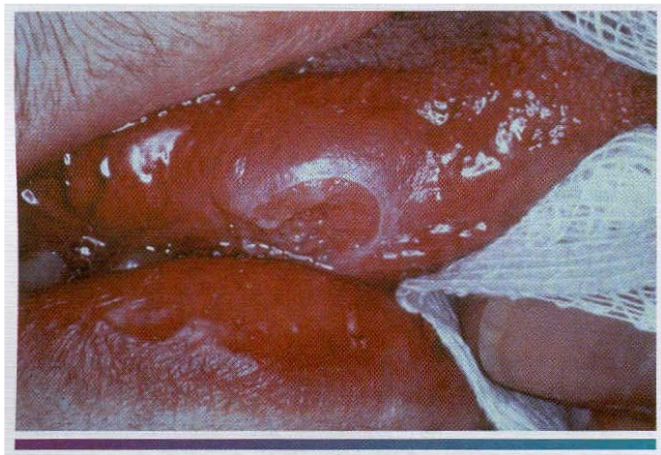

Figure 5-15 • Tuberculosis. Chronic mucosal ulceration of the ventral surface of the tongue on the right side. (Reprinted with permission of the American Dental Association.)

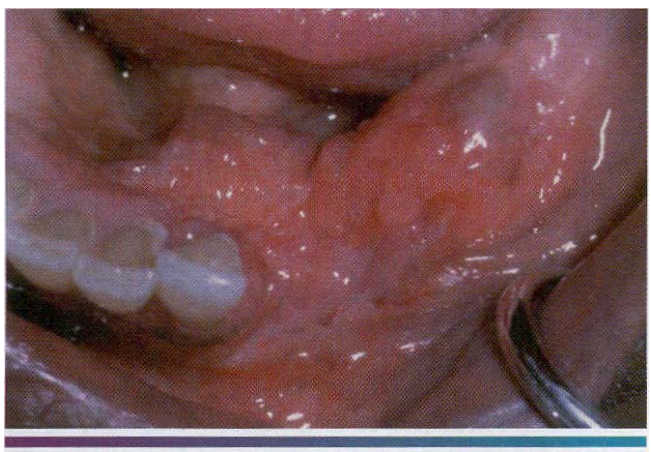

Figure 5-16 • Tuberculosis. Area of granularity and ulceration of the lower alveolar ridge and floor of mouth. (Courtesy of Dr. Brian Blocher}

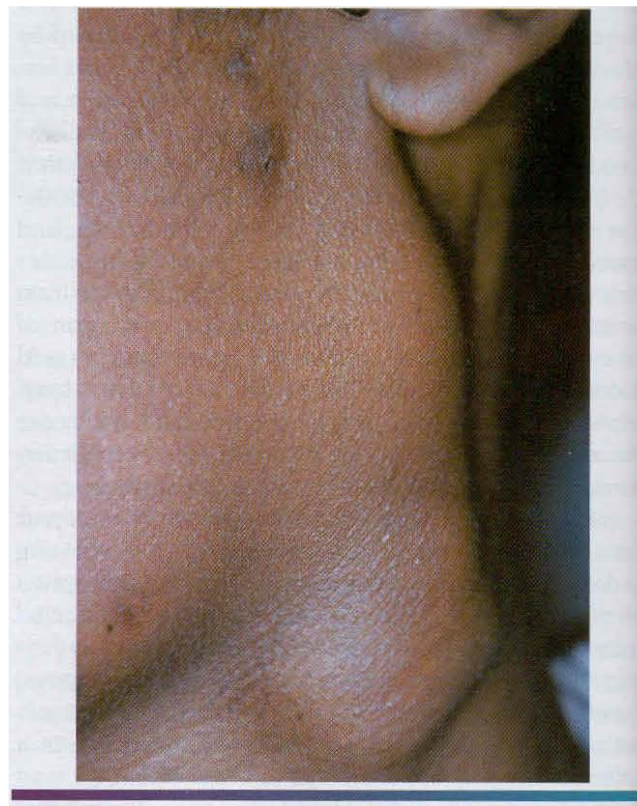

Figure 5-17 • Tuberculosis. Enlargement of numerous cervical lymph nodes. (Courtesy of Dr. George Blozis.]

nonofgranulomas, which are circumscribed collections of epithelioid hlstlocytes. lymphocytes, and multinucleated giant cells, often with central caseous necrosis (Figure 5-20). In a person with tuberculosis, one of these granulomas is called a **tubercle.** Special stains, such as the Ziehl-Neelsen or other acid-fast stains, are required to demonstrate the mycobacteria (Figure 5-21 l. 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 rule out completely the possibility of tuberculosis.

Diagnosis

About 2 to 4 weeks after initial exposure, a cell-mediated hypersensitivity reaction to tubercular antigens develops. This reaction is the basis for the tuberculin (Mantoux or PPD) skin test. 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 **indicates exposure to the organism and does not distinguish** infection from active disease. A negative tuberculin skin test does not rule out totally the possibility of tuberculosis. False-negative reactions have been documented in *very* elderly and immunocompromised patients and when the antigen was placed intradermally. The false-negative rate may be as high as 66% in patients with AIDS.

The diagnosis of active disease must be confirmed by special mycobacterial stains and culture of infected sputum or tissue. 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 fre-

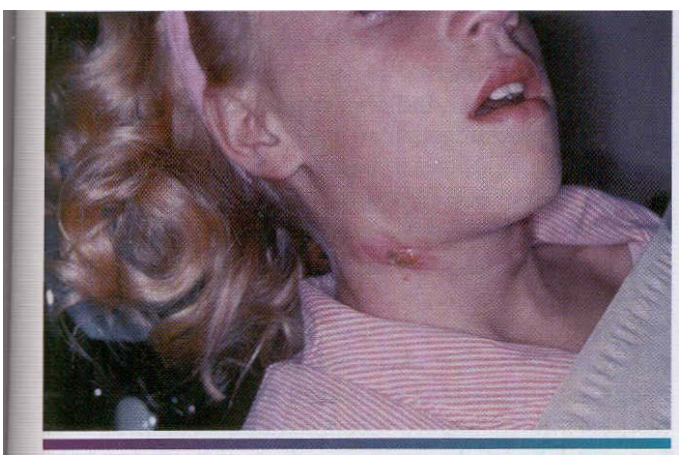

Figure 5-18 • **Tuberculosis. Submandibular fistula secondary to involvement of underlying** cervical lymph **nodes.**

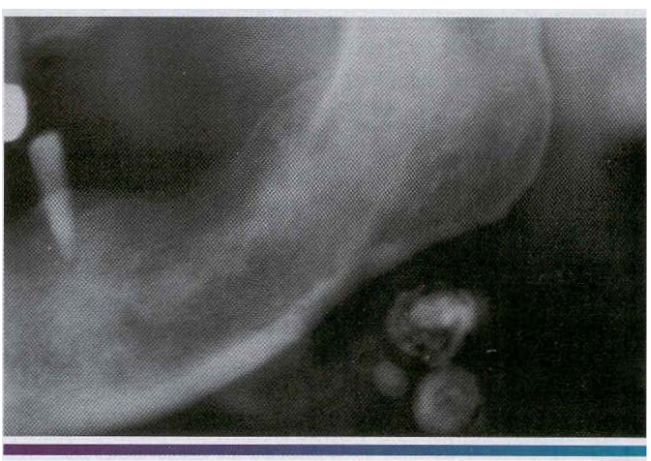

Figure 5-19 • **Tuberculosis. Multiple calcified** cervical lymph **nodes.**

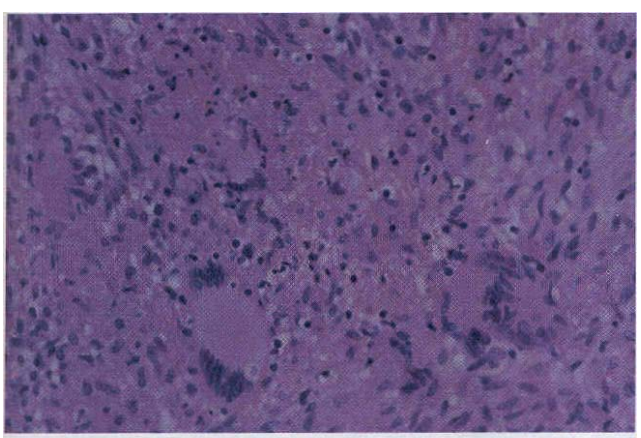

figure 5-20 . **Tuberculosis. Histopathologic presentation of the same lesion depicted in Figure 5-16. Sheets of** histiocytes **are intermixed with multinucleated giant cells and areas of necrosis.**

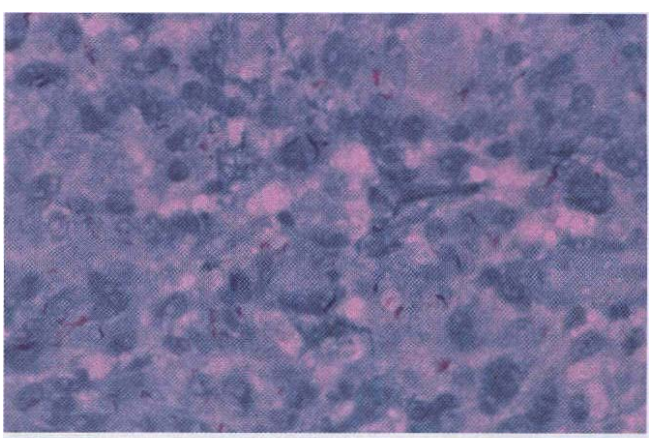

Figure 5-21 • **Tuberculosis. Acid-fast stain of specimen depicted in Figure 5-20 exhibiting scattered clusters of small mycobacterial organisms.**

quently 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. In the future, polymerase chain reaction (PCR) to identify M. *tuberculosis* DNA may accelerate the diagnosis without the need to wait on 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. Two multiagent protocols are recommended as first-line therapy against drug-susceptible tuberculosis. The choice is between (1) isoniazid (INH) plus rifampin for 9 months or (2) INH. ritampin. and pyrazinamide for 2 months, followed by INH and rifampin for 4 months. Other first-line medications include ethambutol and streptomycin. Relapse rates of approximately 1.5% are seen. 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.

LEPROSY (HANSEN'S DISEASE)

Leprosy is a chronic infectious disease produced by *Mycobacterium leprae*. Because of worldwide efforts coordinated by the World Health Organization, a dramatic decrease in the prevalence of leprosy has been seen over the past 15 years. Since the mid-1980s. the number of estimated cases of active leprosy has dropped from between 10 and 12 million to 1.15 million. with the number of officially registered cases falling 85%. However, leprosy remains a public health problem in many areas of the world; approximately 82% of all currently reported cases are noted in five countries: Brazil, India, Indonesia. Myanmar. 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. The organism is thought by many to require 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. mangabey monkey) are thought to be additional possible reservoirs of infection. The nine-banded armadillo is relatively unique because of its low body core temperature, and it is naturally susceptible to the infection. Infected armadillos have been discovered in Louisiana.

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.

Historically, two main clinical presentations are noted, 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 tests to heat-killed organisms (lepromin) are positive, and the disease is usually 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. Borderline and less common variations exist. Active disease progresses through stages of invasion. proliferation, ulceration, and resolution with fibrosis. The incubation period Is prolonged. with an average oi 2 to 5 years for the tuberculoid type and 8 to 12 years for the lepromatous variant.

Clinical Features

Currently. leprosy is classified into two separate categories. paucibacillary and multibacillary. with the distinction influencing the recommended form of therapy. Because laboratory services such as skin smears often are not available. patients are increasingly being classified on clinical grounds using the number of lesions (primarily skin) and the number of body areas affected.

Paucibacillary leprosy corresponds closely to the tuberculoid pattern of leprosy and 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.

Multibacillary leprosy corresponds well to the lepromatous pattern of leprosy and begins slowly with numerous, ill-defined. hypopigmented macules or papules on the skin that, with time, become thickened (Figure 5-22). 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 (Figure 5-23). 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

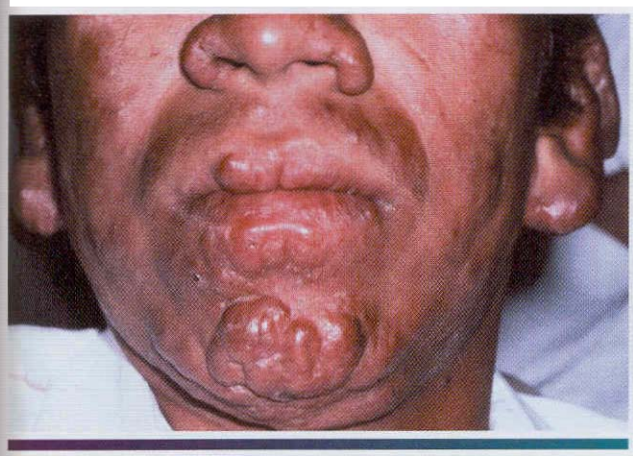

figure 5-22 • **Multibacillary (lepromatous) leprosy.** Numerous thickened facial nodules.

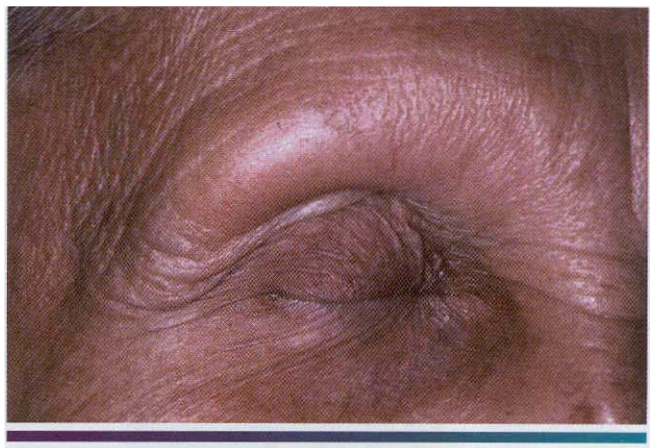

Figure 5-23 • **Multibacillary (lepromatous) leprosy. loss of eyebrows and eyelashes.**

ottheSense 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.

Oral lesions are not rare in multibacillary leprosy, and reports on their prevalence vary from I9% to 60%. In an excellent review by Prabhu and Daftary of 700 patients with leprosy, the prevalence of facial skin Involvement was 28%, and oral lesions were noted in 11.5%. The lesions tended to be more frequent during the firstS years of the disease.

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, labial maxillary gingiva, tongue. lips, buccal maxillary gingiva. labial mandibular gingiva. and buccal mucosa. Effected 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.

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** ollesions 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.

The facial and trigeminal nerves can be involved with the infectious process. Facial paraiysis may be unilateral or bilateral. Sensory deficits may affect any branch of the trigeminal nerve, but the maxillary division is the most commonly affected.

Histopathologic Features

Biopsy specimens of paucibacillary leprosy typically reveal the tuberculoid pattern that demonstrates granulomatous inflammation with well-formed clusters of epithelioid histiocytes, lymphocytes. and multinucleated giant cells (Figure 5-24). There is a paucity of organisms; when present. they can be demonstrated only when stained with acid-fast stains, such as the Fite method. Multibacillary leprosy is associated with lepromatous pattern that demonstrates no well-formed granulomas; the typical finding is sheets of lymphocytes intermixed with vacuolated histiocytes known as lepra cells (Figure 5-25). Unlike tuberculoid leprosy, an abundance of **organisms can be demonstrated with acid-fast stains in** the lepromatous variant (Figure 5-26).

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. *feprae* can be identified by using molecular biologic techniques.

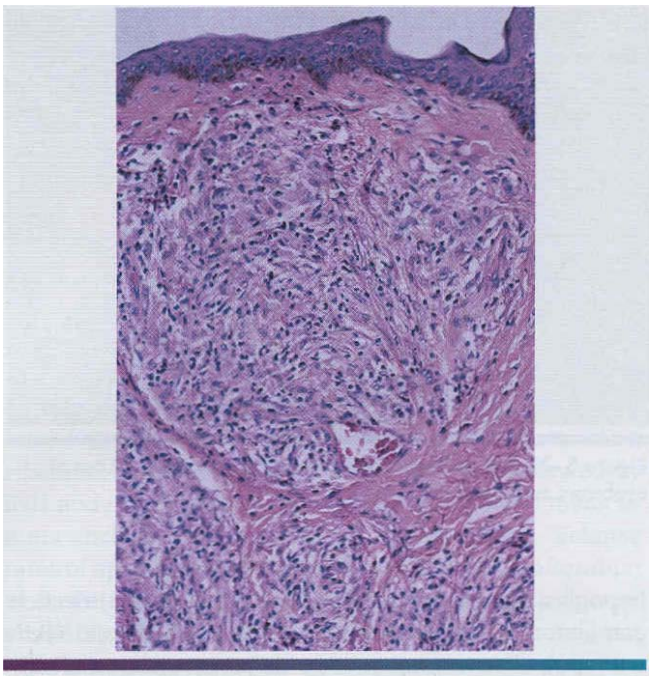

Figure 5-24 • Paucibacillary (tuberculoid) leprosy. Well-formed granulomatous inflammation demonstrating clusters of lymphocytes and histiocytes.

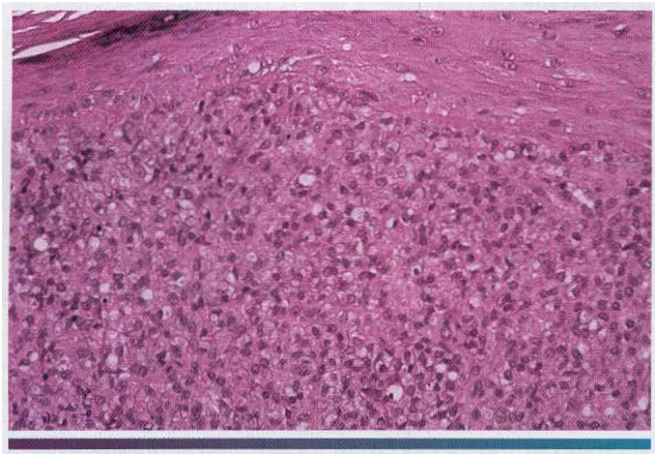

Figure 5-25 • Multibacillary (lepromatous) leprosy. Sheets of lymphocytes and histiocytes exhibiting scattered vacuolated lepra cells.

There is no reliable test to determine whether a person has been exposed to M. *leprae* without developing the disease; this creates difficulties in establishing the diagnosis **and determining the prevalence of the infection.**

Treatment and Prognosis

One of the major reasons for the decreasing prevaience of leprosy is the provision of an uninterrupted supply of free. high-quality medications in caiendar blister packs to all

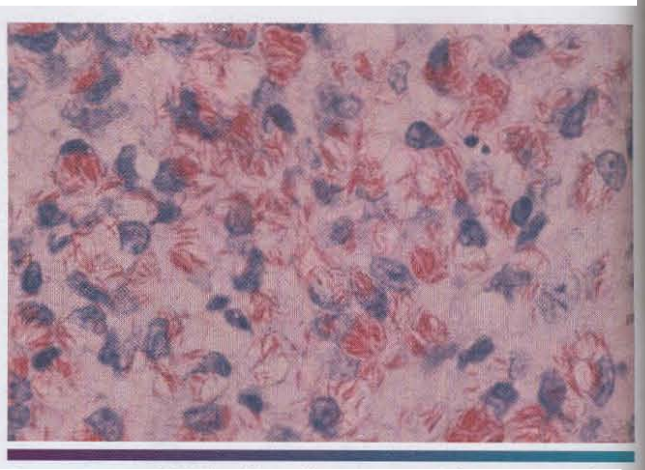

Figure 5-26 . Multibacillary (lepromatous) leprosy. Acid-fast stain exhibiting numerous small mycobacterial organisms seen individually and in clusters.

patients regardless of the living conditions or remoteness of the location. Paucibacillary leprosy is treated with a 6-month regimen of rifampin and dapsone, whereas patients with multibacillary ieprosy receive 24 months of rifampin, dapsone, and ciofazimine. Long-term follow up is recommended because of occasional reiapses. Patients allergic to rifampin are treated with a 24-month course of *ciofaz*-imine. ofloxacin, and minocyciine.

After resolution of the infection, the therapy must be directed toward reconstruction of the damage, in addition to physiotherapy and education of the patients who must live not only with their physical damage but also with the psychologic stigmata. As medical therapy **becomes more successful. the number of long-term survivors of the infection increases. Worldwide. it is estimated there are currently about 3 million individuals with** leprosy-related impairments and disability.

NOMA (CANCRUM ORIS; GANGRENOUS STOMATITIS; NECROTIZING STOMATITIS)

The term noma is derived from the Greek word *nomem*, meaning "to devour." Noma is a rapidly progressive. opportunistic infection caused by components of the normai oral flora that become pathogenic during periods **of compromised immune status.** ***Fusobacterium*** *necrophorum* or *F. nucleatum* and *Prevotella intermedia* are thought to be key players in the process and interact with one or more other bacterial organisms. of which the most com**monly implicated are** ***Borrelia*** *vincenttt,* **S.** ***aureus.*** **and non-**hemolytic *Streptococcus* species. The reported predisposing factors include the following:

- **Poverty**
- Malnutrition or dehydration
- Poor oral hygiene

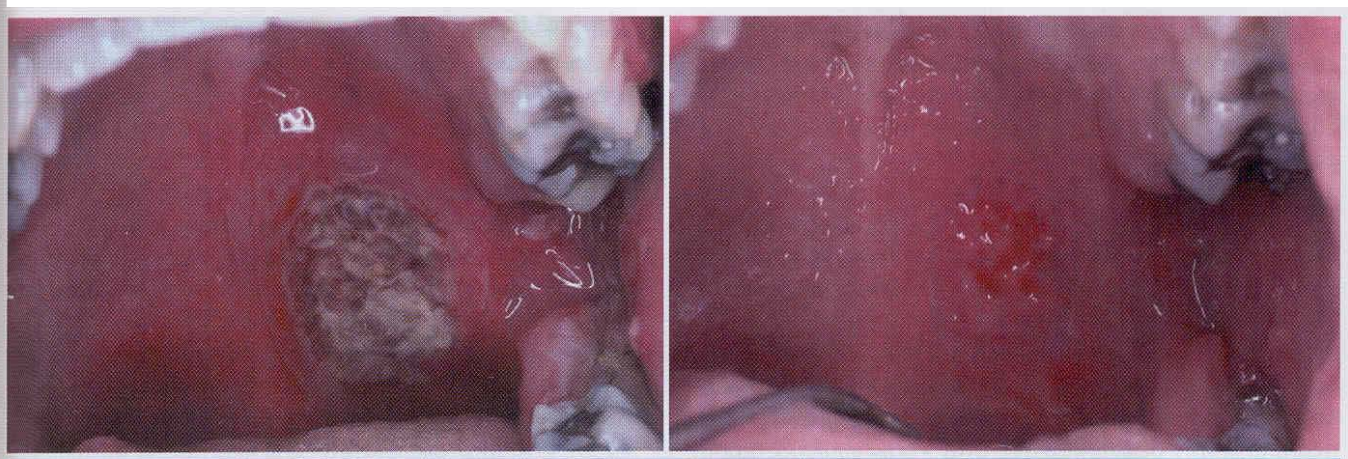

Figure 5-27. Necrotizing ulcerative mucositis. A, Large area of soft tissue necrosis of the posterior soft palate on the left side. B, Healing site of necrotizing mucositis 6 days after initiation of tetracycline therapy.

- Poor sanitation
- Proximity to 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 140). and several investigators believe that noma is merely an extension of the same process. Because the disease is usually 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 estimates the global yearly incidence to be approximately 140,000, with 100,000 of these patients being between the ages of 1 and 7 years and living in sub-Saharan Africa.

Clinical Features

Noma typically arises in children aged 1 to 10 years and 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 continuous with the gingiva, particularly in areas of trauma (Figure 5-27). The necrosis can extend into deeper tissues; over the next few days, zones of bluish-black discoloration of the overlying skin surface may develop (Figure 5-28). These discolored zones break down into areas of yellowish necrosis that also frequently spreads into adjacent bone, with large areas of osteomyelitis possible. Fetid odor, significant pain, fever, malaise, and regional lymphadenopathy are typical. Additional lesions also may occur in distant sites, such as the scalp, neck, ear, shoulders, chest, perineum, and vulva.

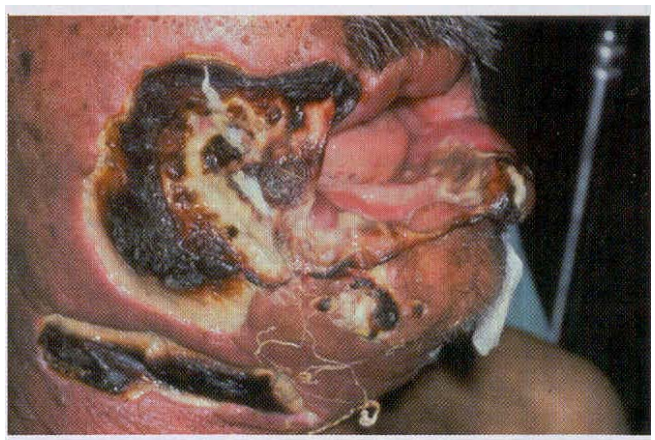

Figure 5-28 • Noma. Extensive blackish orofacial necrosis of the right cheek in an immunocompromised patient.

A related disorder, noma neonatorum, arises in the first month of life in low-birth weight infants who also demonstrate malnutrition and frequently a debilitating illness. These patients almost always have infection with *Pseudomonas aeruginosa*, often combined with *Escherichia*

coli, *Klebsiella* species, or *Staphylococcus* species. The affected infants frequently have lesions on the lips, nose, mouth, and anal area and less commonly on the scrotum and eyelids. Devastating *Pseudomonas*-related septicemia often is present.

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 in necrotizing stomatitis. The therapy of noma neonatorum is directed against the *Pseudomonas* organisms and often consists of piperacillin, gentamicin, or clindamycin. Conservative debridement 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. Necrotic bone is left in place to help hold the facial form but is removed as it sequestrates. Reconstruction should be delayed for 1 year to ensure complete recovery.

Before the discovery of antibiotics, the mortality rate approached 95% and still remains high In many portions of the world. In the United States, less than 10% of appropriately treated patients die. 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. Trismus from significant scarring associated with mandibular involvement can occur. Noma neonatorum is much more dangerous because the septicemia that is related to *Pseudomonas* infection is usually fatal.

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, 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. In surveys of documented actinomycosis. *Actinomyces israeli!* is the causative organism in the majority. with A. *viscosus* being a close second. Much less frequent causes of the infection are A. *naesiundii*, A. *odontolyticus*, A. *meyert*, 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 in the genitourinary region (often linked 10 use of intrauterine contraceptive devices).

The suppurative reaction of the infection may discharge large yellowish flecks that represent colonies 01 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 (Figure 5-29). Pain often is minimal. The soft tissues of the submandibular, submental, and cheek areas arc 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 fibrasing reaction have been reported in soft tissue that has received minor trauma. The tongue is the most fre-

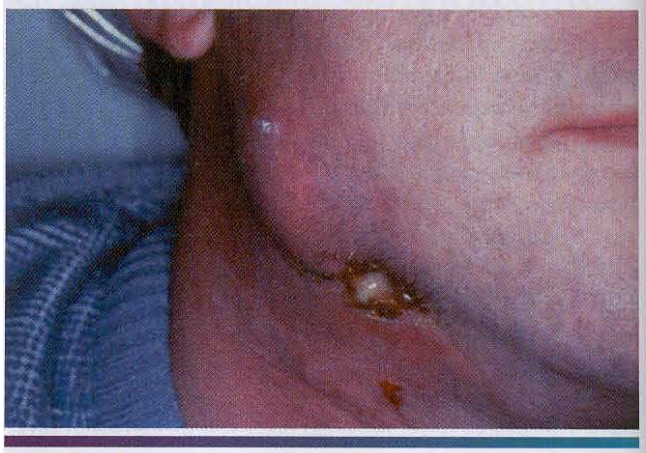

Figure 5-29 • Actinomycosis. Draining fistula of the right submandibular area.

quently mentioned site, but any oral mucosal location is possible. Involvement of the tonsils may produce infectious symptoms; in many cases, however, the primary change is one of significant hyperplasia. Investigators have suggested that trial courses of antibiotics be directed against actinomycosis in patients who have obstructive symptoms related to tonsillar hyperplasia.

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 submandibuiar and masseter spaces, respectively.

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. The anterior maxillary teeth, followed by the mandibular first molars, are the most common areas to be involved. Draining sinuses, pain. and swelling are frequently reported.

Histopathologic Features

The tissue removed from areas *ot* 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 (Figure 5-30!. The colonies consist of club-shaped filaments that form a radiating rosette pattern (Figure 5-31. With hematoxylin and eosin 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, 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 is typically 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, fluorescein-conjugated antiserum can be used 011 the granules to specifically identify the *Actinomyces* species.

Treatment and Prognosis

The treatment of choice *tor* actinomycosis in chronic fibrosing cases is prolonged high doses of antibiotics ill association with abscess drainage and excision of the sinus tracts. A high antibiotic concentration is required to penetrate larger areas of suppuration and fibrosis. Penicillin remains the standard of care, and no *in vivo* resistance has been documented. In spite of this, some investigators have demonstrated *in vitro* resistance 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 e-week course of penicillin: patients with deep-seated infections may require up to 12 months.

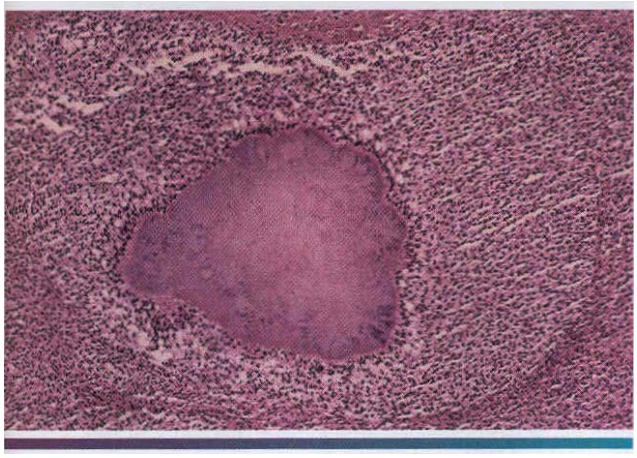

Figure 5-30 • Actinomycosis. Numerous colonies of actinomycotic organisms surrounded by a collection of polymorphonuclear leukocytes.

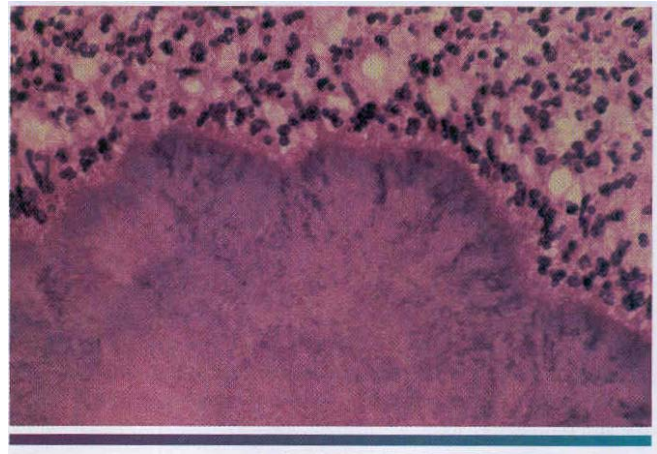

Figure 5-31 • Actinomycosis. Actinomycotic colony exhibiting club-shaped filaments arranged in a radiating rosette pattern.

Several authors have indicated that the localized acute infections often associated with a dental focus of contamination may be treated more conservatively than the deep, chronic cases of actinomycosis. Localized tongue abscesses, periapical actinomycosis, and pericoronal infections frequently respond well to removal of infected tissue and a shorter 2- to 6-week course of penicillin.

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. Almost all cases arise after contact with a cat, usually a kitten. The organism typically enters the skin through a scratch, bite, or previous site of injury. Infection from other sources is highly unlikely. This disease has been recognized since 1931, but the definitive cause was not determined until the 1980s. Isolation and culture of the organism were achieved finally in 1988. The causative organism was initially named *Rochalimaea henselae* but was reclassified as *Bartonella henselae*.

Clinical Features

Eighty percent of the cases occur in patients under 21 years of age. Cat-scratch disease begins as a papule or pustule that develops in 3 to 14 days along the initial scratch line (Figure 5-32). The lymph node changes *develop* in approximately 3 weeks and often may be accompanied by fever or malaise (Figure 5-33). Scratches on the face typically lead to submandibular lymphadenopathy, and the patient may be referred to dental **practitioners to rule out an odontogenic infection. Often** the primary site of trauma may *have* resolved by the time that the symptomatic lymphadenopathy is diagnosed. Therefore, cat-scratch disease must be considered strongly in the differential diagnosis of patients with unexplained symptomatic lymphadenopathy.

A few patients with cat-scratch disease demonstrate **unusual presentations. The infection can appear as an** intraoral mass in the buccal mucosa when lymphoid **aggregates become involved from an adjacent** cutaneous **primary site. Scratches in the preauricular area** may localize in parotid lymphoid tissue and can cause significant parotid pain or *even* temporary facial paralysis. Other less common problems include encephalopathy, erythematous and maculopapular rashes, splenomegaly, hepatic lesions, thrombocytopenia, pneumonia, anemia, pleural effusions, and recurrent bacterial infections.

Primary lesions adjacent to the eye can result in a conjunctival granuloma that is associated with preauricular lymphadenopathy (oculoglandular syndrome of Parinaud). This pattern is thought to occur when an individual touches fur moistened with the cat's saliva during grooming. When the individual rubs his or her eye, the **organism is transmitted to the conjunctiva.**

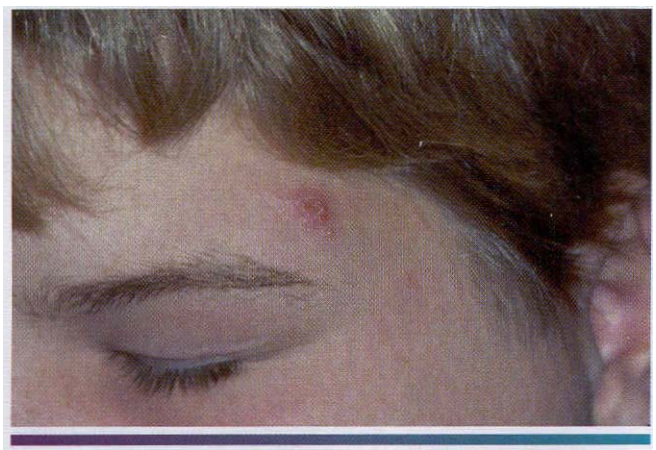

Figure 5-32 • **Cat-scratch disease. Papule that developed at initial site of injury.**

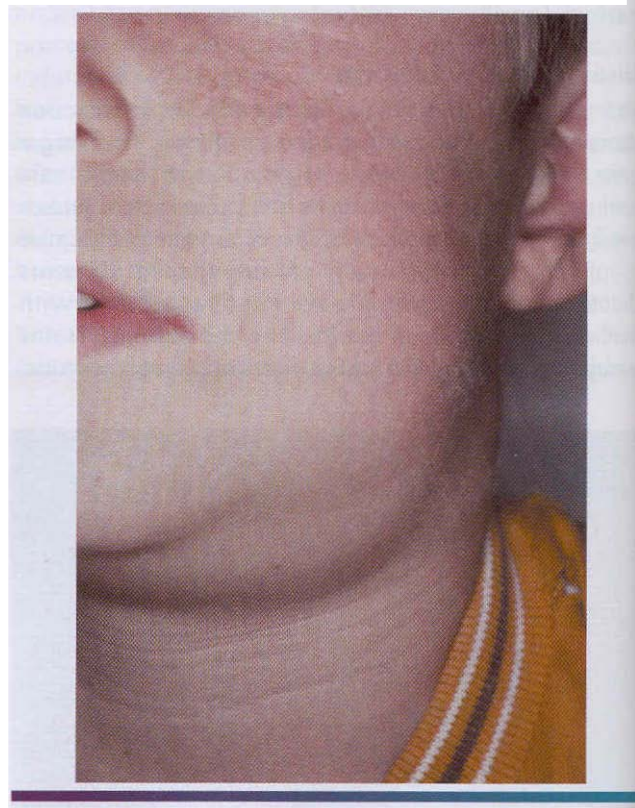

Figure 5-33 • **Cat-scratch disease. Submandibular lymphadenopathy has developed after initial trivial injury to skin. (Courtesy of Dr. George Blozis.)**

During the past decade, an unusual subcutaneous vascular proliferation, histopathologically similar to histiocytoid hemangioma, has been recognized in patients with AIDS, This proliferation has been termed bacillary angiomatosis, with most cases being definitively associated with *Bartonella henselae*. In a minority of the cases, bacillary angiomatosis is caused by a related organism, B. *outntana*. The affected areas often resemble Kaposi's sarcoma (see page 242) and appear asvarlable numbers of rod-to-purple skin lesions. These may be macular, papular, or pedunculated and exhibit awidespread distribution on the skin. Pain and tenderness are **common. The larger lesions are friable and** bleed easily.

Oral lesions have been seen in bacillary angiomatosis and also may resemble Kaposi's sarcoma. The affected **areas may exhibit zones of alveolar bone loss or may be** within the soft tissue and appear as a proliferative vascular lesion.

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 (Figure 5-34). In **some cases, significant necrosis is absent, but areas of** karyorrhexis are present around proliferations of plump vascular channels that often exhibit thickened eosInophilicwalls. On staining with the Warthin-Starry method. cat-scratch bacilli are usually found in areas without sig**nificant necrosis. As the disease progresses and necrosis** increases, the **organisms become more difficult to iden**tify. In addition, the Brown-Hopps method of gram staining may be used to highlight the bacilli.

Bacillary angiomatosis reveals lobular proliferations ofsmallblood vessels in an edematous to fibrotic stroma.

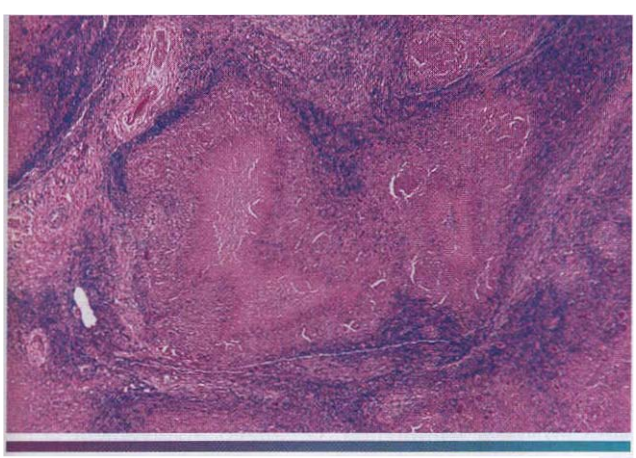

Figure 5-34 • **Cat-scratch disease. Intranodal area of abscess formation surrounded by band of histiocytes and neutrophHs.**

The supporting connective tissue typically demonstrates a significant number of neutrophils and leukocytoclasis, **important clues to the diagnosis. Also present are vari**ably sized amphophilic and granular aggregates that upon Warthin-Starry staining prove to be masses of the **causative bacteria.**

Diagnosis

The diagnosis of cat-scratch disease has been simplified by the development of serologic tests that demonstrate a high degree of sensitivity and specificity. The most widely used is an indirect fluorescent antibody assay for detecting antibodies to Bartonella henselae. Another method that is gaining in popularity is an enzyme-linked immunosorbent assay (ELISA) for IgM antibodies to the organism. Polymerase chain reaction (PCR) techniques also are available but are not used widely.

Before the development of these serologic tests, the diagnosis of cat-scratch disease was based on finding three of the four following criteria:

1. **Contact with a cat, presence of a scratch. or a pri**mary dermal or ocular lesion
2. Positive cat-scratch disease skin test finding (Hangar-Rose skin test-no longer Widely used)
3. Negative results for other causes of lymphadenopathy
4. Characteristic histopathologic findings of infected tissue, especially if pleomorphic bacilli can be found on staining with the Warthin-Starry method

Because the currently available tests are not 100% accurate. the use of these criteria are occasionally beneficial.

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, drainage should be achieved with a needle that is tunneled into the node laterally through normal skin I to 2 em 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.** Antibiotics are typically reserved for those cases that **demonstrate a prolonged course or severe involvement.** Antibiotics in patients with AIDS and bacillary angio**matosis have produced dramatic resolution within 2 days.** Although a number of antibiotics have been used successfully. the primary antibiotic used for cat-scratch disease or bacillary angiomatosis is erythromycin, with doxycycline being the first alternative.

SINUSITIS

Sinusitis is one of the most common health complaints in the United States. To understand the problem, the clinician must first have some knowledge of sinus anatomy. Adults have bilateral maxillary, frontal, and sphenoid sinuses. These large cavities drain into the nose through openings called ostia. All three of the major sinuses must drain through the middle meatus. in addition, located bilaterally in this area of the nose is a labyrinth of 3 to 15 small ethmoid sinuses, which drain through smaller ostia. The ostiomeatal complex, with its numerous narrow openings (Figure 5-35), 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. Normal function of the paranasat sinuses depends on the following:

- Patency of the ostial openings
- Proper function of the ciliary apparatus
- Quality of the nasal secretions
- Disruption of this balance leads to sinusitis

For a long time, primary inflammation of the lining of the maxillary antrum was thought to be 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.

All of the sinuses contain bacteria. In a person with sinusitis. infection is present initially or as the disease evolves. 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 are a recent upper respiratory viral infection or allergic rhinitis. Other less common causes include cystic fibrosis. immotile cilia syndrome. bronchiectasis, developmental abnormalities, and immunodeficiency, including AIDS.

In otherwise heaithy patients, the most common organisms responsible for acute sinusitis are S. *pneumoniae,* H. *infiuenzae,* and *Moraxeiia catarrhalis*.

If not corrected, some cases of acute sinusitis may become chronic. Chronic sinusitis is defined as recurring episodes of acute sinusitis or symptomatic sinus disease

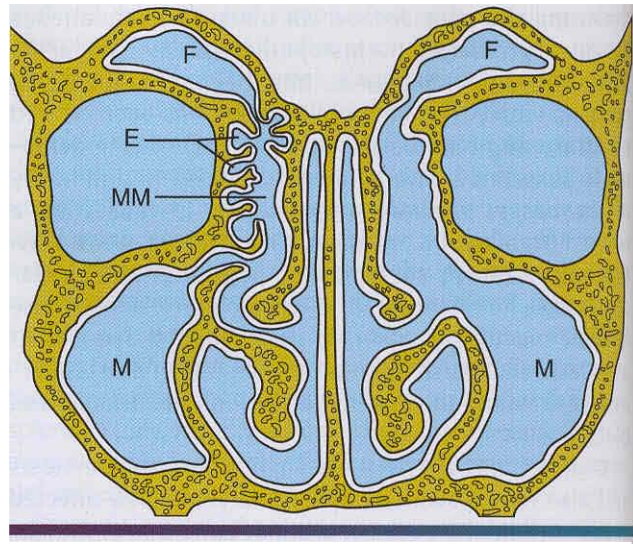

Figure 5-35 • Illustration demonstrating the ostiomeatal complex and its importance to appropriate sinus drainage. M, Maxillary sinus; *F*, frontal sinus; *E*, ethmoid sinuses; *MM*, middle meatus. The left side demonstrates the typical narrow middle meatus through which all sinus drainage must pass. The right side reveals enlargement of the middle meatus, such as that achieved through corrective endoscopic surgery.

lasting longer than 3 months. in these cases, the bacteria tend to be anaerobes and are most frequently *Streptococcus, Bacteroides,* or *Veilloncila* species.

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 *Aspergiius fumigatlls* (noninvasive mycetoma) (see page 207). 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, lighthcadedness. or generalized fatigue, also may be present or even dominate. Radiographically, the involved sinus has a cloudy, increased density (Figure 5-36).

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 and computed tomography (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.

Treatment and Prognosis

Although acute sinusitis is usually a self-limiting disease, antibiotics frequently are prescribed. Few placebo-controlled, double-blind, randomized clinical trials have been published, and the results are inconsistent. Although the supporting evidence is weak, the few well-performed trials appear to suggest that patients with more severe signs and symptoms may benefit from an antibiotic, whereas those with less severe manifestations do not require antibiotic therapy.

If antibiotics are used, the first-line therapy for acute sinusitis in otherwise healthy patients is amoxicillin. Because of drug resistance, additional medications are used if the patient does not respond to the initial antibiotic. Amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, or cefaclor are good antibiotics for resistant cases. Although topical decongestants shrink nasal membranes and improve ostial drainage, they are not recommended because of the resultant decreased ciliary function and decreased mucosal blood flow, which leads to impaired antibiotic delivery. The effect of systemic antihistamines and decongestants on sinusitis has not been studied adequately.

In otherwise healthy adult patients, chronic sinusitis that is not responsive to typical medical management often is corrected surgically. In the past, radical stripping of the diseased sinus mucosa was the therapy of choice. Today, nasal endoscopy has shown that sinusitis is a dis-

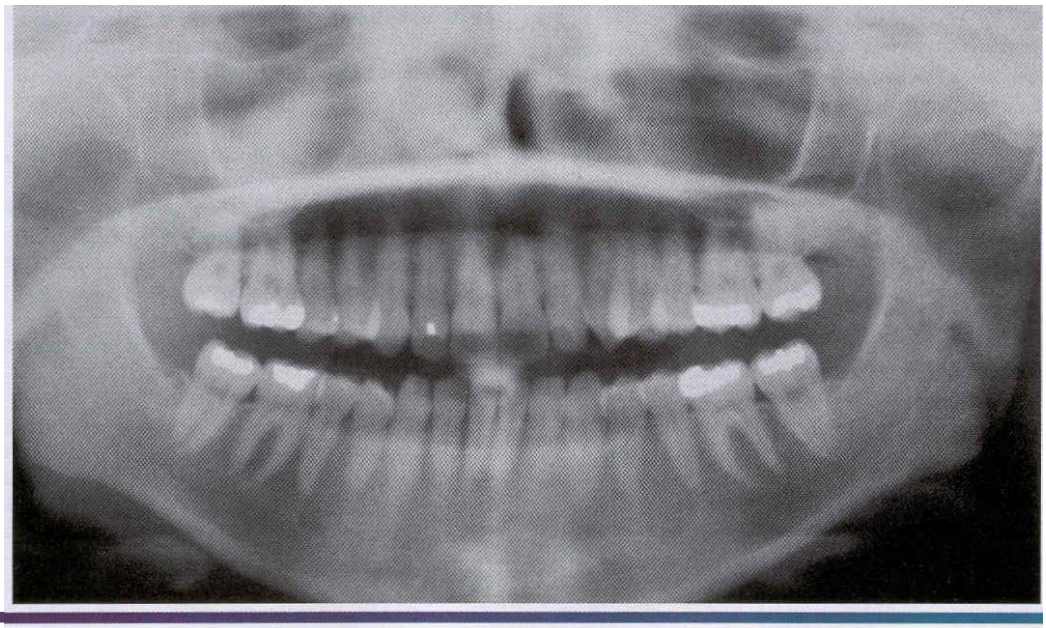

Figure 5-36 • Sinusitis. Cloudy right maxillary antrum.

ease 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 Figure 5-35). The surgery is delicate because it extends close to the orbit and the central nervous system. Each patient's unique anatomy should be evaluated carefully by CT and nasal endoscopy before surgery.

Although endoscopic surgery is considered by many to be the current standard of care for chronic sinusitis, a few investigators still use the more invasive Caldwell-Luc procedure in selected patients. Although the Caldwell-Luc procedure is associated with a higher prevalence of significant complications. it also is associated with a lower number of reoperations when compared with the less invasive endoscopic procedure. Therefore. someclinicians continue to use the old technique in patients who demonstrate recurrent disease limited to the maxillary sinus and prefer a single major operation rather than multiple less invasive procedures.

In children. continued medical management is the therapy of choice for uncomplicated acute or recurrent acute sinusitis. The anatomy in the child. with the decreased distance between the orbit and brain. increases the difficulty of any surgical procedure. Surgical management is indicated in only a small number of childhood sinusitis cases. Suppurative sinusitis extending into surrounding tissues or true chronic sinusitis caused by serious underlying systemic disease are examples of indications for the surgical management of sinus disease in a child.

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CHAPTER 6

Fungal and Protozoal Diseases

CHAPTER OUTLINE

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. *parapsiiosts*, and C. *guitliermondi*, 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 over the age of 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.

Table 6-1 *Clinica! Forms of Oral Calldidiasis*

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. immuno-suppression, idiopathic
Central papillary atrophy (median rhomboid glossitis)	Red. atrophic mucosal areas; asymptomatic	Midline posterior dorsal tongue	Idiopathic. immuno-suppression
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, immuno-suppression. 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, immuno-suppression; care must be taken not to confuse this with other keratotic lesions with super-imposed 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

Clinical Features

Candidiasis of the oral mucosa may exhibit a variety of clinical patterns. which are summarized in Table 6-1 . Many patients will display a single pattern, although some individuals will 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 (Figure 6-1). 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. the mucosa has probably also been affected by another process, such as 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 5tO) or those infected with human immunodeficiency virus (HIV) (see

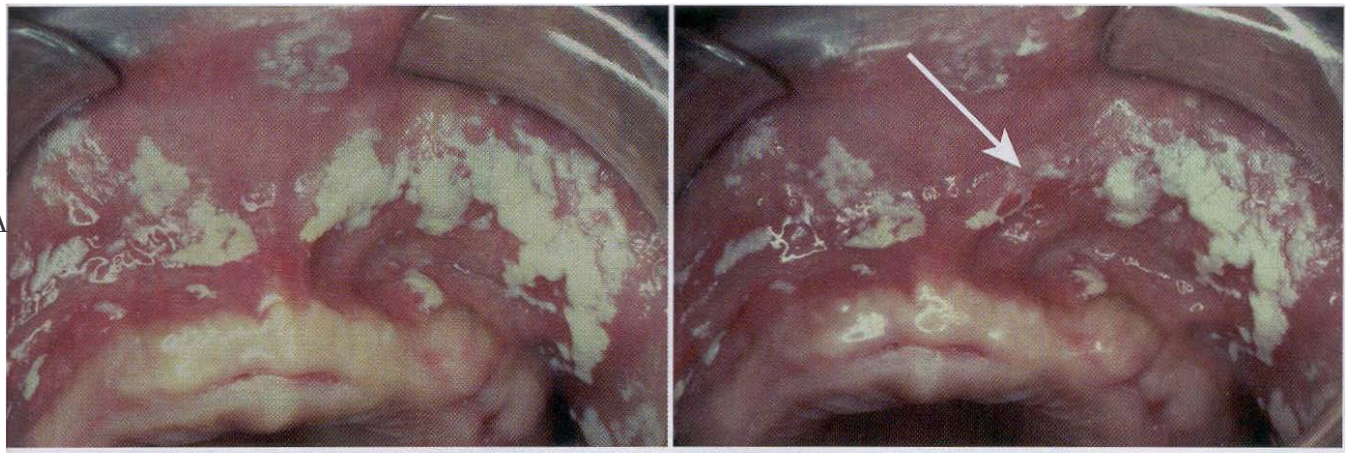

Figure 6' • Pseudomembranous candidiasis. A, Classic "curdled milk" appearance of the oral lesions of pseudomembranous candidiasis. This patient had no apparent risk factors for candidiasis development. 8, Removal of one of the pseudomembranous plaques *(atTOw)* reveals a mildly erythematous mucosal surface. (From Allen CM, Blozis GG: Oral mucosal lesions. In Cummings CW, Fredrickson JM. Harker LA, Krause Q. Schuller DE. editors: *Otolaryngology: head and neck surgery.* ed 3. St Louis. 1998. Mosby.)

page 238) are often associated with pseudomembranous candidiasis. Infants may also be affected. ostensibly because of their underdeveloped immune system. 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.

Erythematous candidiasis. **In contrast to the pseudo-**membranous form. patients with erythematous candidiasis either do not show white flecks or a white component **is not a prominent feature. Several clinical presentations may be seen. The first. known as acute atrophic candidiasis or ··antibiotic sore mouth." typi-**cally follows a course of broad-spectrum antibiotics. Patients often complain that their 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 (Figure 6-2).

Other forms of erythematous candidiasis are usually asymptomatic and chronic. Included in this category is the condition known as central papillary atrophy of the

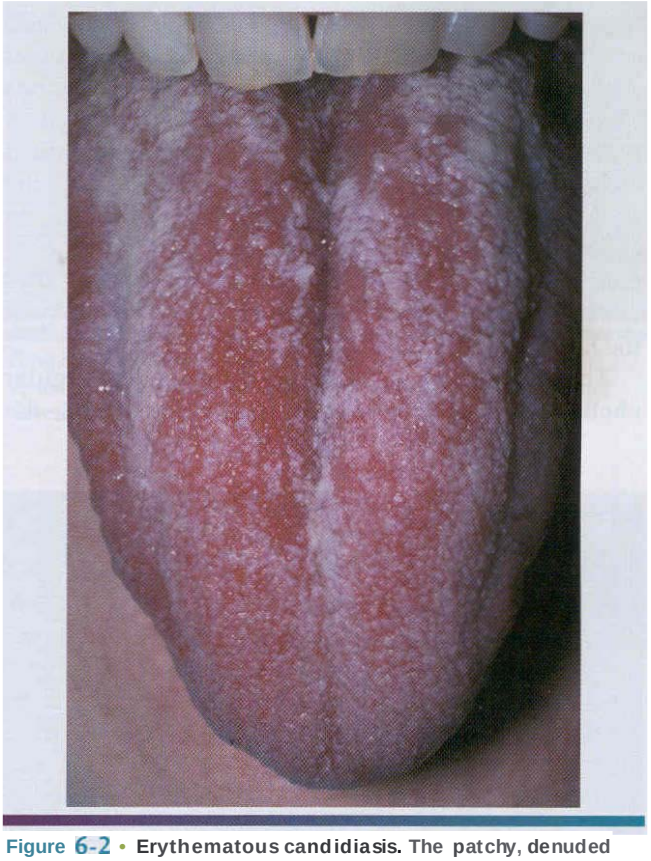

Figure 6-2 • Erythematous candidiasis. The patchy, denuded areas (not the white areas) of the dorsal tongue represent erythematous candidiasis. The patient had received broad-spectrum antibiotics.

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 (Figure 6-3). The erythema is due in part to the loss of the filiform papillae in this area. The lesion is usually symmetric, 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 candida! 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 (Figures 6-4 and 6-5).

The involvement of the angles of the mouth (angular cheilitis. perlèche) is characterized by erythema. fissuring. and scaling (Figure 6-6). Sometimes this condi**tion is seen as a component of chronic multifocal can**didiasis. 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. *aibicans* 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>. creating a clinical pattern known as cheiJocandidiasis (Figure 6-7). Other causes of exfoliative cheilitis often must be considered in the differential diagnosis (see page 266).

Denture stomatitis should be mentioned because it is often classified as a form of erythematous candidiasis. and the term chronic atrophic candidiasis may be used synonymously by some authors. This condition is characterized by varying degrees of erythema. sometimes accompanied by petechial hemorrhage. localized to the denture-bearing areas of a rnaxIllarv removable dental prosthesis (Figures 6-8 and 6-9). 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 con**troversial. The clinician should also rule out the possibility that this reaction could be caused by improper design of the denture (which could cause unusual pres-

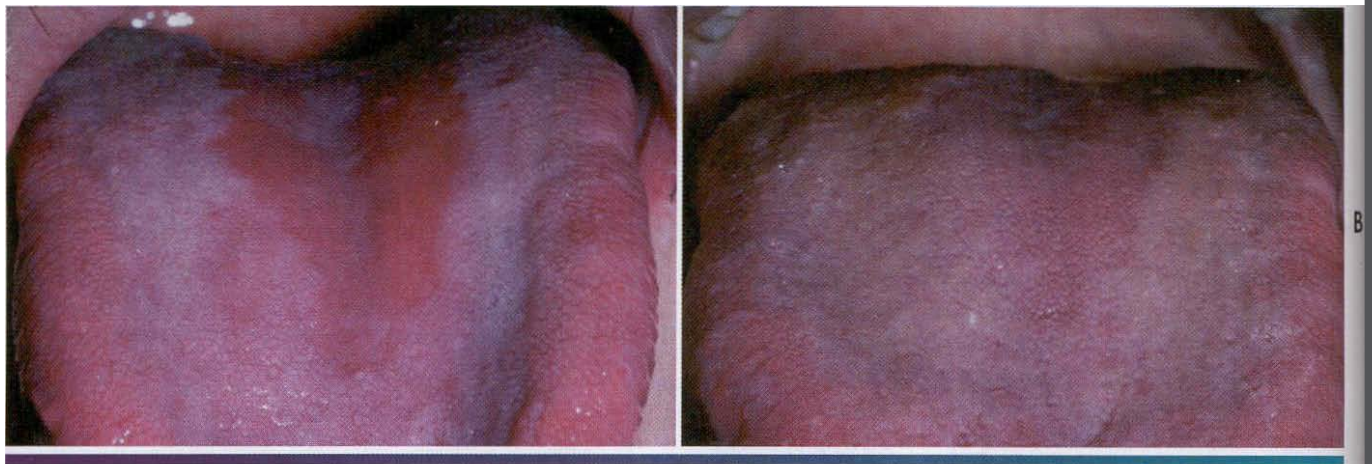

Figure 6-3 **Erythematous candidiasis. A, Severe presentation of central papillary atrophy. In this patient the lesion was asymptomatic. B. There was marked regeneration of the dorsal tongue papillae 2 weeks after antifungal therapy with fluconazole.**

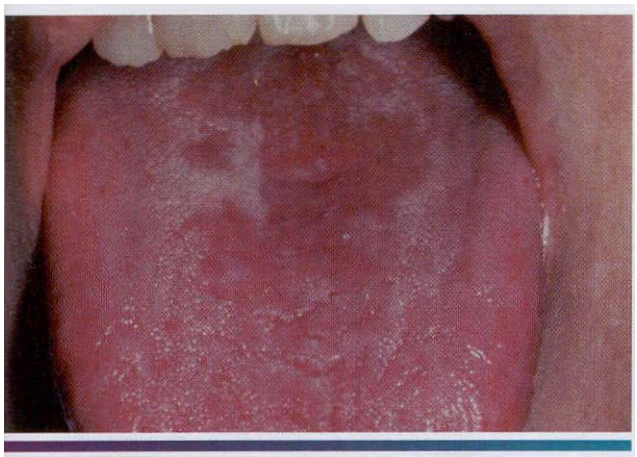

Figure 6-4 • Candidiasis. Multifocal oral candidiasis characterized by central papillary atrophy of the tongue and other areas of involvement.

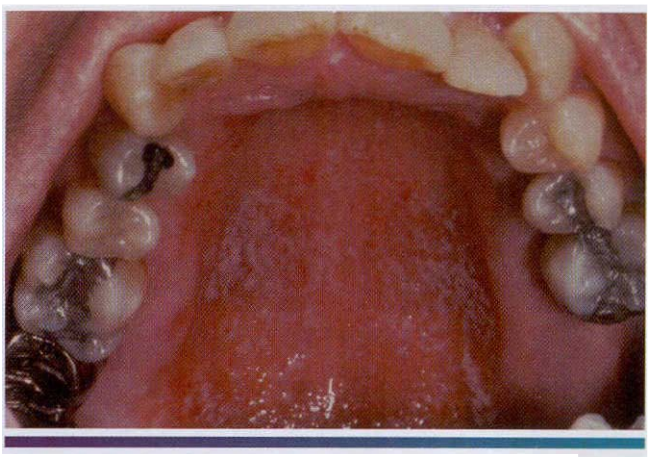

Figure 6-5 • Candidiasis. Same patient as in Figure 6-4. A "kissing" lesion of oral candidiasis involves the hard palate.

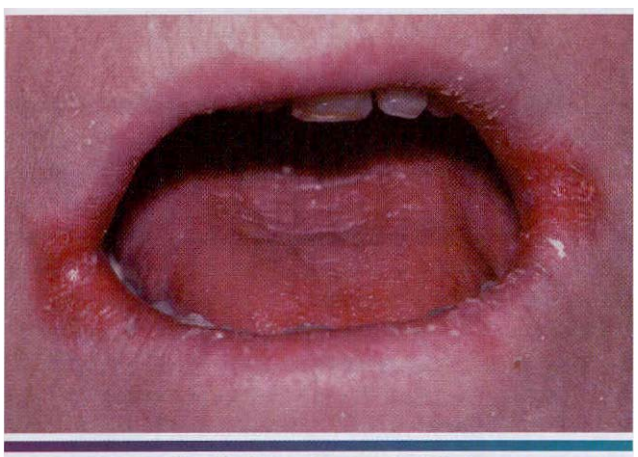

Figure 6-6 • Angular cheilitis. Characteristic lesions appear as fissured. erythematous alterations of the skin at the corners of the mouth.

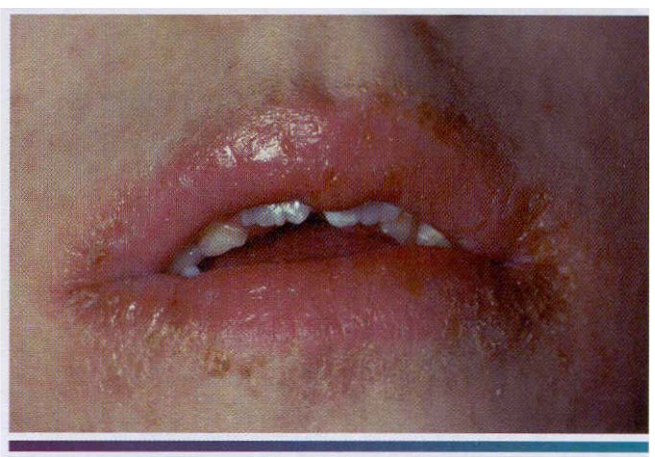

Figure 6-7 • Cheilocandidiasis. The exfoliative lesions of the vermilion zone and perioral skin are due to superficial candida! infection.

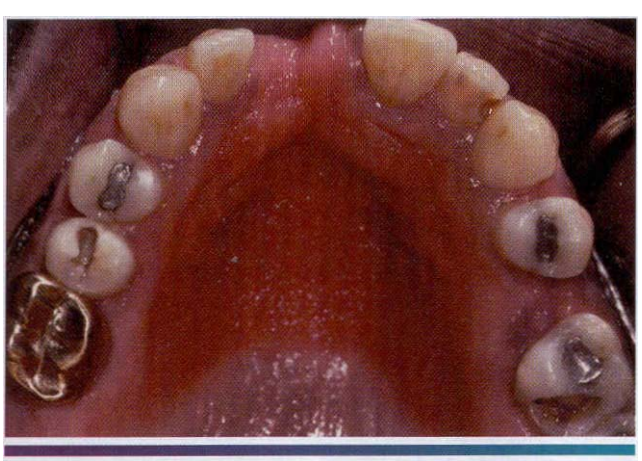

Figure 6-8 • Denture stomatitis. Denture stomatitis in association with an interim partial denture. Note that the mucosal alteration is confined to the denture-bearing mucosa.

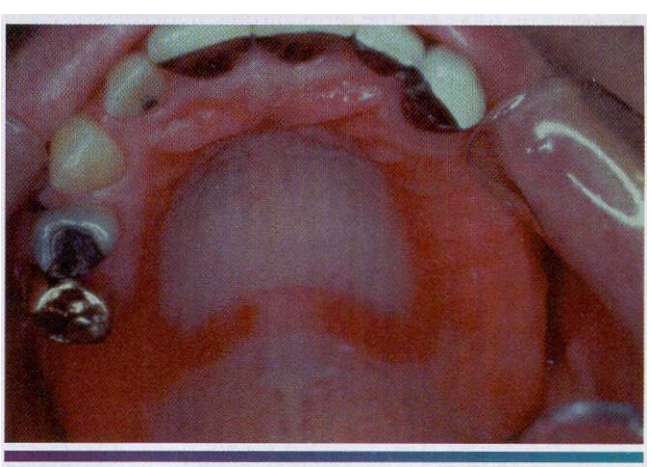

Figure 6-9 • Denture stomatitis. Denture stomatitis. not associated with *Candida albicans*. confined to the denture-bearing mucosa of a maxillary partial denture framework.

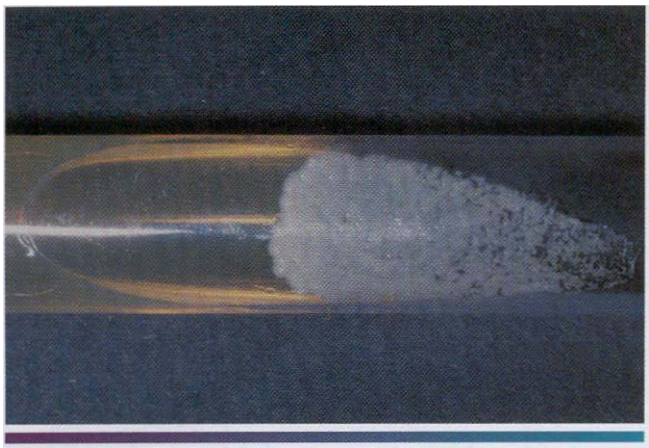

Figure 6-10 • Denture stomatitis. This Sabouraud's agar slant has been streaked with swabs obtained from erythematous palatal mucosa *(left side of the slant)* and the tissue-bearing surface of the denture *(right side of the slant).* Extensive colonization of the denture is demonstrated, whereas little evidence of yeast associated with the mucosa is noted.

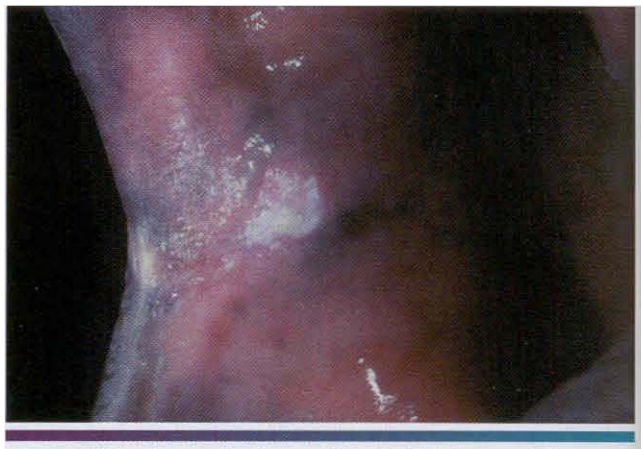

Figure 6-11 • Hyperplastic candidiasis. This lesion of the anterior buccal mucosa clinically resembles a leukoplakia because it is a white plaque that cannot be removed by rubbing. With antifungal therapy, such a lesion should resolve completely.

sure on the mucosa), allergy to the denture base, or inadequate curing of the denture acrylic.

Although *C. albimans* 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, one of the main defining criteria for the diagnosis of infection—host tissue invasion by the organism—is not met by this lesion. Furthermore, if the palatal mucosa and tissue-contacting surface of the denture are swabbed and separately streaked onto a Sabouraud's agar slant, the denture typically shows much heavier colonization by yeast (Figure 6-10).

Chronic hyperplastic candidiasis (calldidal 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 (Figure 6-11). Often the leukoplaklc lesion associated with candidal infection has a fine intermingling of red and white areas, resulting in a speckled leukoplakia (see page 341). 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 by complete resolution of the lesion after antifungal therapy (Figure 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. 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 appear as thick, white plaques that typtcally do not rub off (essentially chronic hyperplastic candidiasis).

Patients should be evaluated periodically because any **one of a variety of endocrine abnormalities (endocrine-**candidiasis syndrome), as well as iron-deficiency anemia, may develop in addition to the candidiasis. These endocrine disturbances include hypothyroidism, hypoparathyroidism, hypoadrenocorticism (Addison's disease), and diabetes mellitus. Typically, the endocrine abnormality develops months or even years after the onset of the candida! infection. Interestingly, the candidal infection remains relatively superficial rather than disseminating throughout the body. Both the oral lesions and the rather grotesque, roughened, foul-smelling cutaneous plaques and nodules can be controlled with continuous use of relatively safe systemic antifungal drugs.

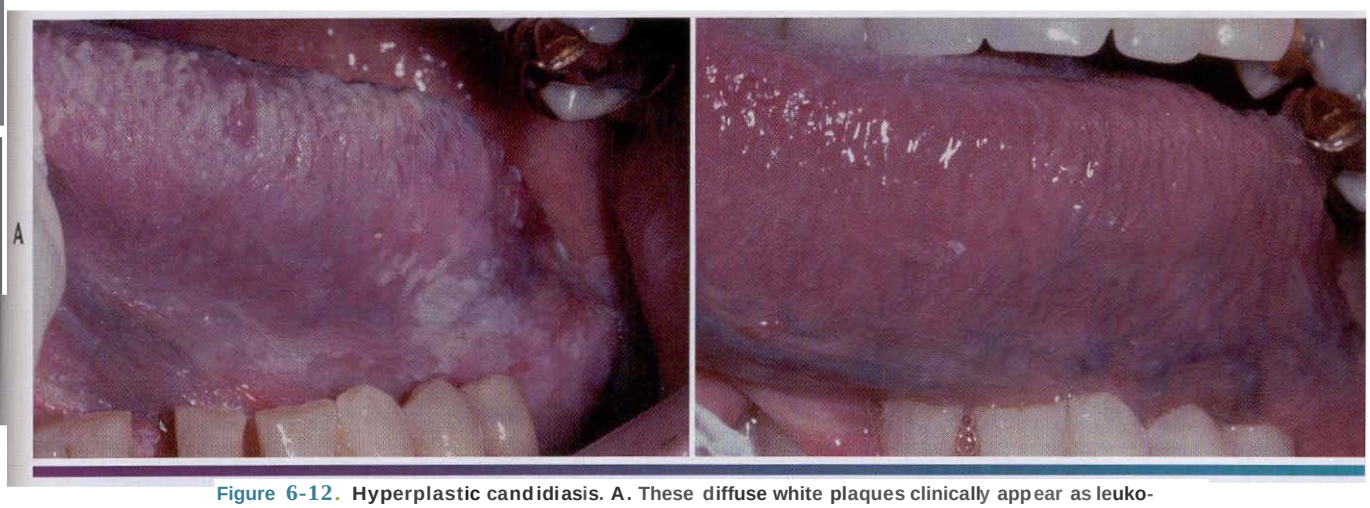

Figure 6-12. Hyperplastic candidiasis. A. These diffuse white plaques clinically appear as leukoplakia. but they actually represent an unusual presentation of hyperplastic candidiasis. B, Treatment with c1otrimazole oral troches shows complete resolution of the white lesions within 2 weeks. essentially confirming the diagnosis of hyperplastic candidiasis. If any white mucosal alteration had persisted. a biopsy of that area would have been mandatory.

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. the candidal hyphae and yeasts can be readily identified (Figure 6-13l. The PAS method stains carbohydrates. contained in abundance by fungal cell walls: the organisms are easily identified by the bright magenta color imparted by the 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 (KOHl 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 parakcratin on the surface of the lesion in conjunction with elongation of the epithelial rete ridges (Figure 6-14l. 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 (Figure 6-15). 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.

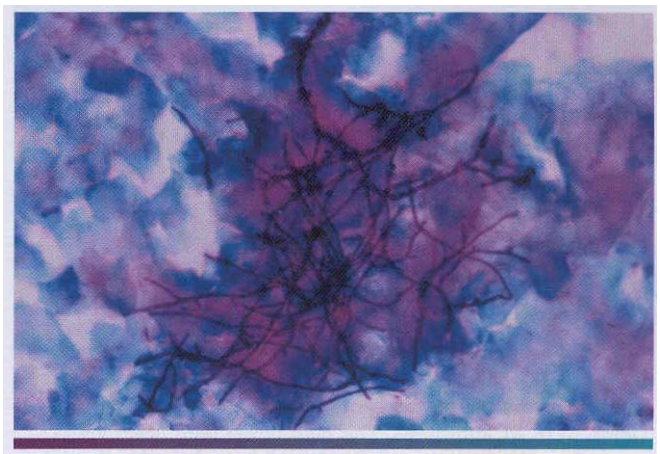

Figure 6-13 • Candidiasis. This cytologic preparation demonstrates tubular-appearing fungal hyphae and ovoid yeasts of *Candida albicans.* (PAS stain)

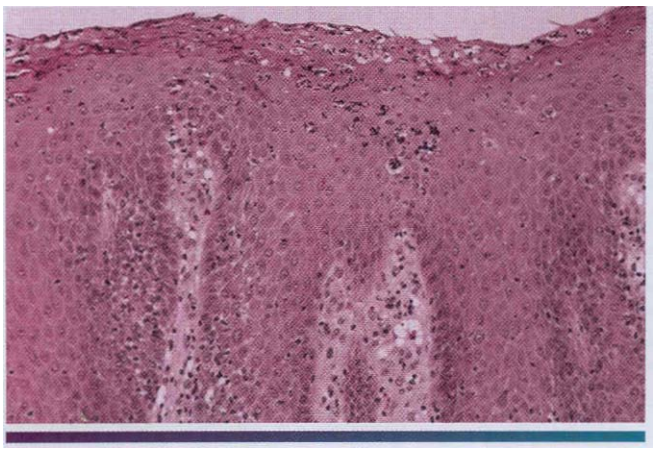

figure 6-14 • Candidiasis. This medium-power photomicrograph shows a characteristic pattern of paraleratosis, neutrophilic microabscesses. a thickened spinous layer, and chronic inflammation of the underlying connectivetissue associated with long-standing candidal infection of the oral mucosa.

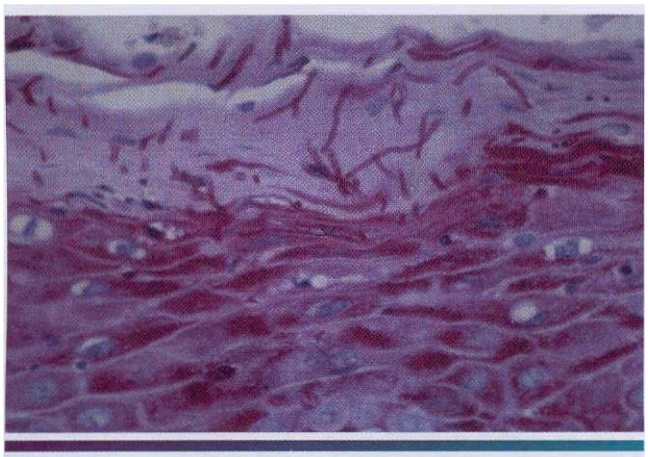

Figure 6-15 • Candidiasis. This high-powerphotomicrograph shows the tubular hyphae of *Candida afbicons* embedded in the parakeratin layer. (PAS stain)

Diagnosis

The diagnosis of candidiasis in clinical practice is usually established by the clinical signs in conjunction with exfoliative cytoiogic examination, Although a culture can definitively identify the organism as C. *albtcans,* this process *may* not be practical in most office settlngs, The cytologic findings should demonstrate the hyphal phase of the organism, and antifungal therapy can then be instituted, If the iesion is clinically suggestive of chronic hyperplastic candidiasis but does not respond to antifungal therapy, a biopsy should be performed to rule out the possibility of C. *olbicans* 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 colton swab over the lesion and then streaking the swab on the surface of a Sabouraud's agar slant. C. *aibicans* 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***

Nystattn. 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 both nystatin and the other polyene antibiotic, amphotericin; therefore, their effectiveness depends on direct contact with the candida! organisms. This necessitates multiple daily doses so that the yeasts are adequately exposed to the drug. Nystatin combined with triamcinoione acetonide cream or ointment can be applied topically and is effective for angular cheilitis that does not have a bacterial component.

Amphotencin B. For many years in the United States, the use of amphotericin B was restricted to intravenous 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 Figure 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 the patient to use; however, several disadvantages

have been noted. Patients must not take antacids or Hz-blocking agents because an acidic environment is required for proper absorption. If a patient is to take ketoconazole for more than 2 weeks, liver function studies are recommended because approximately I in 10.000 individuals will experience idiosyncratic *liver* toxicity from the agent. For this reason. the u.s. 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 the macrolide antibiotics (e.g.. erythromycin). the gastrointestinal motility-enhancing agent clsaprtdc, and the antihistamine astemizole, all of which may produce potentially life-threatening cardiac arrhythmias.

Triazole agents. The trtazoles are the newest group of 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 (Dilantln). 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 c1otrimazole and fluconazole. As with fluconazole, significant drug interactions are possible. and itraconazole is contraindicated for patients taking asternizolc, triazolam, midazolam, and cisapride. (See Table 6-2 for other potential drug interactions.)

***Other** anli{lll1gal 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. 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 (Figure 6- 16).

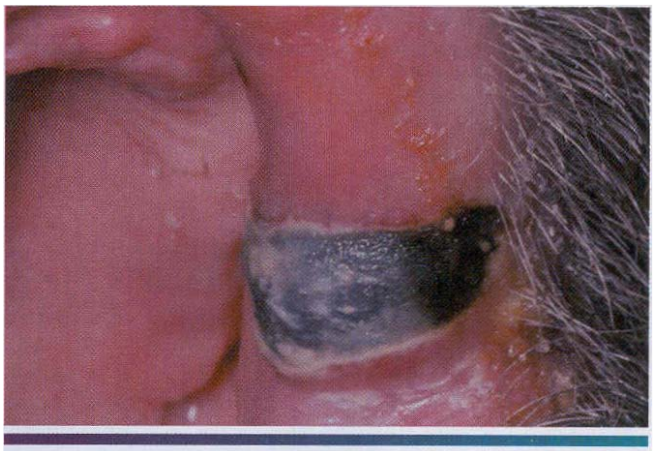

Figure 6-16 • Candidiasis. This necrotic lesion of the upper lip developed in a man with uncontrolled type I diabetes mellitus. Biopsy and culture showed a rare example of invasive oral infection by C. *albicans*.

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 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 Mississtppl 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 have either no symptoms or they have a mild.

Table 6-2 *Antifungal Medications*

GENERIC NAME	TRADE NAME	INDICATIONS	DOSAGE
Nystatin	Mycostatin Pastilles Mycostatin Oral Suspension	Oral candidiasis	1 or 2 pastilles (200,000-400,000 units) dissolved slowly in the mouth 4-5 times daily for 10-14 days
Clotrimazole	Mycelex Oral Troches	Oral candidiasis	Dissolve 1 troche (10 mg) slowly in the mouth, 5 times daily for 10-14 days
Ketoconazole	Nizoral Tablets	Oral candidiasis Blastomycosis Coccidioidomycosis Histoplasmosis Paracoccidioidomycosis	Not to be used as initial therapy for oral candidiasis 1 tablet (200 mg) daily for 1-2 wk for candidiasis Minimum treatment period for systemic mycoses is 6 mo
Fluconazole	Diflucan Tablets	Oral candidiasis Cryptococcal meningitis	For oral candidiasis: 2 tablets (200 mg) on day 1 and then 1 tablet (100 mg) daily × 1-2 wk
Itraconazole	Sporanox Capsules	Blastomycosis Histoplasmosis Aspergillosis refractory to amphotericin B therapy	For blastomycosis and histoplasmosis: 2 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: 200-400 mg daily For life-threatening situations: loading dose of 200 mg TID for first 3 days, then dose can be reduced Treatment should continue for at least 3 mo for all the above
Itraconazole	Sporanox Oral Solution	Oral candidiasis	10 ml (100 mg) vigorously swished in the mouth and swallowed, twice daily for 1-2 wk
Amphotericin B	Fungizone Oral Suspension	Oral candidiasis	1 ml (100 mg) rinse and hold in the mouth for as long as possible, QID, PC and HS × 2 wk

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, 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 elderly, 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

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 pre-existing hepatic problems, patients who develop symptoms of hepatic failure, or patients treated for > 28 days Serum testosterone is lowered Nausea, vomiting Anaphylaxis	Serious and/or life-threatening interactions with terfenadine, asternizole. or cisapride 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: oral hypoglycemics, coumarin-like drugs, phenytoin, cyclosporine, rtfampln. theophylline, terfenadtne. cisapride. astemizole, rifabutin, and tacrolimus
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 terfenadine, astemizole, plmozide. quinidine, oral triazolarn, oral midazolam, and cisapride Lovastatin and simvastatin should be discontinued Increased plasma concentrations may be seen with warfarin, ritonavir, indinavir, vinca alkaloids, diazepam, dihydropyridines, cyclosporine, tacrolimus, methylprednisolone, and digoxin
Rare cases of hepatotoxicity Liver function should be monitored in patients with preexisting hepatic problems on therapy for more than 1 mo Nausea, diarrhea, vomiting	Serious and/or life-threatening interactions with terfenadine, astemizole. oral triazolem. oral midazolam, and cisapride Lovastatin and simvastatin should be discontinued
Rash, gastrointestinal symptoms	No significant drug interactions

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, from 2% to 10% of patients with acquired immunodeficiency syndrome (AIDS) (see page 245) develop disseminated histoplasmosis. Tissues that may be affected include the spleen. adrenal glands, liver, lymph nodes. gastrointestinal tract. central nervous system (eNS), kidneys. and oral mucosa. Adrenal involvement may produce hypoadrenocorticism (Addison's disease) (see page 727).

. 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 (Figure 6-17). The ulcerated lesions have firm, rolled margins. and they may be indistinguishable clinically from a malignancy (Figure 6-i8).

Histopathologic Features

Microscopic examination of lesional tissue shows either a diffuse Inftltrate of macrophages or. more commonly, collections of macrophages organized into granulomas (Figure 6-19). 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-stained section; however, special stains, such as the PAS and Grocott-Gomori methenamine silver methods, readily demonstrate the characteristic 1- to z-urn yeasts of H. *capsulatum* (Figure 6-20).

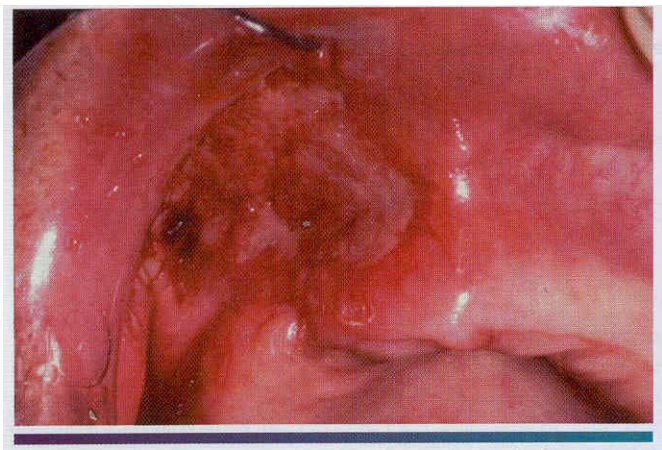

Figure 6-17 • Histoplasmosis. This ulcerated granular lesion involves the maxillary buccal vestibule and is easily mistaken clinically for carcinoma. Biopsy established the diagnosis. (From Allen eM, Blozis GG: Oral mucosal lesions. In Cummings CW, Fredrickson JM, Harker LA, Krause C). Schuller DE, editors: *Otolaryngology: head and neck surgery*, ed 3, St louis, 1998, Mosby.)

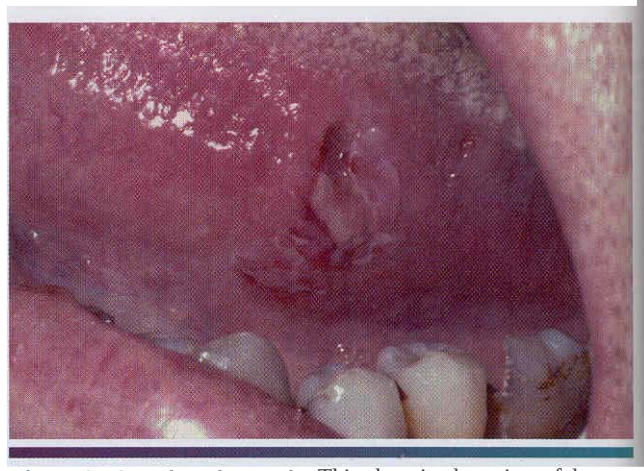

Figure 6-18 • Histoplasmosis. This chronic ulceration of the ventral and lateral tongue represents an oral lesion of histoplasmosis that had disseminated from the lungs. The lesion clinically resembles carcinoma; because of this high-risk site, biopsy is mandatory.

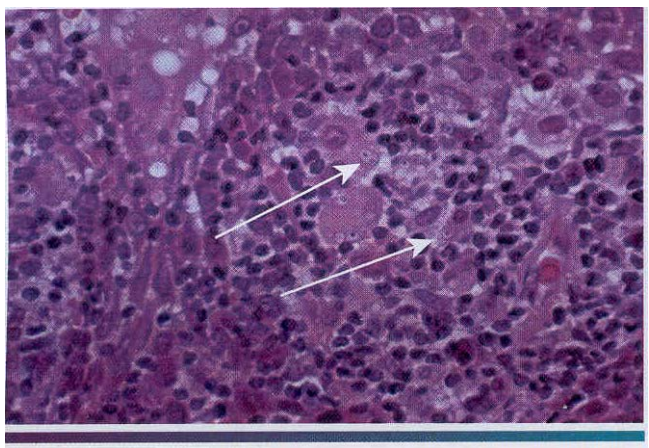

Figure 6-19 • Histoplasmosis. This medium-power photomicrograph shows scattered epithelioid macrophages admixed with lymphocytes and plasma cells. Some macrophages contain organisms of *Histoplasma capsulatum (arrows)*.

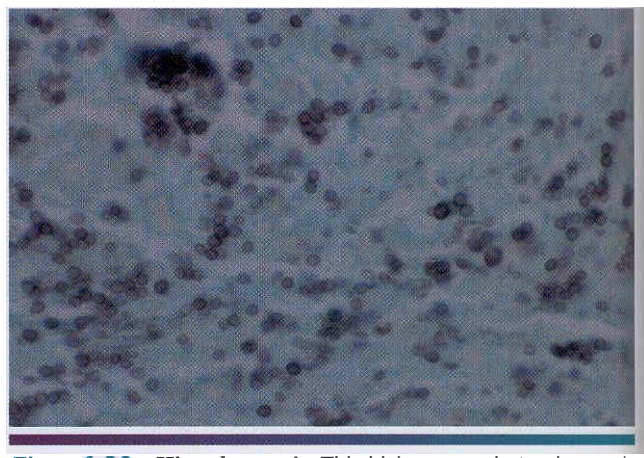

Figure 6-20 • Histoplasmosis. This high-power photomicrograph of a tissue section readily demonstrates the small yeasts of *Histoplasma capsulatum*. (Grocott-Gomori methenamine silver stain)

Diagnosis

The diagnosis of histoplasmosis can be made by histopathologic identification of the organism in tissue sections or by culture. Other helpful diagnostic studies inciude serologic testing in which antibodies directed against H. *copsulatum* are demonstrated and antigen produced by the yeast is identified.

Treatment and Prognosis

Acute histoplasmosis, because it is a self-limited process, generally warrants no specific treatment other than supportive care with analgesics and antipyretics. Often the disease is not treated because the symptoms are so nonspecific and the diagnosis is not readily evident.

Patients with chronic histoplasmosis usually require treatment, despite the fact that up to half of them *may* recover spontaneousiy. Often the pulmonary damage is progressive if it remains untreated, and death may result in up to 20% of these cases. The treatment of choice is intravenous amphotericin B, although significant kidney damage can result from this therapy. For that reason, ketoconazole may be used in nonimmunosuppressed patients because it is associated with fewer side effects. The triazole compound itraconazole can also be used for treatment

ofhistoplasmosis. This agent appears to be more effective than ketoconazole and less likely to produce toxicity.

Disseminated histoplasmosis is a very serious condi- tion that results in death in 90% of the patients if they remain untreated. Amphotericin B is usually indicated for such patients. Despite therapy, however, a mortality rate of 7% to 23% is observed. Itraconazole or ketoconazole **may also be used if the patient is nonimmunocompromised: however, the response rate is slower than** lor 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 *Btostomyces dermatilidis.* 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. *capsula/urn* (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 10 times more common than** blastomycosis. In several series of cases, a prominent adult male predilection has been noted, often with a male-to-female ratio as high as 9:I. This has been attributed to the greater degree of outdoor activity (e.g., hunting, fishing) by men in areas where the organism grows. 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 hernatogenously **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-Ihreatenlng adult respiratory distress syndrome.

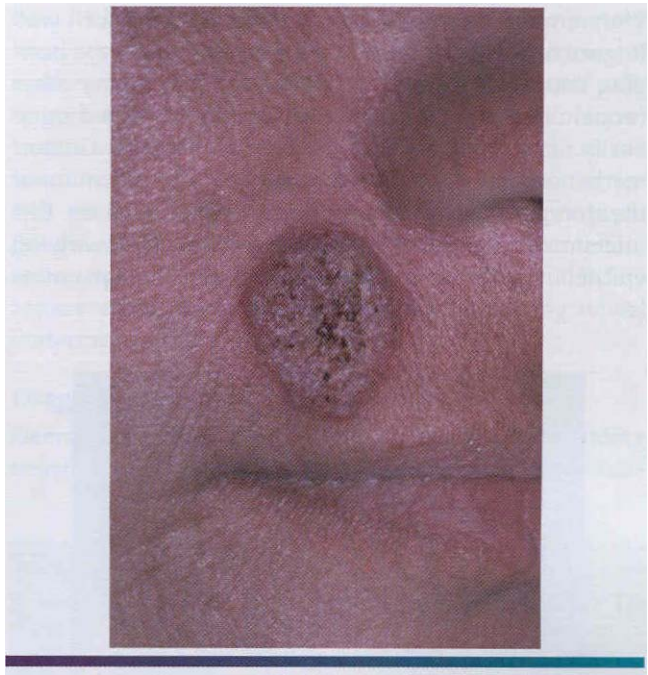

Figure 6-21 • Blastomycosis. This granular erythematous plaque of cutaneous blastomycosis has affected the facial skin. (Courtesy of Dr. William Welton.)

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 (Figures 6-21 and 6-22).

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 (Figure 6-23). Clinically, because the lesions 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 urn in diameter.

They are characterized by a doubly refractile cell wall (Figure 6-24) and a broad attachment between the budding daughter cell and the parent cell. Like many other fungal organisms, B. *dermattudis* 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 Cpseudocarcinomatousl 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.

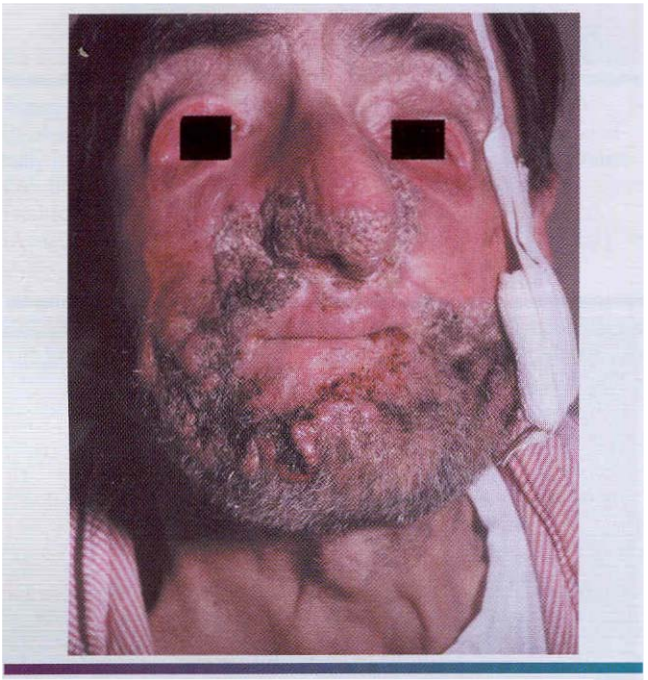

figure 6-22 • Blastomycosis. Severe cutaneous infection by *Bfastomyces desmatitidis.* (Courtesyof Dr. Emmitt Costich.)

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 froma suspected lesion. The most accurate method of identifyi ng B. *dermatttidis* is by obtaining a culture specimen from sputum or fresh biopsy material and growing the organism on Sabouraud's 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 cultu re. Serologic studies are usually not helpful.

Treatment and Prognosis

As stated previously, most patients with blastomycosis require no treatment. Even in the case of symptomatic acute blastomycosis, administration of systemic amphotericin B is indicated only if the patient:

- Is seriously ill,
- Is not improving clinically, or
- Is ill for more than 2 or 3 weeks.

Patients with chronic blastomycosis or extrapulmonary lesions need treatment. Itraconazole is generally recommended, particularly if the infection is mild or

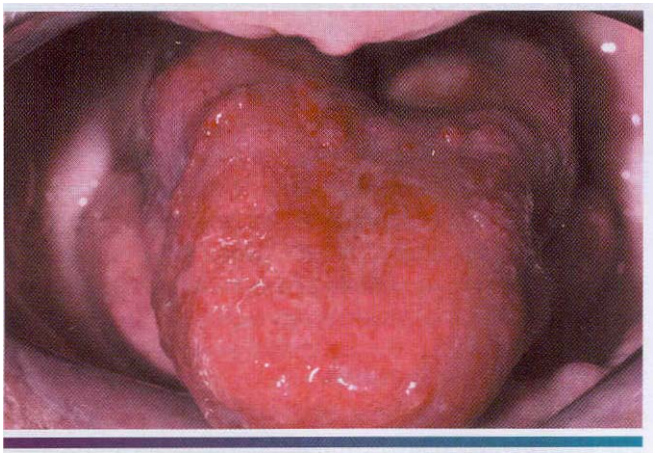

Figure 6-23 • Blastomycosis. These irregular ulcerations of the tongue represent blastomycosis. Direct inoculation was thought to have occurred from the patient's habit of chewing dried horse manure r Kentucky field candy"), in which the organism was probably growing.

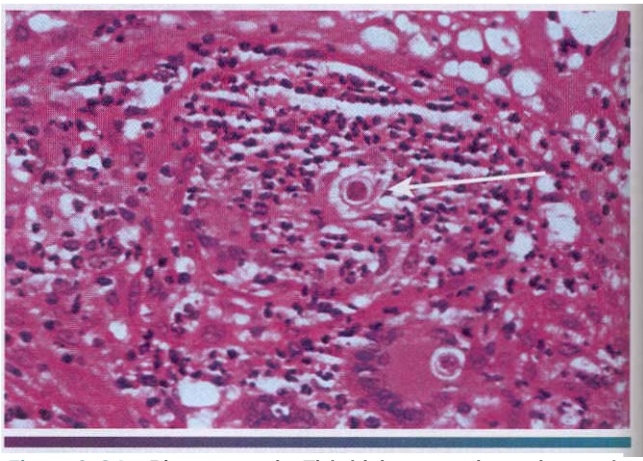

Figure 6-24 • Blastomycosis. This high-power photomicrograph shows the large yeasts of *Blastomyces dermatitidis (arrow)* and a pronounced host inflammatory response to the organism.

moderate. Although ketoconazole is active against B. *dermatitidis*, it has been shown to be less effective than itraconazole. Amphotericin B is reserved for patients who are severely ill or show no response to itraconazole.

Disseminated blastomycosis occurs in only a small percentage of infected patients and, with proper treatment, the outlook for the patient is reasonably good.

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 recently has been shown to harbor P. *brasiliensis* (similar to the situation seen with leprosy) (see page 176). 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 25:1 male-to-female ratio typically reported. This striking difference is thought to be attributable to a protective effect of female hormones (because beta-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's disease) (see page 72).

Oral lesions appear as mulberry-like ulcerations that most commonly affect the alveolar mucosa, gingiva, and palate (Figure 6-25). The lips, 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.

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 (Figure 6-26). 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 ade-

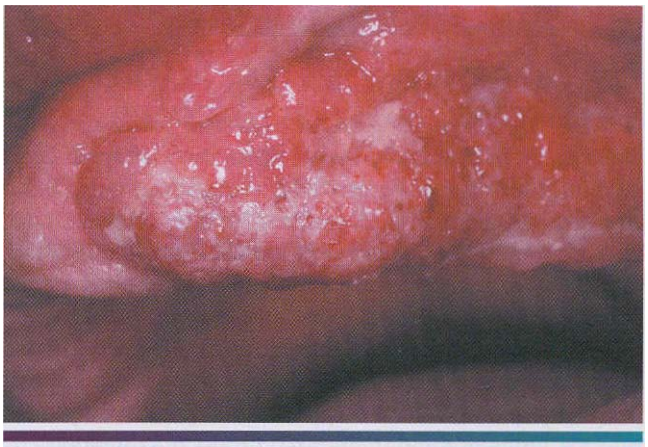

Figure 6-25 • Paracoccidioidomycosis. This granular, erythematous, and ulcerated lesion of the maxillary alveolus represents infection by P. *brasiliensis*. (Courtesy of Dr. Ricardo Santiago Gomez.)

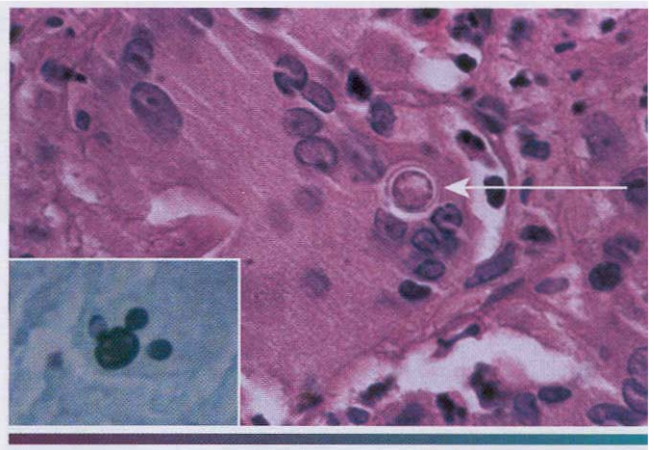

Figure 6-26 • Paracoccidioidomycosis. This high-power photomicrograph shows a large yeast of P. *brasiliensis (arrow)* within the cytoplasm of a multinucleated giant cell. A Grocott-Gomori methenamine silver-stained section *(inset)* illustrates the characteristic "Mickey Mouse ears" appearance of the budding yeasts. (Courtesy of Dr. Ricardo Santiago Gomez.)

quare to establis h 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 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, intravenous amphotericin B is usually indicated. Cases that are not life-threatening 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)

Coccidioides immitis is the fungal organism responsible for coccidioidomycosis. C. *immitis* grows saprophytically in the alkaline. semiarid, desert soil of the southwestern United States and Mexico, with isolated regions also noted in Central and South America. As with several other pathogenic fungi, C. *immitis* is a dimorphic organism, appearing as a mold in its 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.

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 asyrnptomanc.

Clinical Features

Most infections with C. *immitis* are asymptomatic, although approximately 40% of infected patients experience a f1ulike illness and pulmonary symptoms within I to 3 weeks after inhaling the arthrospores. Fatigue, cough, chest pain. myalgias, and headache are commonly reported, lasting severai weeks with spontaneous resolution in most cases. Occasionally, the immune response may trigger a hypersensitivity reaction that causes the development of erythema rnultlforrne (see page 674) or erythema nodosum. Erythema nodosum 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. This occurs in less than 1% of the cases. but it is a more serious problem. The most commonly involved areas include skin , 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 (organ transplant recipients)
- Patients being treated with cancer chemotherapy
- Patients in the end stages of HIV infection

Infants and older 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, 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 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.

Histopathologic Features

Biopsy material shows large (20 to 60 urn). 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 01 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. Cytologic preparations from bronchial swabbings 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 immunocompe**lent person do not warrant treatment. Amphotericin** B **is** administered for the following groups:

- Immunosuppressed patients
- Patlenjs with severe pulmonary infection
- Patients who have disseminated disease
- Patients who appear to be in a life-threatening sit**uation concerning the infection**

For many cases of coccidioidomycosis. fluconazole is the drug of choice. usually given in high doses for an extended period of time. Although the response of the disease to fluconazole may be somewhat slower than that of amphotericin B. the side effects and complications of therapy are far fewer. Ketoconazole may be used **as an *alternative* treatment for** mild-to-moderate **cases of coccidioidomycosis.**

CRYPTOCOCCOSIS

Cryptococcosis is a relatively uncommon fungal disease caused by the yeast *Cryptococcus neoformans*. This organism normally causes no problem in immunocompetent people. but it can be devastating to the immunocompromised patient. The incidence of cryptococcosis has increased dramatically during the past decade. primarily because of the AIDS epidemic; it is the most common life-threatening fungal infection in these 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 that destroy most of the yeasts. Macrophages soon follow. although resolution of infection in the immunocompetent host ultimately depends on an intact cell-mediated immune system.

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. AIDS). It is estimated that 5% to 10% of AIDS patients acquire this infection (see page 234).

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.

Cryptoeoeeal 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 20% 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 (Figure 6-27).

Although oral lesions are relatively rare. they have been described as craterlike. nonhealing ulcers that are tender on palpation. 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 or**ganism. 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 J.lm in diameter. surrounded by a clear halo that represents the capsule. Staining with the PAS or **Grocott-Gomori methenamine silver method can readily identify the fungus; moreover, a mucicarmine** stain uniquely demonstrates its mucopolysaccharide capsule.

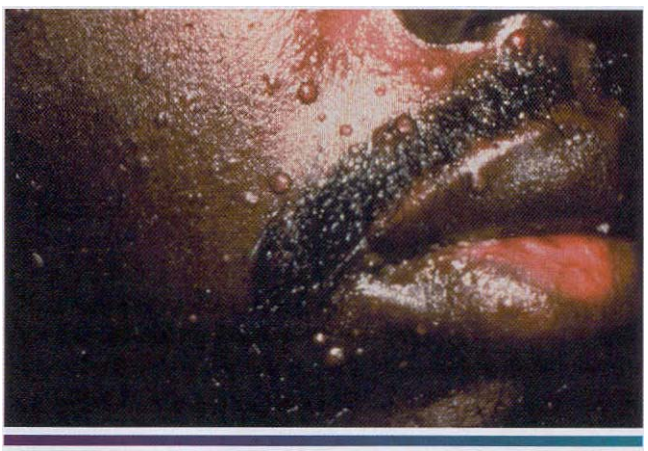

Figure 6-27 • Cryptococcosis. These papules of the facial skin represent disseminated cryptococcal infection in an HIV-infected patient. (Courtesy of Dr. Catherine Flaitz.]

Diagnosis

The diagnosis of cryptococcosis can be made by several methods, including biopsy and culture. Detection of cryptococcal 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. A combination of systemic amphotericin B and another antifungal drug (flucytosine) is used in most cases to treat this disease. The triazoles fluconazole and itraconazole have been effective in controlling cryptococcosis, and fluconazole has been approved for this purpose. These drugs produce far fewer side effects than do amphotericin B and flucytosine, and they should prove useful in the future.

ZYGOMYCOSIS (MUCORMYCOSIS; PHYCOMYCOSIS)

Zygomycosis is an opportunistic, frequently fulminant, fungal infection that is caused by normally saprobic organisms of the class Zygomycetes, including such genera as *Absidia*, *Mucor*, *Rhizomucor*, and *Rhizopus*. These 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.

Zygomycosis may involve any one of several areas of the body, but the rhinocerebral form is most relevant to the oral health care provider. Zygomycosis is noted especially in insulin-dependent diabetics who have uncontrolled diabetes and are ketoacidotic; however, as with many other fungal diseases, this infection affects immunocompromised patients as well. Only rarely has zygomycosis been reported in apparently healthy individuals.

Clinical and Radiographic Features

The presenting symptoms of rhinocerebral zygomycosis 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 (Figures 6-28 and 6-29).

Radiographically, opacification of the sinuses may be observed in conjunction with patchy effacement of the bony walls of the sinuses (Figure 6-30). 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 (Figure 6-31). 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.

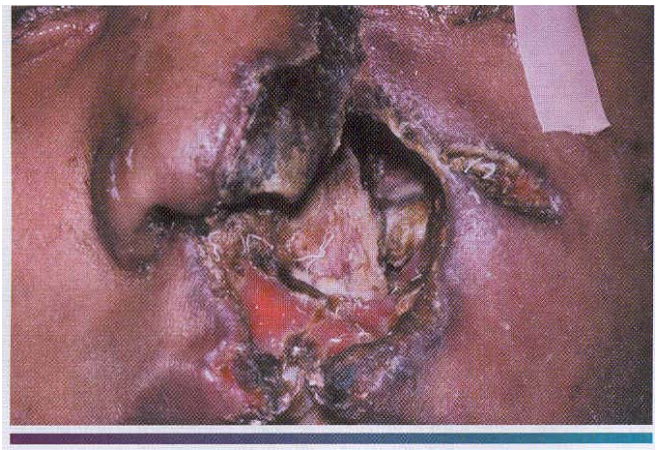

Figure 6-28 • Zygomycosis. Diffuse tissue destruction involving the nasal and maxillary structures caused by a *Mucor* species. (Courtesy of Dr. Sadru Kabani.)

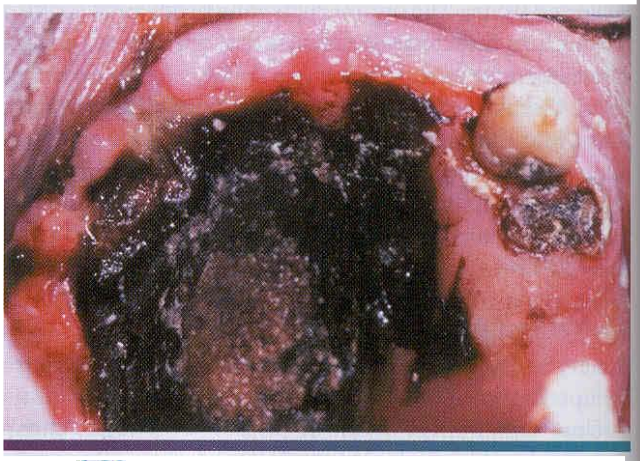

Figure 6-29 • Zygomycosis. The extensive black, necrotic lesion of the palate represents zygomycotic infection that extended from the maxillary sinus in a patient with poorly controlled type I diabetes mellitus. (Courtesy of Dr. Michael Tabor.)

Diagnosis

Diagnosis of zygomycosis 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

Treatment of zygomycosis consists of radical surgical debridement of the infected, necrotic tissue and systemic administration of high doses of amphotericin B. Magnetic resonance imaging of the head is useful in determining the extent of disease involvement so that surgical margins can be planned. In addition. control of the patient's underlying disease (e.g.. diabetic ketoacidosis) must be attempted. Despite such therapy. the prognosis is usually poor. Should the patient survive, the massive tissue destruction that remains presents a challenge both functionally and aesthetically. Prosthetic obturation of palatal defects may be necessary.

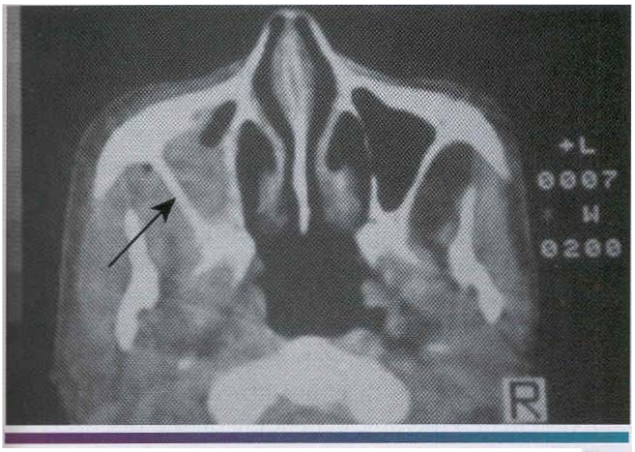

Figure 6·30 • **Zygomycosis. This (T scan demonstrates the opacification of the left maxillary sinus *(arrow)*.**

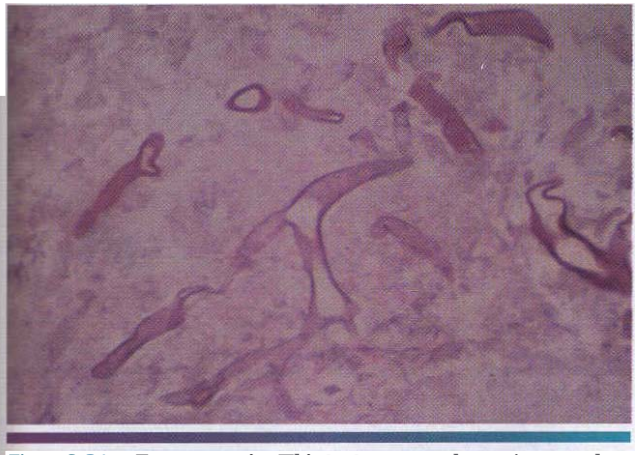

Figure 6-31 • **Zygomycosis. This** high-power **photomicrograph shows the large, nonseptate fungal hyphae characteristic of the** zygomycot**ic organisms.**

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. Local**ized invasive infection of damaged tissue may be seen in a normal host. but a more extensive invasive infection is often evident in the immunocompromiscd 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* infections. Rarely. invasive aspergillosis has been reported to affect the paranasal sinuses of apparently normal immunocompetent individuals.

Normally. the various species of the *Aspergillus* genus **reside worldwide as saprobic organisms in soil. water, or decaying organic debris. Resistant spores arc 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. *{favus* and A. *[umigalus.* with A. *[umigatus* being responsible for 90% of the 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 an aspergilloma. Occasionally. the mass will undergo dystrophic calcification. producing a radiopaque body called **an antrolith within the sinus.**

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 mar-

ginal 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 (Figure 6-32). If the disease is not treated, extensive necrosis, 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 blood stream, infection can spread to such sites as the CNS, eye, skin, liver, gastrointestinal tract, bone, and thyroid gland.

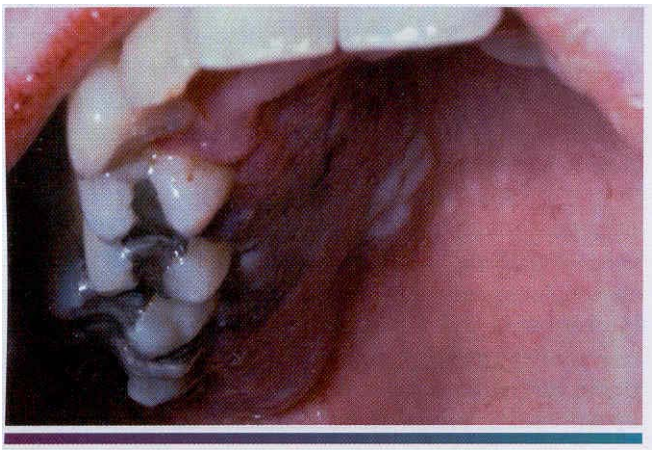

Figure 6-32 • Aspergillosis. This young woman developed a painful purplish swelling of her hard palate after induction chemotherapy for leukemia.

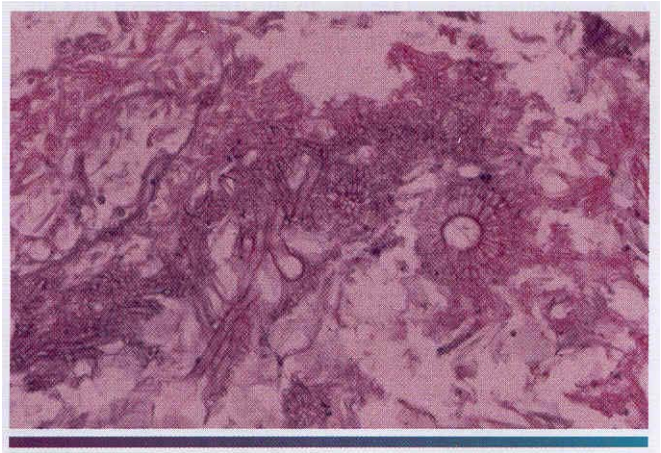

Figure 6-33 • Aspergillosis. This photomicrograph reveals fungal hyphae and a fruiting body of an *Aspergillus* species.

Histopathologic Features

Tissue sections of *Aspergillus* lesions show varying numbers of branching, septate hyphae, 3 to 4 um in diameter (Figures 6-33 and 6-34). 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.**

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 01 **aspergillosis. For immunocompetent patients with a** noninvasive aspergilloma, surgical debridement may be all that is necessary. Patients who have allergic fungal **sinusitis are treated with debridement and corticosteroids.** For localized *invasive* aspergillosis in the **immunocompetent host, debridement is indicated.** This may be combined with either itraconazole or systemic amphotericin B therapy, depending on the severity of the

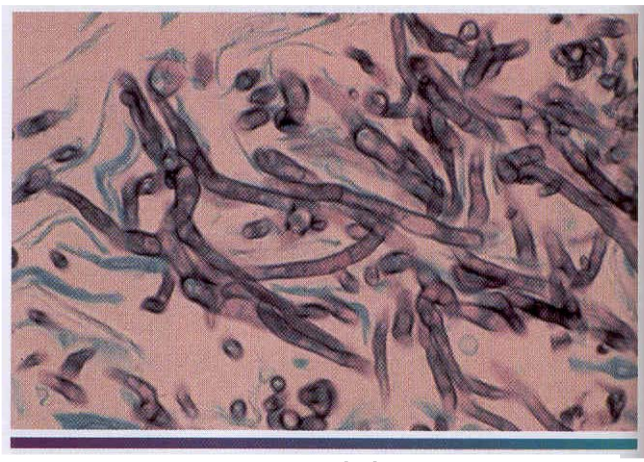

Figure 6-34 • Aspergillosis. This high-power photomicrograph shows the characteristic septate hyphae of *Aspergillus* species. (Grocott-Gomori methenamine silver stain)

infection. Itraconazole is preferred if the patient can take oral medication. has reasonable gastrointestinal function. and is not taking any other medications that contraindicate the use of itraconazole (see Table 6-2). Immunocompromised patients who have invasive aspergillosis should be treated by aggressive debridement 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*.

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 20% to 30% of adults in the United States may have had asymptomatic infection. 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. These oocysts can then be ingested by another animal or human. 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 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 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 (see page 234) 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 nonimmune mother contracts the disease during her pregnancy and the organism crosses the placental barrier, infecting the developing fetus. The potential effects of blindness. mental retardation, 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 (Figure 6-35).

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; however, the diagnosis should be confirmed by serologic studies. if possible.

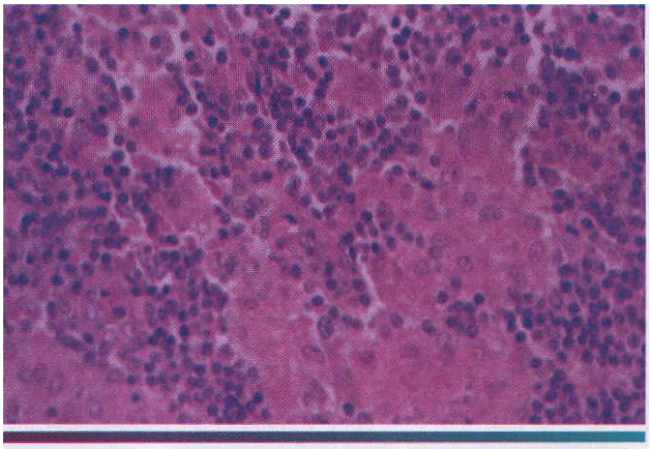

Figure 6·35 • Toxoplasmosis. This high-power photomicrograph shows an accumulation of eosinophilic macrophages that obscures an adjacent germinal center.

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 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. 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 c1indamycin 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.

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CHAPTER 7

Viral Infections

CHAPTER OUTLINE

HERPES SIMPLEX VIRUS

Herpessimplex virus (HSV) is a DNA virus and a member of the human herpesvirus (HHV) family. officially known **asHerpctoviridac. Two types of HSVs are known to exist:** type I (HSV-! or HHV-!) and type 2 (HSV-2 or HHV-2). Other members of the HHV family include varicella-zoster virus (VZV or HHV-31. Epstein-Barr virus (EBV or HHV-41. cytomegalovirus (CMV or HHV-S). and several more recently discovered members. HHV-6. HHV-7. and HHV-8. The latter virus. HHV-8. appears to be involved in the pathogenesis of Kaposi's sarcoma (KS) (see page 484). Humans are the only natural reservoir. and all HHVs have the ability to reside for life within the infected host. After the initial infection. variable periods of latency and reactivation with viral shedding are seen. **Because each affected individual remains a reservoir of** infection for life. the viruses are endemic worldwide.

The two types of HSV are similar structurally but different antigenically. In addition. the two exhibit epi**demiologic variations.**

H5V-1 is spread predominantly through infected saliva oradtive perioral lesions. HSV-I is adapted best and performs more efficiently in the oral. facial. and ocular areas. The pharynx. intraoral sites. lips. eyes. and skin above the waist are involved most frequently.

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. Exceptions to these rules do occur. and HSV-I can be seen in a pattern similar to that of HSV-2 and vice versa. The clinical lesions produced by both types are identical. and **both produce the same changes in tissue. The viruses are so similar that antibodies directed against one cross-react** against the other. Antibodies to one of the types decrease the chance of infection with the other type; if infection **does occur, the manifestations often are less severe.**

Clinically evident infections with HSV-I exhibit two patterns. The initial exposure to an individual without antibodies to the virus is called the primary infection. This typically occurs at a young age. often is asymptomatic. and usually does not cause significant morbidity. At this point, the virus is taken up by the sensory nerves and transported to the associated sensory or, less frequently. the autonomic ganglia. With oral HSV-I infection, the trigeminal ganglion is colonized. and the virus **remains at this site in a latent state. The virus uses the** axons of the sensory neurons to travel back and forth to the peripheral skin or mucosa.

Secondary, recurrent, or recrudescent HSV-I infection occurs with reactivation of the virus, although many

patients may show only asymptomatic viral shedding in the saliva. Symptomatic recurrences are fairly common and affect the epithelium supplied by the sensory ganglion. Spread to an uninfected host can occur easily during periods of asymptomatic viral shedding or from symptomatic active lesions. When repeatedly tested, approximately one third of individuals with HSV-I antibodies occasionally shed infectious viral particles, even without active lesions being present. In addition, the virus may spread to other sites in the same host to establish residency at the sensory ganglion of the new location. Numerous conditions such as old age, ultraviolet light" emotional stress, pregnancy, allergy, trauma, respiratory illnesses. menstruation. systemic diseases, or malignancy have been associated with reactivation of the virus, but only ultraviolet light exposure has been demonstrated unequivocally to induce lesions experimentally. More than 80% of the primary infections are purported to be asymptomatic, and reactivation with asymptomatic viral shedding greatly exceeds clinically evident recurrences.

HSV does not survive long in the external environment. and almost all primary infections occur from contact with an infected person who is releasing the virus. The usual incubation period is 3 to 9 days. Because HSV-I usually is acquired from contact with contaminated saliva or active perioral lesions. crowding and poor hygiene promote exposure. 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 almost universal exposure by 30 years of age. On the other hand, upper socioeconomic groups in developed nations exhibit less than 20% exposure at five years of age and only 50% to 60% in adults. The low childhood exposure rate in the privileged groups is followed by a second peak during the college years of life. The age of initial infection also affects the clinical presentation of the symptomatic primary infections. People exposed to HSV-I at an early age tend to exhibit gingivostomatitis; those initially exposed later in life often demonstrate pharyngotonsillitis.

As mentioned previously, antibodies to HSV-I decrease the chance of infection with HSV-2 or lessen the severity of the clinical manifestations. The dramatic increase recently seen in HSV-2 is due partly to lack of prior exposure to HSV-I and to increased sexual activity and lack of barrier contraception. HSV-2 exposure correlates directly with sexual activity. Exposure of those younger than age 14 is close to zero, and most initial infections occur between the ages of 15 and 35. The prevalence varies from near zero in celibate adults to more than 80% in prostitutes.

In addition to clinically evident infections, *HSV* has been implicated in a number of 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 674). In some instances. the attacks of erythema multiforme are chronic enough to warrant antiviral prophylaxis. An association with cluster headaches and a number of cranial neuropathies has been proposed, but definitive proof is lacking.

On rare occasions. asymptomatic release of HSV will coincide with attacks of aphthous ulcerations. The ulcerations are not infected with the *virus.* In these rare cases, the virus may be responsible for the initiation of the autoimmune destruction; conversely. the immune dysregulation that produces aphthae may have allowed the release of the virions. In support of the lack of association between HSV and aphthae in the general population of patients with aphthous ulcerations, prophylactic oral acyclovir does not decrease the recurrence rate of the aphthous ulcerations. Although the association between HSV and recurrent aphthous ulcerations is weak. it may be important in small subsets of patients (see page 28;).

HSV also has been associated with oral carcinomas. but much of the evidence is circumstantial. The DNA from HSV has been extracted from the tissues of some tumors but not from others. HSV may aid carcinogenesis through the promotion of mutations, but the oncogenic role. if any. is uncertain.

Clinical Features

Acute herpetic gingivostomatitis is the most common pattern of symptomatic primary HSV infection, and more than 90% are the result of HSV-I. In a study of more than 4000 children with antibodies to HSV-I, Juretic found that only 12% of those infected had clinical symptoms and signs severe enough to be remembered by the affected children or their parents. In spite of this study, some health care practitioners suspect that the percentage of primary infections that exhibit clinical symptoms is much higher. Further studies are needed to fully answer this question.

Most cases of acute herpetic gingivostomatitis arise between the ages of 6 months and 5 years, with the peak prevalence occurring between 2 and J years of age, In spite of these statistics, 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° to 105° Fl. nausea. anorexia, irritability. and sore mouth lesions. The manifestations vary from mild to severely debilitating.

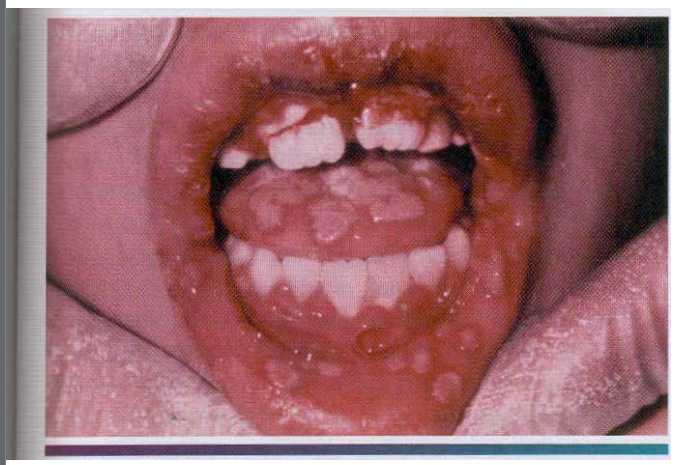


Figure 7-1 • **Acute herpetic gingivostomatitis. Widespread yellowish mucosal ulcerations. (Courtesy of Dr. David Johnsen.)**

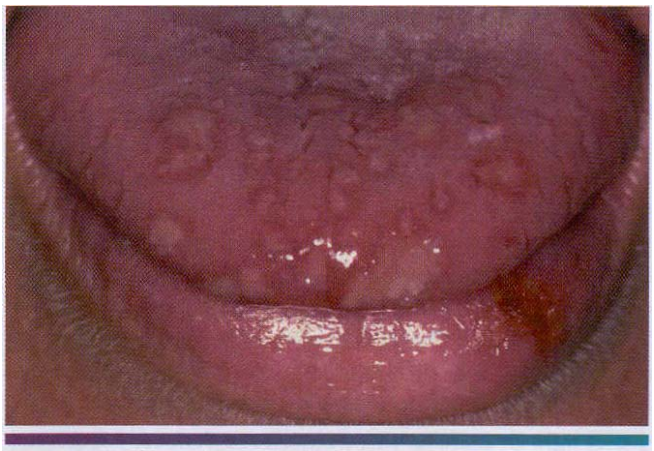


Figure 7-2 • **Acute herpetic gingivostomatitis. Numerous coalescing, irregular, and yellowish ulcerations of the dorsal surface of the tongue.**

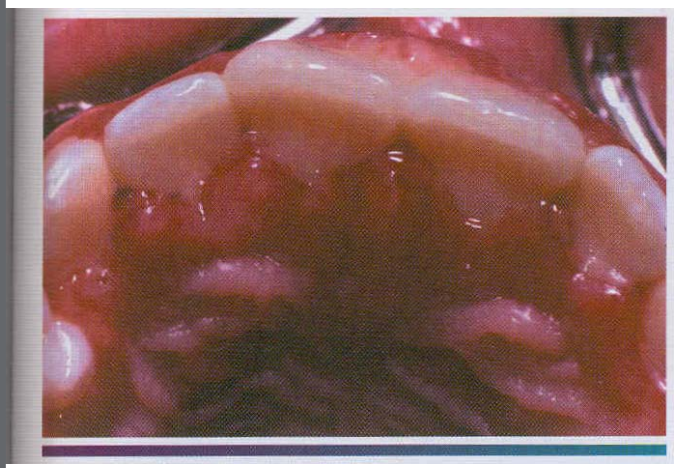


Figure 7-3 • **Acute herpetic gingivostomatitis. Painful, enlarged, and erythematous palatal gingiva.**

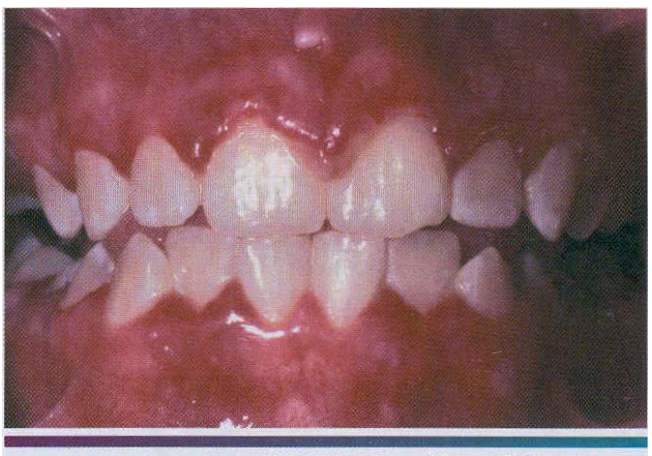


Figure 7-4 • **Acute herpetic gingivostomatitis. Painful, enlarged, and erythematous facial gingiva. Note erosions of the free gingival margin.**

Initially the affected mucosa develops numerous pinhead vesicles, which rapidly collapse to form numerous small. red lesions. These initial lesions enlarge slightly and develop central areas of ulceration, which are *covered* by yellow fibrin (Figure 7-1), Adjacent ulcerations may coalesce to form larger, shallow, irregular ulcerations (Figure 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 (Figure 7-3). In addition, the affected gingiva often exhibits distinctive punched-out erosions along the midfacial free gingival margins (Figure 7-4). It is not unusual for the involvement of the labial mucosa to extend past the wet line to include the adjacent vermilion border of the lips. Satellitevesicles 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 extend to 2 weeks.

As mentioned previously, when the primary infection occurs in adults. some symptomatic cases exhibit 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 numerous shallow ulcerations. which often coalesce with one another. A diffuse, grayish-yellow exudate forms over the ulcers in many cases. Involvement of the oral mucosa anterior to Waldeyer's ring occurs in less than 10% of these cases. HSV appears to be a significant cause of pharyngotonsillitis in young adults who are from the higher socioeconomic groups with previously negative test findings

for *HSV* antibodies. Most of these infections are HSV-1, but increasing proportions are *HSV-2*. The clinical presentation closely resembles pharyngitis secondary to **streptococci or infectious mononucleosis, making the** true frequency difficult to determine.

Recurrent infections may occur either at the site of primary inoculation or in adjacent areas of surface epithe-lium 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 from 15% to 45% of the United States population have a history of herpes labialis. In some patients, ultra-**violet light or trauma call trigger recurrences. Prodromal** signs and symptoms (e.g., pain, burning, itching, tingling, localized warmth, erythema of the involved epithelium) arise 6 to 24 hours before the lesions develop. Multiple small, erythematous papules develop and form clusters of fluid-filled vesicles (Figure 7-5). The vesicles rupture and crust within 2 days. Healing usually occurs within 7 to 10 **days. Mechanical rupture of intact vesicles and the release** of the virus-filled fluid may result in the spreading of the lesions on lips previously cracked from sun exposure (Figure 7-6). Recurrences are observed less commonly on the skin of the nose, chin, or cheek.

Recurrences also can affect the oral mucosa. In the immunocompetent patient, involvement is limited almost always to keratinized mucosa that is 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 (Figures 7-7 and 7-8). The damaged epithelium is lost, and a central yellowish area of ulceration develops. Healing takes place within 7 to 10 days.

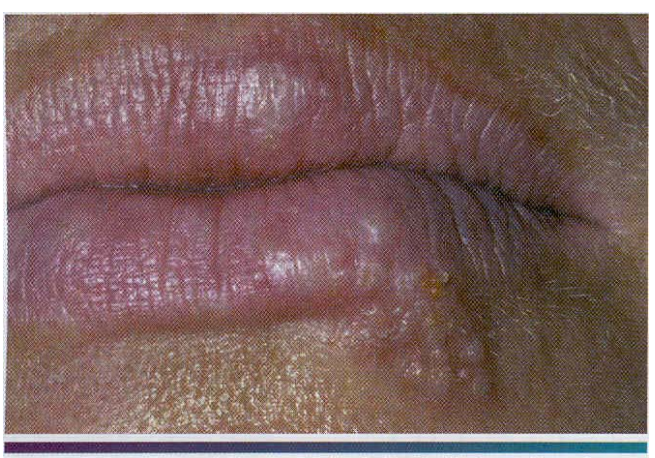


Figure 7-5 • Herpes labialis. Multiple fluid-filled vesicles adjacent to the lip vermilion.

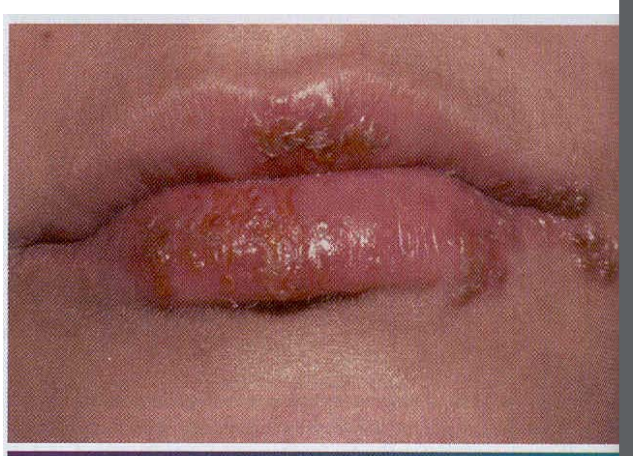


Figure 7-6 • Herpes labialis. Multiple sites of recurrent herpetic infection secondary to spread of viral fluid over cracked lips.

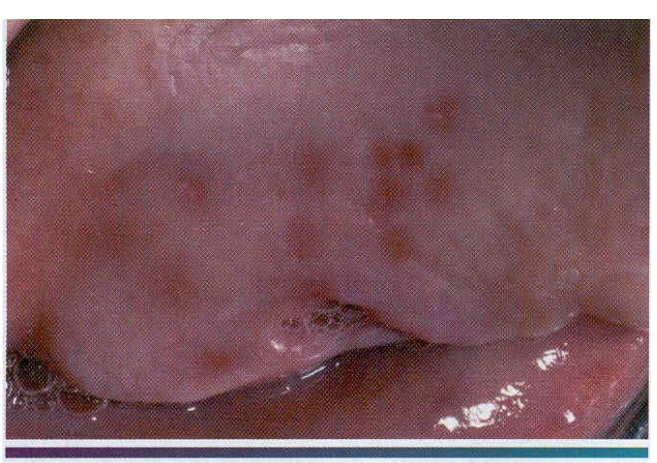


Figure 7-7 • Intraoral recurrent herpetic infection. Early lesions exhibiting as multiple erythematous macules on the hard palate. Lesions appeared a few days after extraction of a tooth.

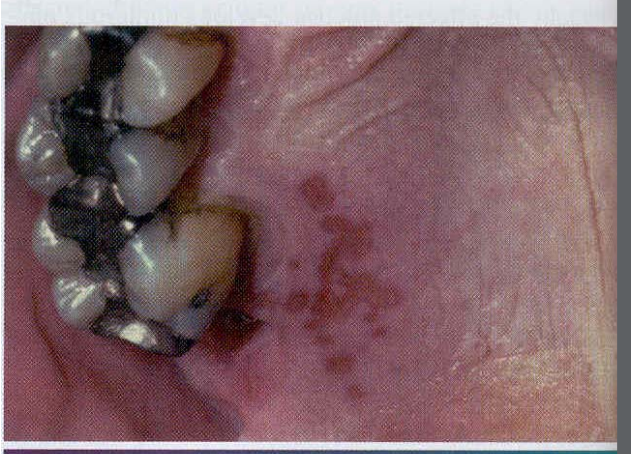


Figure 7-8 • Intraoral recurrent herpetic infection. Multiple coalescing ulcerations on the hard palate.

Less common presentations of HSV-I do occur. Infeclion of the thumbs or fingers is known as herpetic whitlow (herpetic paronychia), which may occur as a result of self-inoculation in children with orofacial herpes (Figure 7-9). Before the uniform usc of gloves. medical and dental personnel could infect their digits from contact with infected patients. and they were the most likely group affected by this form of HSV-I infection. Recurrences on *the* digits are *not* unusual and may result in paresthesia and permanent scarring.

Primary cutaneous herpetic infections can also arise in areas of previous epithelial damage. Parents kissing areas of derrnatologlc injury in children represent one vector. Wrestlers and rugby players also may contaminate areas of abrasion, a lesion called herpes gladiatorurn **or scrumpox. Ocular involvement may occur in** children. often resulling from self-inoculation. Patients with diffuse chronic *skin* diseases. such as eczema. pemphigus, and Darter's disease, may develop diffuse life-threatening HSV *infection,* known as eczema herpeticum (Kaposi's varicelliform eruption). Newborns may become infected after delivery through a birth canal contaminated with HSV, usually HSV-2. Without treatment. there is greater than a 50% mortality rate.

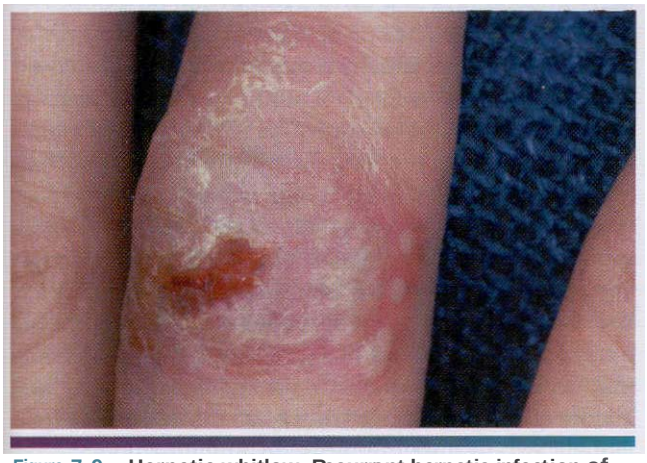


Figure 7-9 • **Herpetic whitlow. Recurrent herpetic infection of the finger.**

HSV recurrence in immunocompromised hosts can be significant. Without proper immune function, recurrent herpes can persist and spread until the infection is **treated with antiviral drugs. until immune status returns.** or until the patient dies. On the skin, the lesions continue to enlarge peripherally, with the formation of an **increasing zone of superficial cutaneous erosion. Oral** mucosa also can be affected and usually is present in conjunction with herpes iabialis. Although most oral mucosal involvement begins on the bound mucosa. it **often is not confined to these areas. The involved sites** begin as areas of necrotic epithelium, which is brownish and raised above the surface of the adjacent intact epithelium. Typically these areas are much larger than the usual pinhead lesions found in immunocompetent patients. With time, the area of involvement spreads laterally. The enlarging lesion is a zone of superficial **necrosis or erosion, often with a distinctive circinate,** raised. yellow border (Figures 7-10 and 7-11). This border represents the advancing margin of active viral destruction. Microscopic demonstration of HSV infection **in a chronic ulceration on the movable oral mucosa is** ominous, and all such patients should be evaluated thoroughly for possible immune dysfunction or underlying **occult disease processes.**

One group of investigators has described a pattern of chronic herpes that occurs on the dorsal surface of the tongue and appears as a deep midline fissure that typically exhibits multipie peripheral branches. This pattern

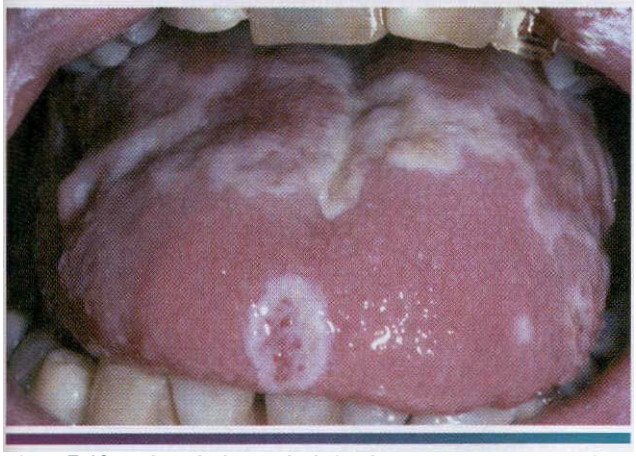


Figure 7-10 . **Chronic herpetic infection. Numerous mucosal erosions. each of which is surrounded by a slightly raised. yellowish-white border. in a patient with acute myelogenous leukemia.**

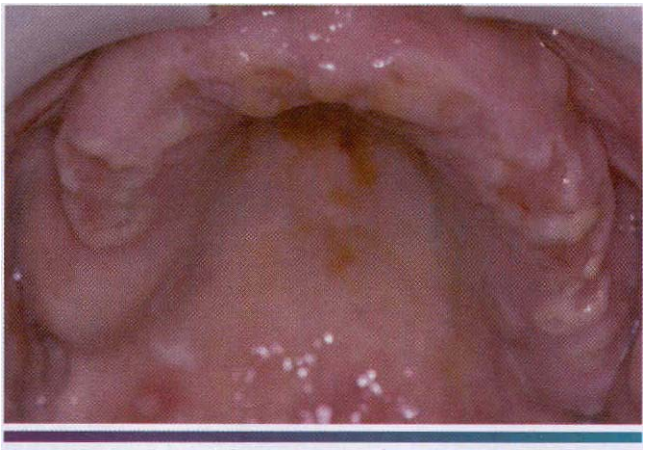


Figure 7-11 • **Chronic herpetic infection. Numerous shallow herpetic erosions with raised. yellow and circinate borders on the maxillary alveolar ridge in an immunocompromised patient.**

has been nicknamed "geometric glossitis" and usually is symptomatic with areas of erosion in the depth of the fissures. However, the investigators used only culture for diagnosis. Because of the high prevalence of asymptomatic shedding of HSV in immunocompromised patients, viral culture is inadequate for diagnosis of intraoral lesions (see Diagnosis section). Although the association between herpes simplex and geometric glossitis needs to be confirmed through cytologic or histopathologic techniques, clinicians should investigate the possibility of HSV infection in immunocompromised patients with symptomatic lingual fissures.

Although a yellow curvilinear border often is present in many chronic herpetic ulcerations noted in immunocompromised patients, this distinctive feature might be missing. Several authors have reported persistent oral ulcerations in patients with acquired immunodeficiency syndrome (AIDS) that lack the distinctive periphery, often are nonspecific clinically, and may mimic aphthous ulcerations, necrotizing stomatitis, or ulcerative periodontal disease. Biopsy of persistent ulcerations in patients with AIDS is mandatory and may reveal any one of a number of infectious or neoplastic processes. These ulcers may reveal histopathologic evidence of herpesvirus, often combined with diagnostic features of CMV (HHV-5) co-infection (see page 240).

Histopathologic Features

The virus exerts its main effects on the epithelial cells. Infected epithelial cells exhibit acantholysis, nuclear clearing, and nuclear enlargement, which has been termed ballooning degeneration (Figure 7-12). The acantholytic epithelial cells are termed Tzanck cells. Nucleolar fragmentation occurs with a condensation of chromatin around the periphery of the nucleus. Multinucleated, infected epithelial cells are formed when fusion occurs between adjacent cells (see Figure 7-12). Intercellular edema develops and leads to the formation of an intraepithelial vesicle (Figure 7-13). Mucosal vesicles rupture rapidly; those on the skin persist and develop secondary infiltration 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

With a thorough knowledge of the clinical presentations, the clinician can make a strong presumptive diagnosis of HSV infection. On occasion, HSV infections can be confused with other diseases, and laboratory confirmation is desirable. Viral isolation from tissue culture inoculated with the fluid of intact vesicles is the most definitive diagnostic procedure. The problem with this technique in primary infections is that up to 2 weeks can be required for a definitive result. Clinical tests for HSV antigens or nucleic acids in specimens of active lesions also are available. Serologic tests for HSV antibodies are positive 4 to 8 days after the initial exposure. These antibody titers are useful in documenting past exposure and are used primarily in epidemiologic studies.

Intact vesicles are rare intraorally. Therefore, using intraoral viral culture as the sole means of diagnostic confirmation of HSV infection is inappropriate. It has been shown that asymptomatic oral HSV shedding occurs in up to 9% of the general population. During periods of mental or physical stress, asymptomatic viral shedding rises to approximately one third of those previously exposed to the virus. In immunocompromised patients, the prevalence rises to 38%; this percentage is

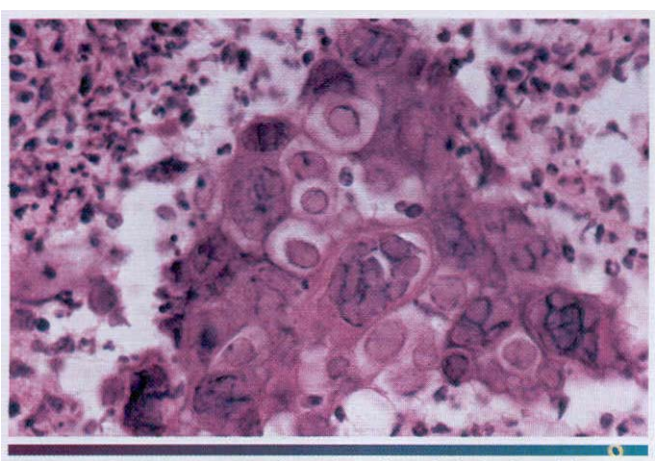


Figure 7-12. Herpes simplex. Altered epithelial cells exhibiting ballooning degeneration, margination of chromatin, and multinucleation.

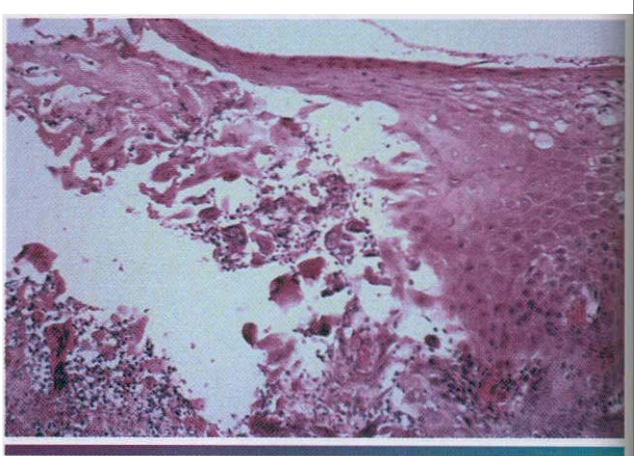


Figure 7-13. Herpes simplex. Intraepithelial vesicle demonstrating acantholytic and vitally altered epithelial cells.

low and most likely would double if the investigation were restricted to those previously exposed to the virus. Therefore. culture of lesions contaminated with saliva lhal might contain colncidentally released HSV is meaningless unless supplemented by addittonal diagnostic procedures.

Two of the most commonly used diagnostic procedures are the cytologic smear and tissue biopsy, with cylologic study being the least invasive and most cost-effective. The virus produces distinctive histologic alteraliens within the infected epithelium. Only VZV produces similar changes. but these two infections usually can be differentiated on a clinical basis. Fluorescent monoclonal antibody typing can be performed on the direct smears or on infected cells obtained from tissue culture.

If diagnostic features of herpesvirus are discovered in a biopsy of a persistent ulceration in an immunocompromised patient, immunocytochemical studies for CMV also should be performed to rule out co-infection. The histopathologic features of CMV can be missed easily, resulting in patients not receiving the most approprlate therapy.

Treatment and Prognosis

In the past. primary herpetic gingivostomatitis was treated best symptomatically; however, if the infection is diagnosed early. anti viral medications can have a significant impact. Patients should be instructed to restrict contact with active lesions to prevent the spread to other sites and people. As mentioned previously. autoinoculation of the eyes can result in ocular involvement with the possibtlity of recurren ce. Repeated ocular reinfection can produce permanent damage and blindness. HSV is the leading infectio us cause of blindness in the United States.

When acyclovir suspension is administered in a rinse and swallow technique during the first 3 symptomatic days, significant acceleration in clinical resolution is seen. Once therapy is initiated. development of new lesions ceases. In addition, the associated eating and drinking difficulties, pain. healing time, duration of fever, and viral shedding are shortened dramatically. In addition, topical rinsing with 0.5% or 1.0% dyclonine hydrochloride (Dyclone has been discontinued, but pharmacists can make the generic form easily) drarnatically, but temporarily, decreases the mucosal discomlort. Viscous lidocaine should be avoided in pediatric patients because of reports of lidocaine-induced seizures in children. Nonsteroidal antiinflammatory medications, such as ibuprofen, also help alleviate the discomfort. Use ofantiviral medications in capsule or tablet form is much less effective because of the increased *time* these formulations require to exert a significant effect.

Recurrent herpes labialis has been treated with everything from ether to voodoo; nothing has solved the problem. Some minor successes have been achieved with the current brands of antivirals. Acyclovir and the two newer related medications, valacyclovir and famciclovir, appear to demonstrate similar effectiveness against *HSV.* Although valacyclovir and famciclovir exhibit improved bioavailability and more convenient oral dosing schedules, acyclovir remains an effective option. Although research by different investigators of drug effectiveness has produced variable results, these antiviral medications appear capable of minimizing recurrences if administered prophylactically. If begun early in the prodrome, the antiviral medications may reduce the number of lesions and the length of time to crusting. Pain and the length of time to healing are not affected significantly if the medication is not initiated during the prodro me. If prophylactic therapy is inltlated before a known trigger, a further reduction in severity of the recurrence often is seen.

Because most cases of recurrent herpes labialis are mild and infrequent. regular use of systemic antiviral medications can be justified rarely in immunocompetent individuals without severe involvement. In recent years, the emergence of acyclovlr-reslstant HSV has been seen with increasing frequency. Such resistance has arisen almost exclusively in immunocompromised patients receiving intermittent therapy, and the use of prophylactic therapy does not "ppear to be associated with emergence of resistant strains. In immunocompromised patients. the viral load tends to be high and replication is not suppressed completely by antlvlral therapy, creating the environment for generating drug-resistant mutants. Although resistance is seen primarily in chro nic therapy in immunocompromised patients. cavalier use of antiviral medications for mild cases of recurrent herpes infection is tnapproprlate.

Acyclovir ointment in polyethylene glycol has been of limited benefit for herpes labialis in immunocompetent patients, because its base is thought to prevent significant absorption. In contrast. penciclovir cream is supplied in a base that allows increased absorption through the vermilion border. Use of this formulation has been shown to result in a statistically significant, although clinically mlnlmal. reduction in healing time and pain (duration decreased less than I day). Although the effects of this therapy were minimal in a large study group initiating therapy during the prodromal period, some patients experienced dramatic respo nse, especially many with more severe involvement. It may be that the inltlatlon of topical therapy during the prodrome is too late, and significant success may be possible only in patients who associate recurrences wit h a known trigger

and are able to begin prophylactic treatment before the first symptoms appear.

Two recent additions to current topical therapies mandate further independent study. A heavily advertised over-the-counter formulation of 10% n-docosanol cream is available and has been reported in a limited number of evaluations to shorten mean healing time by approximately 3 days. Recently a formulation of "quantanary ammonium chlorides. dimethyl carbonal, and other chemicals" has been marketed through dentists and dermatologists for the treatment of herpes labialis. Until this treatment has been sufficiently scientifically tested and proven to be effective. its use cannot be recommended.

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 vivo and in vitro. 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 in patients who desire or** require therapy of intraoral lesions.

Immunocompromised hosts with *HSV* infections often **require intravenous antiviral medications to control the** problem. Furthermore. severely immunosuppressed individuals. such as bone marrow transplant patients and those with AIDS. often need prophylactic doses of **oral acyclovir, valacyclovir, or famciclovir. On occasion.** viral resistance develops. resulting in the onset of significant herpetic lesions. Any herpes lesions that do not respond to appropriate therapy within 5 to 10 days most **likely are the result of resistant strains. These resistant** strains have been treated successfully with trisodium phosphonoformate hexahydrate (foscarnetl, but this **medication is reserved as a second-line therapy because** of its significant side effects. In these cases. it appears that only the peripheral virus mutates. because future **recurrences are once again sensitive to the first-line** antlvirals. Ulcerations that reveal co-infection with HSV and *CMV* respond well to ganciclovlr, with foscarnet used **in refractory cases.**

Although a successful live-virus vaccine has been available for the closely related varicella virus for over 25 years. similar approaches against *HSV* have produced **less satisfactory results. Significant research for a potential** vaccine is ongoing and offers hope for the future.

VARICELLA (CHICKENPOX)

The varicella-zoster virus *(VZV;* HHV-3) is similar to herpes simplex virus *(HSV)* in many respects. Chickenpox represents the primary infection with the VZV; **latency ensues. and recurrence is possible as herpes** zoster. often after many decades. The virus is presumed to be spread through air droplets or direct contact with **active lesions. Most cases of chickenpox arise between** the ages of 5 and 9. with greater than 90% of the United States population being infected by t5 years of age. In contrast to infection with *HSV*. most cases are symptomatic. The incubation period is 10 to 21 days. with an average of 15 days.

Clinical Features

The symptomatic phase of *VZV* infection usually begins with malaise. pharyngitis. and rhinitis. In older children and adults, additional symptoms (e.g.• headache. myalgia, **nausea, anorexia, vomiting) occasionally** are **seen. This** is followed by a characteristic. intensely pruritic exanthem. The rash begins on the face and trunk. followed by involvement of the extremities. Each lesion rapidly progresses through stages of erythema. vesicle. pustule, and hardened crust (Figures 7-14 and 7-15). The early

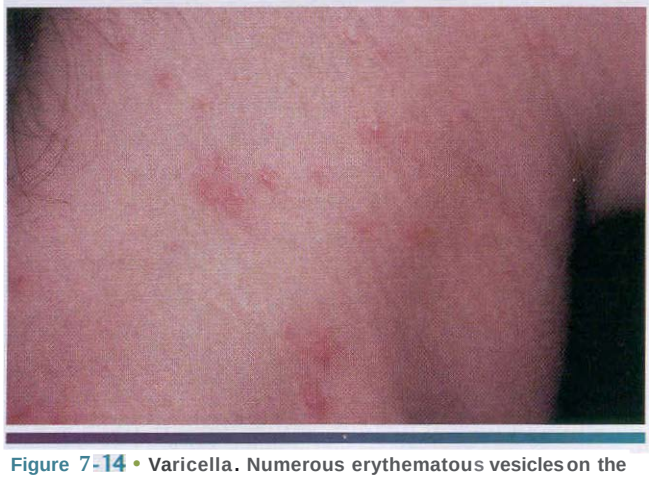


Figure 7-14 • Varicella. Numerous erythematous vesicles on the right side of the neck.

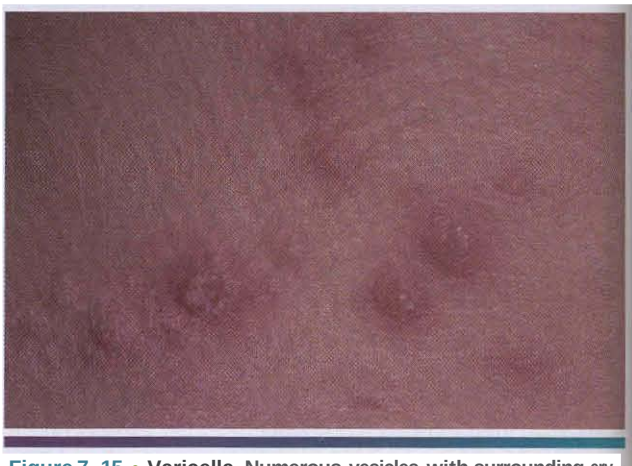


Figure 7-15 • Varicella. Numerous vesicles with surrounding erythema and early crusting.

vesicular stage is the classic presentation. The centrally located 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 eruptfor 4 days; in some cases, the exanthem's arrival may extend to 7 or more days. Old crusted lesions intermixed with newly formed and 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. **The severity of the cutaneous involvement is variable** and often more severe in adults and in household members secondarily infected by the initial patient.

Oral lesions are fairly common and may precede the skin lesions. The palate and the buccal mucosa are involved most frequently. Occasionally. gingival lesions resemble those noted in primary HSV infections. 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 (Figure 7-16),

Complications can occur, with the need for hospitalization in children approximating I in 600 in the pre-**vaccine era. Possible complications include Reye's syndrome**, secondary skin infections. encephalitis, cerebellar **ataxia. pneumonia. gastrointestinal disturbances** (e.g.. vomiting. diarrhea, and associated dehydration). and hematologic events (thrombocytopenia, pancytopenia, hemolytic anemia, sickle cell crisis).

In childhood. the most frequent complications are secondary skin infections. followed by encephalitis and pneumonia. With enhanced public education and decreased use of aspirin in children, the prevalence of Reye's syndrome is decreasing. Although associated bacterial infections had decreased after the introduction of **antibiotics, an increased prevalence of significant com-**

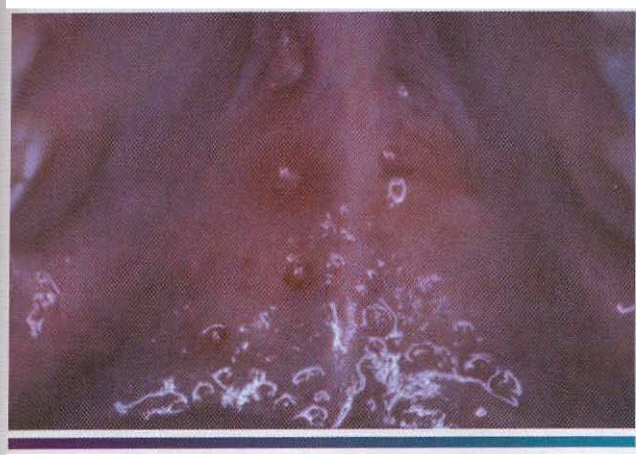


Figure 7-16 • **Varicella. White opaque vesicles on the hard palate.**

plications related to secondary infections caused by group A, β-hemolytic streptococci was seen during the 1990s. These organisms have created life-threatening **infections and areas *of* highly destructive necrotizing fasciitis.**

The prevalence of complications in adults exceeds that noted in children. The risk of death between 15 to 19 years of age is 2.7/ 100,000 but rises to 25.2/ 100,000 in patients aged 30 to 49 years. The most common and **serious complication is varicella pneumonitis, which features** dry cough. tachypnea. dyspnea, hemoptysis, chest pain, and cyanosis. Encephalitis and clinically significant pneumonia are diagnosed in I in 375 affected adults older than 20 years of age. The central nervous system involvement typically produces ataxia but may result in **headaches, drowsiness, convulsions, or coma.**

Infection during pregnancy can produce congenital or neonatal chickenpox. Involvement early in the pregnancy **can result in spontaneous abortion** or congenital **defects.** Although complications can occur in newborns, the effects of maternal varicella infection appear minimal. A **recent multicenter prospective study of live births associated with maternal varicella infection revealed only a** 1.2% prevalence of embryopathy. However. infection of **the mother close to delivery can result in a severe fetal** infection caused by a lack of maternal antibodies.

Infection in immunocompromised patients also can be most severe. The cutaneous involvement typically is extensive and may be associated with high fever. hepa**titis, pneumonitis, pancreatitis, gastrointestinal obstruc**tion, and encephalitis. Before effective antiviral therapy, the mortality rate in immunocompromised individuals was approximately 7%. Secondary bacterial infections often complicate the process.

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

The diagnosis of chickenpox usually can be made from a history of exposure to VZV within the iast 3 weeks and the presence of the typical exanthem. Confirmation can be obtained through a demonstration of viral cytopathologic effects present within the epithelial cells harvested from the vesicular fluid. These cytologic changes are identical to those found in herpes simplex, and further con**firmation sometimes is desired. Viral isolation in cell cul**ture or rapid diagnosis from fluorescein-conjugated VZV monoclonal antibodies can be performed. Finally. serum

samples can be obtained during the acute stage and 14 to 28 days later. The later sample should demonstrate a significant (fourfold) increase in antibody titers to VZV.

Treatment and Prognosis

Before the current antiviral medications became avail- able. the treatment of varicella primarily was symptomatic. Warm baths with soap or baking soda. application of calamine lotion. and systemic diphenhydramine still are used to relieve pruritus. VZV has a lipid envelope that is destroyed rapidly by soap and other detergents. Lotions with diphenhydramine are not recommended **because of reports of toxicity secondary to percutaneous** absorption of the medication. Antipyretics other than aspirin should be given to reduce fever.

Use of peroral antiviral medications such as acyclovir, **valacycJovir. and famciclovir has been shown to reduce** the duration and severity of the infection if it is administered within the first 24 hours of the rash. Routine use **of these antiviral medications is not recommended in** immunocompetent children with uncomplicated chickenpox. Typically, such therapy is reserved for patients at **risk for more severe disease. such as those over 13 years of age and individuals who contract the disease from a family member. Intravenous formulations are used in** immunosuppressed patients or those exhibiting a pro**gressive. severe infection. Treatment with one of the available antiviral medications does not alter the anti-** body response to VZV or reduce immunity later in life.

In immunocompromised patients who become exposed to *VZV,* varicella-zoster immune globulin *(VZIG)* can be given to modify the clinical manifestations of the infection. *VZIG* is available commercially and prevents **severe varicella infections in immunocompromised** patients. In addition, infants born of mothers exhibiting a varicella rash of iess than 4-days duration demonstrate a risk of death that exceeds 30%. Use of *VZIG* in these **infants is associated with a markedly improved prognosis.**

A live attenuated *VZV* vaccine has been available since 1974 and has been used extensively outside the United States. especially in Japan. The vaccine is 98% effective, with a 1% prevalence of rash and fever. In the **United States. routine vaccination of children is recom-** mended between 12 and 18 months of age. Typically, the **vaccine is given at the same time as the** measles-mumps-rubella (MMR) vaccine (but in a separate syringe and in a different injection site). Patients older than i8 months who lack a reliable history of varicella also are recom**mended for vaccination but should receive a systemic review for several contraindications before vaccination.**

During the first year after vaccination. the efficacy appears to be 100% but drops to 95% after 7 years. When breakthrough infections do occur. they usually are very **mild. Because of continued exposure to wild virus.** previ**ously vaccinated patients have not required boosters to maintain immunity. As the wild virus fades. booster vac-** cines may be required to maintain lifelong immunity. Extensive follow-up of vaccinated groups is ongoing: ii **antibody levels wane with time. booster immunizations** will be recommended. Each year slightly fewer than 100 deaths are reported secondary to *VZV* in the United States. However. the number of deaths most likeiy will decrease **as a result of the use of antiviral medications** and vaccine.

It should be remembered that the vaccine is a live virus that can be spread to individuals in close contact. Vaccine recipients who develop a rash should avoid contact **with those at risk. such as immunocompromised or** pregnant individuals.

HERPES ZOSTER (SHINGLES)

After the initial infection with *VZV* (chickenpox), the **virus is transported up the sensory nerves and presum-** ably establishes latency in the dorsal spinal ganglia. Clinically evident herpes zoster occurs after reactivation of the virus. with the involvement of the distribution of the **affected sensory nerve. Zoster occurs during the lifetime** of 10% to 20% of individuals, and the prevalence of attacks **increases with age. With the increasing average** age of the population, an increased prevalence of herpes zoster is expected. Unlike herpes simplex virus IHSV), single rather than multiple recurrences are the rule. **Immunosuppression. treatment with cytotoxic drugs.** radiation. presence of malignancies. old age, alcohol abuse. and dental manipulation are predisposing factors **for reactivation.**

Clinical Features

The clinical features of herpes zoster can be grouped into **three** phases: **prodrome.** acute, and **chronic. During** initial viral replication, active ganglionitis develops with **resultant neuronal necrosis and severe** neuralgia. **This** inflammatory reaction is responsible for the prodromal symptoms of intense pain that precedes the rash in more than 90% of the eases. 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). Typically. one der**matome is affected. but involvement of two or more** can occur. This prodromal pain. which may be accompanied by fever. malaise. and headache, normally is present 1to 4 days before the development of the cutaneous or mucosal lesions. During this period (before the exanthem) **the pain may** masquerade **as sensitive teeth. otitis media,** migraine headache, myocardial infarction, or appendicitis, depending on which dermatome is affected.

Approximately 10% of affected individuals will exhibit no prodromal pain. Conversely. on occasion there may be

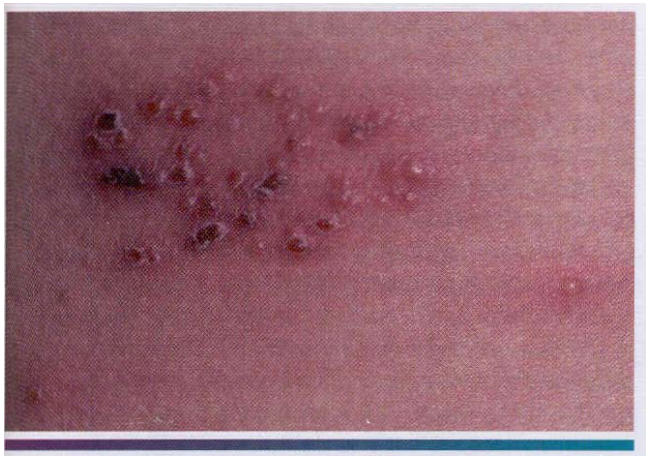


Figure 7-17 • **Herpes zoster. Cluster of vesicles with surrounding erythema of the skin.**

recurrence in the absence of vesiculation of the skin or mucosa. This pattern is called zoster sine herpete (zoster without rashl. and affected patients have severe pain of abrupt onset and hyperesthesia over a specific dermatome. Fever, headache. myalgia. and lymphadenopathy mayor may not accompany the recurrence.

The acute phase begins as the involved skin develops clusters of vesicles set on an erythematous base (Figure)-17). Within 3 to 4 days. the vesicles become pustular and ulcerate. with crusts developing after 7 to [0 days. The lesions tend to follow the path of the affected nerve and terminate at the midline (Figure 7-18). The exanthem typically resolves within 2 to 3 weeks in otherwise healthy individuals. Upon healing, scarring with hypopigmention or hyperpigmention is not unusual.

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 present in conjunction with involvement of the skin overlying the affected quadrant. Like varicella, the Individual lesions present as 1- to 4-mm white opaque vesicles. which rupture to form shallow ulcerations (Figure 7-19). Involvement of the maxilla may be associated with devitalization of the teeth in the affected area. In addition. several reports have documented significant bone necrosis with loss of teeth in areas involved with herpes zoster.

Ocular involvement is not unusual and can be the source of 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. If the tip of the nose is involved. this is a sign that the nasociliary branch of the fifth cranial nerve is involved. suggesting the potential for ocular infection. In these cases. referral to an ophthalmologist is mandatory.

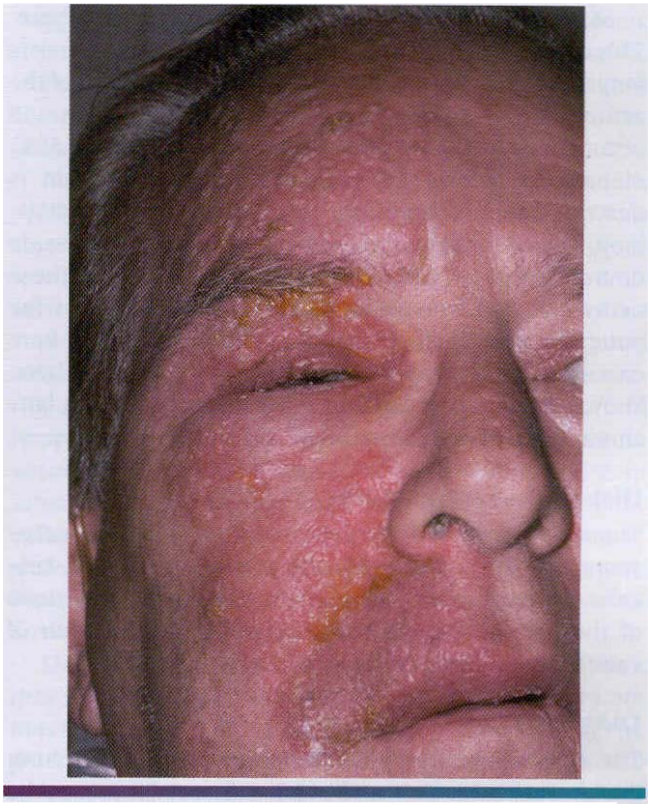


Figure 7-18 . **Herpes zoster. Numerous crusting facial vesicles that extend to the midline**

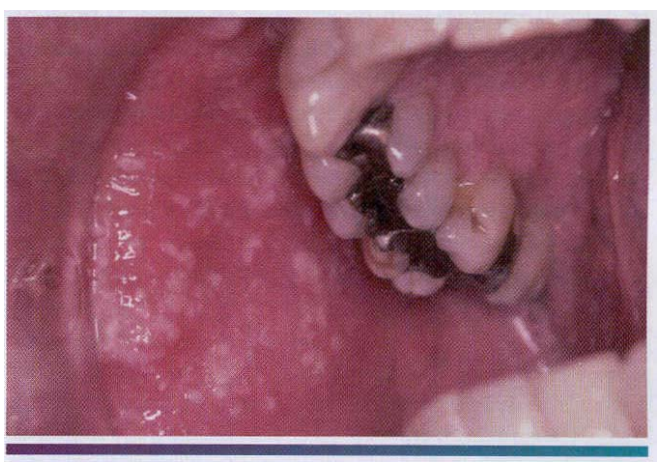


Figure 7-19 • **Herpes zoster. Numerous white opaque vesicles on the right buccal mucosa of the same patient depicted in Figure 7-18.**

Facial paralysis has been seen in association with herpes zoster of the face or external auditory canal. Ramsay Hunt syndrome is the combination of cutaneous lesions of the external auditory canal and involvement of the ipsilateral facial and auditory nerves. The syndrome causes facial paralysis. hearing deficits. vertigo. and a number of other auditory and vestibular symptoms.

Many patients do not progress to the chronic phase. This occurs when the neuralgia-associated pain persists longer than 3 months after the initial presentation of the acute rash. This is termed postherpetic neuralgia and occurs in up to 15% of affected patients and at least 50% of patients older than 60 years of age. The pain is described as burning, throbbing, aching, itching, or stabbing, often with flares caused by light stroking of the area or from contact with adjacent clothing. Most of these neuralgias resolve within 1 year, with one half of the patients experiencing resolution after 2 months. Rare cases may last up to 20 years, and patients have been known to commit suicide as a result of the severe, lancinating quality of the pain.

Histopathologic Features

The active vesicles of herpes zoster are identical microscopically to those seen in the primary infection, varicella. For more information, refer to the previous portions of the chapter on the histopathologic presentation of varicella and herpes simplex.

Diagnosis

The diagnosis of herpes zoster often can be made from the clinical presentation, but other procedures may be necessary in atypical cases. Viral culture can confirm the clinical impression but takes at least 24 hours. Cytologic smears demonstrate viral cytopathologic effects, as seen in varicella and HSV. In most cases, the clinical presentation allows the clinician to differentiate zoster from HSV, but cases of zosteriform recurrent HSV infection, although uncommon, do exist. A rapid diagnosis can be obtained through the use of direct staining of cytologic smears with fluorescent monoclonal antibodies for Vzv. This technique gives positive results in almost 80% of the cases. Molecular techniques such as dot-blot hybridization and polymerase chain reaction (PCR) also can be used to detect VZV.

Treatment and Prognosis

Before the development of the current antiviral medications, therapy for herpes zoster was directed toward supportive and symptomatic measures. Fever should be treated with antipyretics that do not contain aspirin. Antipruritics, such as diphenhydramine. can be administered to decrease itching. Skin lesions should be kept dry and clean to prevent secondary infection; antibiotics may be administered to treat such secondary infections.

Early therapy with appropriate antiviral medications such as acyclovir, valacyclovir, and famciclovir has been found to accelerate healing of the cutaneous and mucosal lesions, reduce the duration of the acute pain, and decrease the duration of postherpetic neuralgia. These medications are most effective if initiated within 72 hours after development of the first vesicle. Although none of these medications has been proven to reduce the *prevalence* of postherpetic pain. the newer formulations, famciclovir and valacyclovlr, have more convenient dosing regimens and greater bioavailability. Although several investigations have suggested the newer drugs are more effective than acyclovir in minimizing the acute phase and reducing the duration of postherpetic neuralgia, such differences have not been demonstrated conclusively.

Once the skin lesions *have* healed, the neuralgia may become the worst aspect of the disease and often is the most difficult to *resolve* successfully. This intense pain has been treated with variable results by a variety of methods including analgesics, narcotics, tricyclic antidepressants, anticonvulsants, percutaneous electric nerve stimulation, biofeedback, nerve blocks, and topical anesthetics.

One topical treatment, capsaicin. has had significant success. with almost 80% of patients experiencing some pain relief; however, the medication's effect often does not occur until 2 weeks or more of therapy. Capsaicin is derived from red peppers and is not recommended for placement on mucosa or open cutaneous lesions. Capsaicin has been associated with significant burning, stinging, and redness in 40% to 70% of patients, with up to 30% discontinuing therapy because of this side effect. After use, patients must be warned to wash their hands and avoid contact with mucosal surfaces.

Corticosteroid therapy has been used in the hope it might decrease the neural inflammation and associated chronic pain. Although conflicting research has been published. studies have shown no long-term benefit when corticosteroids are added to an acyclovir regimen. In addition. an increased prevalence of side effects was noted in groups treated with corticosteroids.

Preliminary studies evaluating a live attenuated varicella vaccine have shown an improved immune response to the virus in elderly patients. Larger studies may lead to the use of this vaccine in an attempt to decrease the frequency of disease in this vulnerable population.

INFECTIOUS MONONUCLEOSIS (MONO; GLANDULAR FEVER; "KISSING DISEASE")

Infectious mononucleosis is a symptomatic disease resulting from exposure to Epstein-Barr virus (EBV, 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."

Exposure during childhood usually is asymptomatic, and most symptomatic infections arise in young adults. 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 close to 50% of college students lacking previous exposure. These unexposed adults become infected at a rate of 10% to 15% per year while in college. Infection in adulthood is associated with a higher risk (I.e.. 30% to 50%) for symptomatic disease.

Besides infectious mononucleosis. EBV has been demonstrated in the lesions of oral hairy leukoplakia (OHL) (see page 241) and has been associated with a number of lymphoproliferative disorders. a variety of lymphomas (most notably African Burkitt's lymphoma) (see page 523). nasopharyngeal carcinoma (see page 372). some gastric carcinomas, and occasional smooth muscle tumors. However, direct proof of a cause-and-effect relationship is lacking.

Clinical Features

Most EBV infections in children are asymptomatic. In children younger than 4 years of age with symptoms, most have fever. lymphadenopathy. pharyngitis. hepatosplenomegaly, and rhinitis or cough. Children older than 4 years of age are affected similarly but exhibit a much lower prevalence of hepatosplenomegaly. rhinitis, and cough.

Most young adults experience fever. lymphadenopathy. pharyngitis, and tonsillitis. Hepatosplenomegaly and rash are seen less frequently. In adults older than 40 years of age. fever and pharyngitis are the predominant findings, with less than 30% demonstrating lymphadenopathy. Less frequent signs and symptoms in this group include hepatosplenomegaly. rash, and rhinitis or cough. Possible significant complications include splenic rupture. thrombocytopenia. autoimmune hemolytic anemia, and neurologic problems with seizures. These complications are uncommon at any age but more frequently develop in children.

In classic infectious mononucleosis in a young adult, prodromal fatigue, malaise. and anorexia occur up to 2 weeks before the development of pyrexia. The temperature may reach 104° F and lasts from 2 to i 4 days. Prominent lymphadenopathy is noted in more than 90% of the cases and typically appears as enlarged, symmetric. and tender nodes. frequently with 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 tonsillar abscesses (Figure 7-20). In rare instances, this enlargement may increase to the point of airway obstruction and even death.

Oral lesions other than lymphoid enlargement also may be seen. Petechiae on the hard or soft palate are present in about 25% of patients (Figure 7-21). The petechiae are transient and usually disappear within 24 to 48 hours. Necrotizing ulcerative gingivitis (NUG) (see page 140) also is fairly common. NUG-like pericoronitis (see page 153) and necrotizing ulcerative mucositis (see page 140) occur less frequently. Cases of NUG that are refractory to normal therapy should be evaluated to rule out the possibility of EBV.

A controversial symptom complex called chronic fatigue syndrome has been described. and several investigators have tried to associate EBV with this problem. Patients complain of rather nonspecific symptoms of chronic fatigue. fever, pharyngitis. myalgias, headaches.

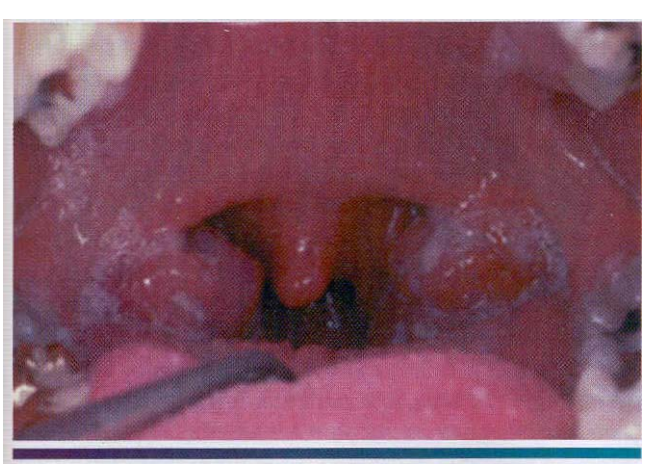


Figure 7-20 e Infectious mononucleosis. Hyperplastic pharyngeal tonsils with yellowish crypt exudates. (Courtesy of Dr. George Blozis.)

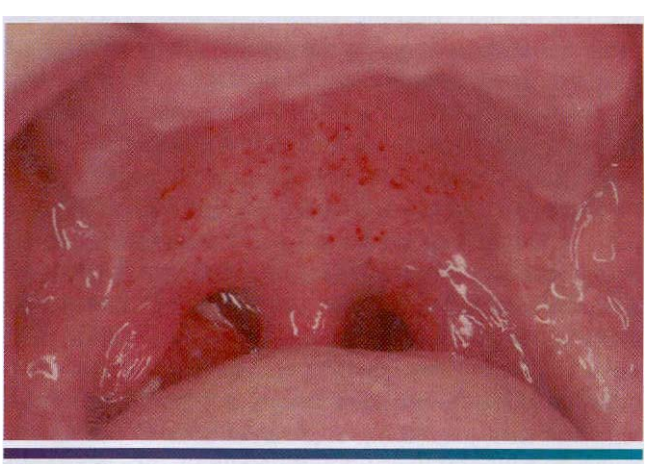


Figure 7-21 • Infectious mononucleosis. Numerous petechiae of the soft palate. (Courtesy of Dr. George Blozis.]

arthralgias. paresthesias. depression. and cognitive defects. These patients often demonstrate elevations in EBV antibody titers. but this finding alone is insufficient to prove a definite cause-and-effect relationship. Several studies have cast serious doubt on a relationship between EBV and the chronic fatigue syndrome.

Diagnosis

The diagnosis of EBV is suggested by the clinical presentation and should be confirmed through laboratory procedures. The white blood cell (WBCI count is increased. with the differential count showing relative lymphocytosis that can become as high as 70% to 90% during the second week. Atypical lymphocytes usually arc present in the peripheral blood. The classic serologic finding in EBV is the presence of the Paui-Bunnell heterophil antibody; a rapid test for these antibodies is available and inexpensive. More than 90% of infected young adults have positive findings for the heterophil antibody. but infected children younger than age 4 frequently have negative results. Indirect immunofluorescent testing to detect EBV-specific antibodies should be used in those suspected of having an EBV infection but whose findings were negative on the Paul-Bunnell test. Enzyme-linked immunosorbent assays (ELISA) and recombinant DNA-derived antigens may soon replace the indirect immunofluorescent test.

Treatment and Prognosis

In most cases. infectious mononucleosis resolves within 4 to 6 weeks. Nonaspirin-containing antipyretics and nonsteroidal antiinflammatory medications can be used to minimize the most common symptoms. Infrequent complications include splenic rupture. EBV-related hepatitis. and Bell's palsy. Patients with significant enlargement of the spleen should avoid contact sports to prevent the rare possibility of splenic rupture. On occasion. the fatigue may become chronic. In immunocompromised patients. a polyclonal B-lymphocyte proliferation may occur and possibly lead to death.

The tonsillar involvement may. on occasion. resemble streptococcal pharyngitis or tonsillitis (sec page 164). However. treatment with ampicillin and penicillin should be avoided because the use of these antibiotics in infectious mononucleosis has been associated with a higher than normal prevalence of allergic morbilliform skin rashes.

Corticosteroid usc is the recommended therapy in many textbooks. Such drugs. however. should not be used indiscriminately because the person's immune response appears to be the most important factor in fighting the infection and preventing a potentially fatal polyclonal B-lymphocyte proliferation. In addition. an increased prevalence of encephalitis and myocarditis has been noted in patients who have infectious mononucleosis and are treated with steroids. Corticosteroid usc produces a shortened duration of fever and shrinkage of enlarged lymphoid tissues. but its usc should be restricted to life-threatening cases (such as those with upper-airway obstruction because of massive lymphadenopathy).

CYTOMEGALOVIRUS

Cytomegalovirus (CMV. HHV-51 is similar to the other human herpes viruses (i.e.. after the initial infection. latency is established and reactivation is possible under conditions favorable to the virus). CMV can reside latently in salivary gland cells. endothelium. rnacrophages, and lymphocytes. Most clinically evident disease is found in neonates or in 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 the exchange of bodily fluids as this group begins sexual activity. Transmission also has been documented from blood transfusion and organ transplantation. The prevalence of neonatal CMV infection varies from 0.5% to 2.5%. By the age of 30. almost 40% of the population is infected; by age 60. 80% to 100% are infected. Screening of healthy middle-aged adult blood donors reveals that approximately 50% have been exposed to CMV.

Clinical Features

At any age. almost 90% of CMV infections arc asymptomatic. In clinically evident neonatal infection. the infant appears ill within a few days. Typical features include hepatosplenomegaly. extramedullary cutaneous erythropoiesis. and thrombocytopenia (often with associated petechial hemorrhages). Significant encephalitis frequently leads to severe-mental and motor retardation.

Acute adult infection exhibits a clinical pattern that is similar to that of infectious mononucleosis. Most patients have fever, malaise, myalgia, abnormal liver function tests. and atypical peripheral lymphocytes. In contrast to patients with infectious mononucleosis, only about one third of patients with CMV demonstrate pharyngitis and lymphadenopathy. Rarely. immunocompetent patients may show signs of an acute sialadenitis that diffusely involves all of the major and minor salivary glands. In such cases, xerostomia often is noted and the affected glands arc painful. Involvement of the major glands usually results in clinically obvious enlargements of the parotid and submandibular glands.

Evident CMV involvement is not unusual in immunocompromised transplant patients. In some cases a temporary mild fever is the only evidence; in others. the infection becomes aggressive and is characterized by significant hepatitis. leukopenia. pneumonitis. and. more rarely. a progressive wasting syndrome.

CMV disease is common in patients with AIDS (see page 234). *CMV* chorioretinitis affects almost one third ofpatients with AIDS and tends to progress rapidly. often resulting in blindness. Bloody diarrhea from *CMV* colitis is fairly common but may respond to appropriate **antiviral medications.**

Although oral lesions from *CMV* infection have been **documented in a number of immunosuppressive conditions.** reports of oral involvement by *CMV* have been increasing since the advent of the AIDS epidemic. Most affected patients have chronic mucosal ulcerations. and *CMV* changesare found on biopsy. Occasionally, chronic **oral ulcerations in immunocompromised patients will** demonstrate co-infection (usually *CMV* combined with HSV),

Neonatal *CMV* also can produce developm ental tooth defects. Examination of liS people with a history of neonatal *CMV* infection 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, areas of enamel hypomaturation, and yellow** coloration from the underlying dentin.

Histopathologic Features

Biopsy specimens of intraoral *CMV* lesions usually demonstrate changes within the vascular endothelial cells. Scattered infected cells arc extremely swollen. showing both intracytoplasmic and intranuclear inclusionsand **prominent nucleoli. This enlarged cell has** been **called an "owl eye" cell. Gomori's methenamine** silver and periodic acid-Schiff (PAS) stains demonstrate the **cytoplasmic inclusions but not the intranuclear changes.** Salivary ductal epithelium also may be affected and form "owl eye" cells (Figure 7-22).

Diagnosis

The diagnosis of CMV is made by considering a combination of the clinical features and by conducting other **examinations. Biopsy material can demonstrate cellular changes that suggest infection. Because effective therapies exist for CMV infections in immunocompromised patients, biopsies are recommended for chronic ulcerationsthat arc not responsive to conservative therapy. More** specific verification can be made by electron microscopy. **detection of viral antigens by immunohistochemistry, *in situ* hybridization, polymerase chain reaction, demonstration of rising viral antibody titers, or viral culture.**

In immunocompromised patients with chronic ulcerations. the typical "owl eye" cells may be few and difficult to discover upon routine light microscopy. When biopsy is performed upon a chronic oral ulceration in **these patients, *in situ* hybridization or immunohistochemical** evaluation for CMV should be performed. even **in the absence of "owl eye"** cells. In **addition, close examination** to rule out co-infection by HSV also should be performed.

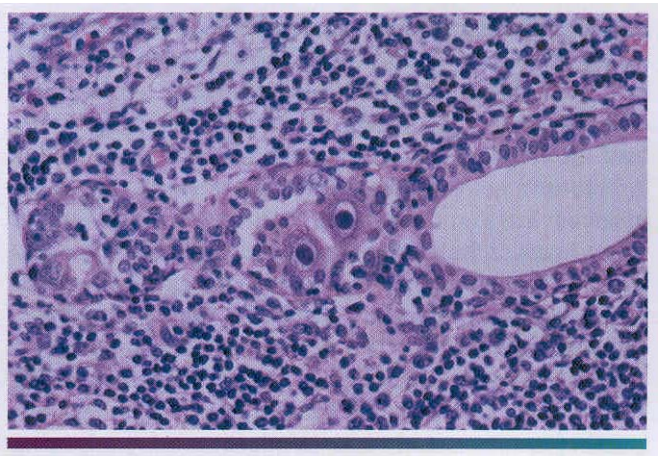


Figure 7-22 • Cytomegalovirus (CMV) infection. Salivary ductal epithelium exhibiting distinctive "owl eye" alterations.

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 co-infected with CMV and *HSV.* **intravenous ganciclovir will produce resolution in most** instances. The development of resistance to ganciclovir **has been reported, but successful resolution of these resistant infections has been achieved with foscarnet.**

ENTEROVIRUSES

The genus enterovirus encompasses the poliovirus, coxsackievirus A and S, echovirus, **and enterovirus groups.** Of these, more than 30 exist that can result in symptomatic **infections associated with rashes. Few are dis**tinctive enough clinically to allow differentiation from **one another. Most are asymptomatic or subclinical. These infections may arise at any age, but most occur in infants or young children. Neonatal cases also have been** reported. Only herpangina, hand-foot-and-mouth disease. and acute lymphonodular pharyngitis deserve **discussion. These three clinical patterns are related** closely and should not be considered entirely separate infections. In reports of epidemics in which a large **number of patients acquire the same strain of the virus,** the clinlcal presentations often arc variable and include both herpangina and hand-foot-and-mouth disease.

Herpangina usually is produced by coxsackievirus A I to 6. 8. 10. or 22. However. it also may represent infection by coxsackievirus A 7. 9. or 16; coxsackievirus B 2 to 6; echovirus 9. 16, or 17; or enterovirus 71. Hand-foot-and-mouth disease usually is caused by coxsackievirus A 16 but may also arise from coxsackievirus A 5. 9. or 10: echovirus II; or enterovirus 71. Acute lymphonodular pharyngitis is less recognized. and coxsackievirus A 10 has been found in the few reported cases. The incubation period for these viruses is 4 to 7 days.

Most cases arise in the summer or early fall in nontropical areas. with crowding and poor hygiene aiding their spread. The fecal-oral route is considered the major path of transmission. and frequent hand washing is emphasized in an attempt to diminish spread during epidemics. During the acute phase. the virus also can be transmitted through saliva or respiratory droplets. Infection confers immunity against reinfection to that one strain. In spite of the developed immunity. people may become infected numerous times with different enterovirus types over several years while still remaining susceptible to other different strains.

Clinical Features

In mJny countries, epidemics occur every 2 to 3 years and primariiy affect children aged I to 4 years. The timing of the epidemics appears to be correlated to the accumulation of a new population of susceptible young children. in all three clinical patterns. the severity and significant complications are variable and appear associated with the particular strain that is responsible. In general, most strains produce a self-limiting disease that requires no therapy. but occasional strains can produce epidemics with an increased number of significant complications and occasional mortalities. Systemic complications include pneumonia. pulmonary edema and hemorrhage. acute flaccid paralysis. encephalitis. meningitis. and carditis.

In 1998. a massive epidemic spread over Taiwan (population 21.178,000)' and it is estimated that approximately 1.5 million patients developed clinical evidence of the infection. A group of sentinel physicians (8.7% of primary physicians) documented 129. 106 infected patients. Of these patients, the vast majority were infected with enterovirus 71: a much lesser number were infected with one of a number of coxsackieviruses (predominantly A 16), When patients infected with the same strain were examined. clinical patterns diagnostic of both herpangina and hand-foot-and-mouth disease were detected. In this epidemic, more than 75% had symptoms of hand-foot-and-mouth disease, but it is clear these two clinical patterns represent variations of the same disorder.

tterpangina. Herpangina begins with an acute onset of significant sore throat. dysphagia. and fever, occasionally accompanied by cough. rhinorrhea, anorexia. vomiting, diarrhea. myalgia, and headache. Most cases, however. arc mild or subclinical. A small number of orai lesions. usually two to six. develop in the posterior areas of the mouth. usually the soft palate or tonsillar pillars (Figure 7-23). The affected areas begin as red rnacules. which form fragile vesicles that rapidly ulcerate. The ulcerations average 2 to 4 mm in diameter. The systemic symptoms resolve within a few days; as would be expected. the ulcerations usually take 7 to 10days to heal.

*ltand-foot-and-mouth dlseas*e, Hand-foot-and-mouth disease is the most well-known enterovirus infection. Like herpangina, the skin rash and oral lesions typically are associated with f1ulike symptoms (e.g., sore throat. dysphagia, fever). occasionally accompanied by cough. rhinorrhea. anorexia. vomiting. diarrhea. myalgia. and headache.

The name fairly well describes the location of the lesions. Oral lesions and those on the hands almost always are present; involvement of other cutaneous sites is more variable. The oral lesions arise without prodromal symptoms and precede the development of the cutaneous lesions. Sore throat and mild fever are present. The cutaneous lesions range from a few to dozens and primarily affect the borders of the palms and soies and the ventral surfaces and sides of the fingers and toes (Figure 7-24). Rarely other sites, especially the buttocks, external genitals. and legs. may be involved, The individual cutaneous lesions begin as erythematous macules that develop central vesicles and heal without crusting (Figure 7-25).

The oral lesions resemble those of herpangina but may be more numerous and are not confined to the posterior areas of the mouth. The number of lesions ranges from I to 30. The buccal mucosa. labial mucosa, and tongue arc the most common sites to be affected, but any

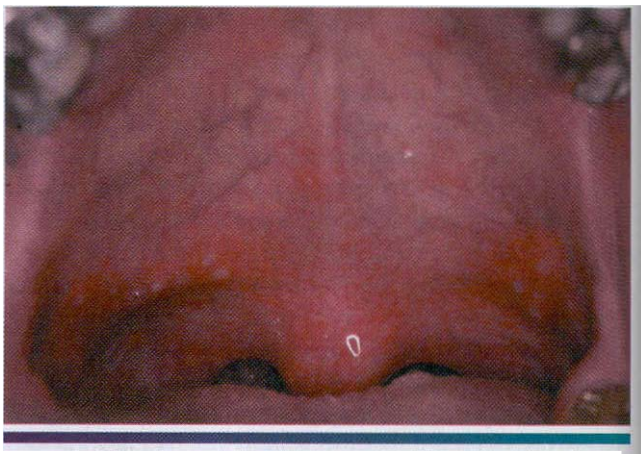


Figure 7-23 • Herpangina. Numerous aphthouslike ulcerations of the soft palate. (From Allen CM, Camisa C: Diseases of the mouth and lips. In Sams WM. Lynch P, editors: *Principles of dermatology.* New York, 1990, Churchill Livingstone.)

area of the oral mucosa may be involved (Figure 7-26). The individual vesicular lesions rapidly ulcerate and are typically 2 to 7 mm in diameter but may be larger than I em. Most of these ulcerations resolve within I week.

Acute *lymphonodular 1,llarytlgitis.* 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 (Figure 7-27). The nodules represent hyperplastic lymphoid aggregates and resolve within 10 days without vesiculation or ulceration. **Few cases have been described. and whether this represents a distinct clinical entity is as yet** unresolved. The possibilitv that the sore throat and palatal lymphoid hyperplasia represent features of herpangina or some other infection cannot be excluded **without further documentation of additional cases.**

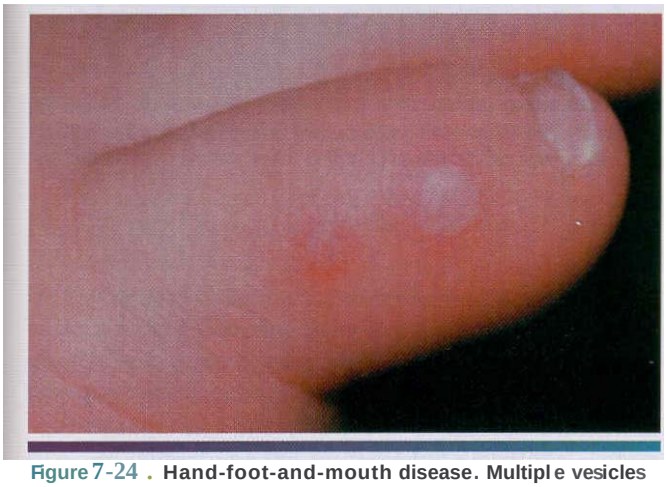


Figure 7-24 . Hand-foot-and-mouth disease. Multiple vesicles of the skin of the toe. (Courtesy of Dr. Samuel J jasper)

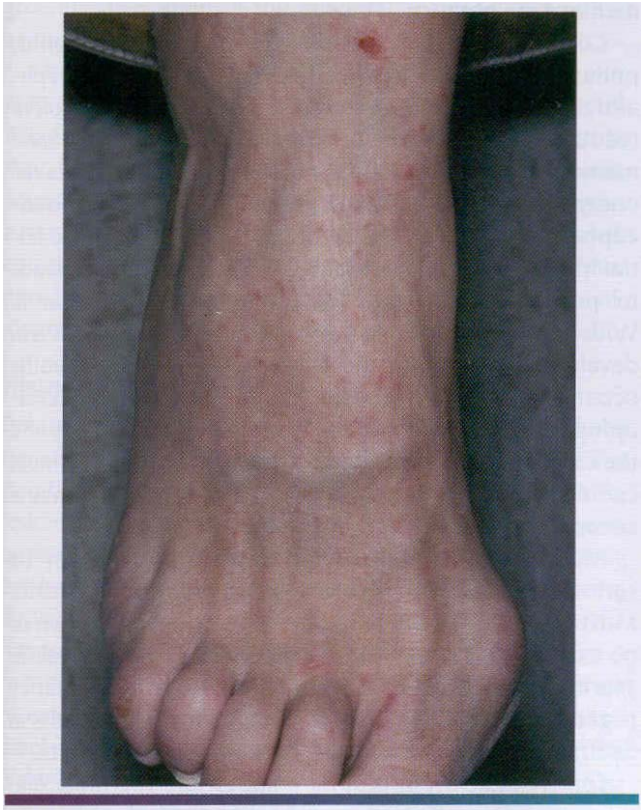


Figure 7-25 • Hand-foot-and-mouth disease. Numerous erythematous macules of the foot.

Histopathologic Features

In patients with herpangina and hand-foot-and-mouth disease, the areas of affected epithelium exhibit intracellular and intercellular edema, which leads to extensive spongiosis and the formation of an intraepithelial vesicle. The vesicle enlarges and ruptures through the epithelial basal cell layer, with the resultant formation of a subepithelial vesicle. Epithelial necrosis and ulceration soon follow. Inclusion bodies and multinucleated epithelial cells are absent.

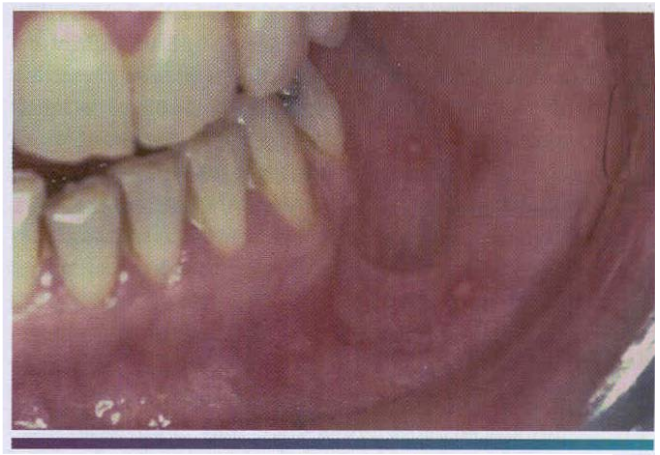


Figure 7-26 • Hand-foot-and-mouth disease. Multiple aphthouslike **ulcerations of the mucobuccal fold.**

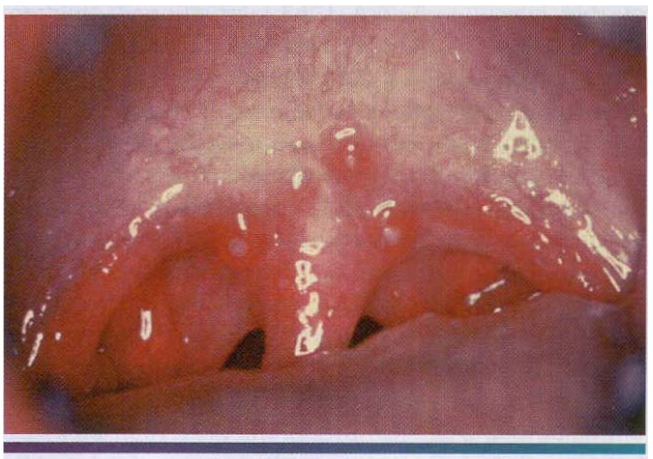


Figure 7-27 • Acute lymphonodular pharyngitis. Numerous dark pink and yellow lymphoid aggregates. (Courtesy of Dr. George Blozis.)

Diagnosis

The diagnoses of herpangina. hand-foot-and-mouth disease, and acute lymphonodular pharyngitis usually are made **from the distinctive clinical manifestations. In** patients with atypical presentations, laboratory confirmation appears **prudent. *Viral* isolation from culture can** be performed. and analysis of stool specimens is the best technique in patients with only mucosal lesions. Throat culture findings tend to be positive predominantly during **the early acute stage. The culture of cutaneous lesions is** best for the diagnosis of hand-foot-and-mouth disease. A serologic demonstration of rising enteroviral antibody **titers between the acute and convalescent stages can be** used to confirm the diagnosis in questionable cases.

Treatment and Prognosis

In most instances, the infection is self-limiting and **without** significant complications. Therapy for patients with an **enterovirus infection 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. During the 1998 epidemic in Taiwan. a large group of physicians reported 405 patients with severe disease and 78 deaths. Patients **with more significant complications demonstrated** higher temperature (>39' C), fever for longer than 3 **days, more serious vomiting. and greater lethargy. When** these findings are present. the physician must monitor the patient more closely for the development of more **serious complications.**

RUBEOLA (MEASLES)

Rubeola is an infection produced by a paramyxovirus and exhibits a variable prevalence that is correlated to **the degree of vaccine use. Measles** vaccine **has** been **in** wide use in the United States since 1963 and is 95% effective. resulting in a 98% reduction in the prevalence of this infection. Before 1963. Virtually all children acquired measles. but the vaccine produced a continued and significant decline until the late 1980s. From 1989 **to 1991. a major resurgence occurred with an increasing** proportion of cases among unvaccinated preschool-aged children. particularly minority residents of densely populated urban areas. In addition. a smaller number **of** cases **appeared to be associated with vaccine failure.**

Clinical Features

Most cases of measles arise in the spring and are spread through respiratory droplets. Affected individuals are infectious from 2 days before becoming symptomatic until 4 days after appearance of the rash. After an incubation period of 10 to 12 days. the infection begins with

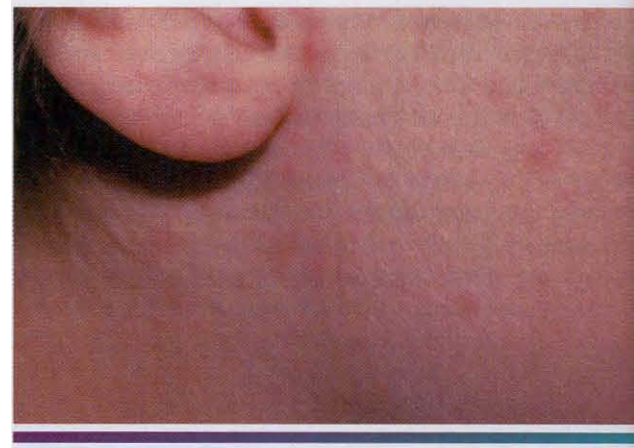


Figure 7-28 • Rubeola. Erythematous maculopapular rash of the face. (Courtesy of Dr, Robert J. Achterberg.)

prodromal symptoms of fever, malaise. coryza (runny **nose), conjunctivitis, and cough.** The **well-known exan**thematous rash follows after a few days and lasts from 4 to 7 days. The face is involved first. with eventual **downward spread to the trunk** and **extremities. Ulti**mately, a diffuse erythematous maculopapular eruption is formed (Figure 7-28). The rash clears in a similar downward progression and is replaced by a brown pig**mentary staining.**

Common complications in young children are otitis, pneumonia, persistent bronchitis. and diarrhea. Encephalitis develops in approximately 1 in 1000 cases. often resulting in death or permanent brain damage and mental retardation. In about I in 100.000 cases, a delayed **complication termed subacute sclerosing** panencephalitis (SSPE) arises as late as II years after the initial infection. This degenerative disorder **of** the CNS leads **to personality changes. seizures. coma. and death.** Widespread vaccine use has virtually eliminated SSPE in developed nations. In the United States, 1 to 2 deaths occur for every 1000 reported cases of measles. In devel**oping countries. the infection often is more severe, and** the case-to-fatality rate can be as high as 25%. The most **common causes of death are pneumonia and acute** encephalitis.

Measles **in imrnunocompromised patients can be** serious, with a high risk of complications and death. Most of these patients exhibit either an atypical rash or **no exanthem. Pneumonitis is the primary complication.** The fatality rate of measles in patients with a malignancy **is greater than 50%; AIDS-associated measles results** in death of more than one third of the affected patients.

Lesions. known as Koplik's spots, are the most dis***tinctive* oral manifestation of measles and develop early**

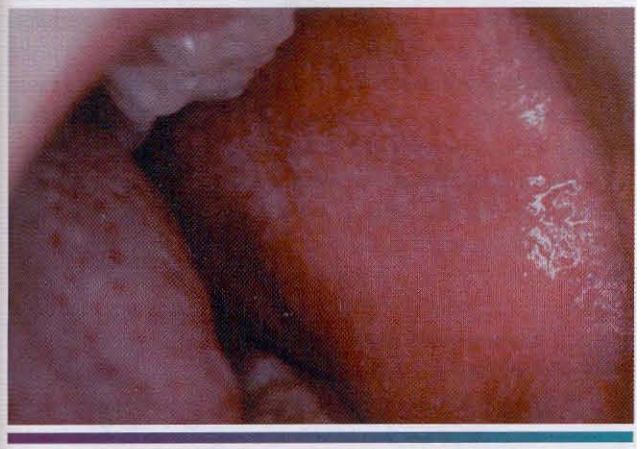


figure 7-29 • **Rubeola. Numerous bluish-white** Koplik's **spots of** buccal **mucosa. (Courtesy of Dr. Robert J Achterberg.)**

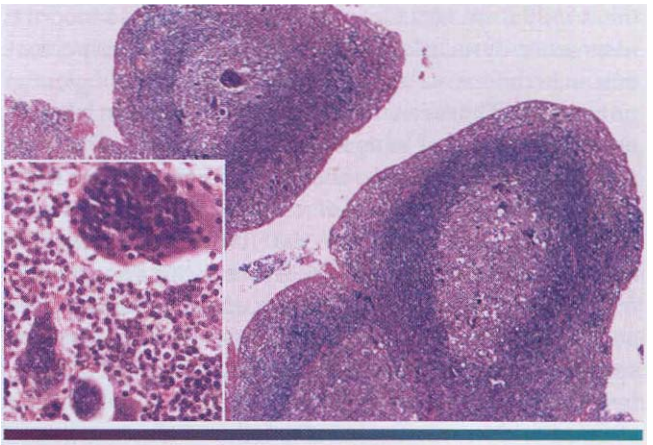


Figure 7-30 . Rubeola . Histopathologic section of pharyngeal **tonsil demonstrating lymphoid hyperplasia with scattered multinucleated giant cells. Inset reveals high power magnification of Warthin-Finkeldey giant cells.**

in the course of the infection. Multiple areas of mucosal erythema are visible on the buccal and labial mucosa or less often on the soft palate; within these areas, there are numerous small, bluish-white macules (Figure 7-29). In **addition, similar spots are noted rarely on the inner con**junctival folds of the eye or the vaginal mucosa. These pathognomonic spots represent foci of epithelial necrosis and have been described as "grains of salt" on a red background. The height of the mucosal eruption occurs just as the exanthem begins to develop and spread.

Koplik's spots arc not the only oral manifestation that **may be associated with measles. Candidiasis,** necrotizing ulcerative **gingivitis. and necrotizing stomatitis may occur if significant malnutrition also is present.** Severe measles in early childhood can affect odontogenesis and result in 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's spots, few oral and maxillofacial pathologists have had the opportunity to view these lesions microscopically. Initially, Koplik's spots represent areas of focal hyperparakeratosis in which the underlying epithelium exhibits spongiosis, intercellular edema, dyskeratosis, and epithelial syncytial giant cells. The number of nuclei within these giant cells ranges from 3 to over 25. Close examination of the epithelial cells often **reveals pink-staining inclusions in the nuclei or less commonly** in the cytoplasm. Upon electron microscopy, the **inclusions have been shown to represent microtubular aggregates characteristic of the causative** para*myxovirus*.

As the spot ages, the epithelium exhibits heavy exocytosis by neutrophils leading to microabscess formation, epithelial necrosis, and, ultimately, ulceration. Frequently, **examination of the epithelium adjacent to the ulceration** will reveal 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 (Figure 7-30). These multinucleated cells subsequently have been termed Warthin-Finkeldey giant cells and were thought for a time to be specific for measles. **Since that time, however, similar-appearing cells *have*** been noted in a variety of lymphoproliferative conditions such as lymphoma, Kimura's disease, AtDS-related lymphoproliferative disease, and lupus erythematosus.

Diagnosis

The diagnosis of typical measles in an epidemic setting usually is straightforward and based on the clinical fea**tures and history. Laboratory confirmation can be of** value in isolated or atypical cases. Viral isolation or rapid detection of viral antigens is possible. but confirmation usually is established through a demonstration of rising serologic antibody titers. The antibodies appear within 1 to 3 days after the beginning of the exanthem and peak **in about 3 to 4 weeks.**

Treatment and Prognosis

With a complication rate of 21%, the best treatment for measles is a good vaccination program; rubeola is part of

the widely used MMR vaccine. In an attempt to stop the resurgence of measles that began in 1989, the vaccination schedule was altered and the pockets of young, unvaccinated children were targeted. This action brought the transmission of indigenous measles to record lows. Although the number is variable from year to year, since 1993, the annual incidence of reported cases in the United States typically is well below 500. Total eradication of the infection is technically feasible with existing vaccines but will require universal cooperation and enthusiasm from across the globe. Renewed emphasis in the noncompliant sections of society must be stressed. In addition, a new two-dose vaccination schedule has been adopted in an attempt to decrease the vaccine failures. Currently, routine vaccination is recommended for all children between the ages of 12 and 15 months, with a second dose administered between the ages of 4 and 6 years.

In otherwise healthy patients with measles, fluids and nonaspirin antipyretics are recommended for symptomatic relief. Immunocompromised patients also may be treated with one of a number of medications that have shown promise but definitively have not been proven to be efficacious. The most promising is ribavirin; however, immunoglobulin, interferon, and vitamin A also are being used.

RUBELLA (GERMAN MEASLES)

Rubella is a mild viral illness that is produced by a togavirus. 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 virus is contracted through respiratory droplets, and it is transmitted to nearly 100% of individuals in close living conditions. The incubation time is from 14 to 21 days, and infected patients are contagious from 1 week before the exanthem to about 5 days after the development of the rash. Infants with a congenital infection may release 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 10,000 fetal deaths (direct effects or secondary to therapeutic abortions) and 20,000 infants born with congenital rubella syndrome (CRS).

An effective vaccine, first released in 1969, is used widely and has dramatically affected the epidemiology of the infection and broken the cycle of occurrences. The vaccine is contraindicated in the following groups:

- Pregnant women
- Immunodeficient patients
- Patients with acute febrile illnesses
- Patients with a known allergy to components of the vaccine

It was postulated that the protection of children also would eliminate the risk of exposure to women in the childbearing years. A 99% decrease in the infection was seen between 1969 and 1988, but young adults remain susceptible. Like rubeola, 1989 and 1990 demonstrated a slight resurgence of rubella, which was the result of a lack of vaccination diligence. More than 70% of the current cases occur in patients older than 15 years of age, and 10% to 25% of young adults remain susceptible. Of course, this should change when the previously vaccinated children grow into adults. For the present, the vaccination of postpubertal females must be stressed. Persons are presumed to be immune if they have received at least one dose of the MMR or were born before 1957. For pregnant females who have not received the vaccine, their immunity should be confirmed by demonstration of serum rubella IgG. Since 1992, the reported cases of indigenous rubella and CRS remain at a low and relatively constant level in the United States with less than 200 patients reported with rubella and no more than six infants affected with CRS annually.

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 exanthematous 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 rash forms discrete pink macules, then papules, and finally fades with flaky desquamation. The rash fades as it spreads and often exhibits facial clearing before the completion of its spread into the lower body areas.

Oral lesions, known as Forchheimer's sign, have been reported to be present in about 20% of the cases. These 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 the patients. This hearing loss may not become evident until 1 years of age and usually is bilateral. Less common, late emerging complications include encephalopathy, mental retardation, 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. Aithough viral culture is possible, serologic analysis is the mainstay of diagnosis.

Treatment and Prognosis

Rubella is mild. and therapy usually is not required. **Nonaspirin antipyretics and antipruritic medications** may be useful in patients with significant fever or symptomatic cutaneous involvement. **Passive immunity may** be provided by the administration of human 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. A two-dose vaccination schedule with the MMR is recommended, with the first dose between 12 and 15 months of age and a second between 4 and 6 years of age. This schedule has effectively prevented major epidemics of rubella and CRS in the United States.

MUMPS (EPIDEMIC PAROTITIS)

Mumps is a paramyxovirus infection that primarily affects the salivary glands. As with measles and rubella, the epidemiology has been affected dramatically by the MMR vaccine. Before the advent of Widespread vaccination, **epidemics were seen every 2 to 5 years. The vaccine** directed against mumps was released in 1967, but its use was not accepted nationally until i977. At that time, vaccination became the norm for children 12 to 15 months of age. The vaccine has a success rate of 75% to 95%. Most individuals born before 1957 are thought to **have immunity from exposure to naturally occurring** mumps virus. Although most authorities assume that natural infection is associated with lifelong immunity, **rare cases of recurrent mumps have been well documented** in patients with a confirmed history of prior natural **infection.**

The incidence of mumps decreased by 98% and reached an all-time low in 1985. In 1986. a resurgence developed. In the past, most cases occurred in children aged 5 to 9 years; during the resurgence. the disease was more prevalent in I0- to 19-year-old patients. Outbreaks have been reported in high schools, on college campuses. and in the workplace. This increased incidence has been **attributed to lack of vaccination, not vaccine failure. Subsequently,** in the early t990s, isolated outbreaks were reported in highly vaccinated populations and thought to be the result of large-scale vaccination failure. Not long after these reports, a second immunization as part of the MMR vaccine was recommended at 4 to 6 years of age. When compared with the prevaccine era. the two-dose MMR vaccination schedule has reduced the prevalence of mumps by 99%. In addition, in an attempt to decrease the **prevalence in the older age groups, it is recommended** that individuals lacking a history of mumps or MMR vaccination be immunized. This primarily affects those born between 1967 and 1977 and, to a lesser extent, those born between 1957 and 1967.

The mumps virus can be transmitted through urine, saliva, or respiratory droplets. The incubation period usually is 16 to 18 days, with a range of about 2 to 4 weeks. Patients are contagious from t day before the clinical appearance of infection to 14 days after its clinical **resolution.**

Clinical Features

Approximately 30% of mumps infections are subclinical. In symptomatic cases, prodromal symptoms of low-grade fever, headache, malaise, anorexia, and myalgia arrive first. Most frequently. these nonspecific findings are followed within I day by significant salivary gland changes. The parotid gland is involved most frequently. 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 (Figure 7-31). The enlargement typically peaks within 2 to 3 days, and the pain is most intense during this period of maximal enlargement. Chewing movements of the jaw or eating saliva-stimulating foods tends to increase the pain. Enlargement of the glands usually begins on one side and is followed by contralateral glandular changes within a few days. Unilateral involvement is seen in about 25% of patients.

The second most common finding is epididymoorchitis, which occurs in about 25% of postpubertal males. In those affected, 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. On** resolution of the swelling, atrophy occurs in the affected testicle. **Permanent sterility from testicular changes is rare. Less commonly. oophoritis and mastitis can be seen in** postpubertal females. In addition, spontaneous abortion occurs in approximately 25% of females 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. Isolated changes,

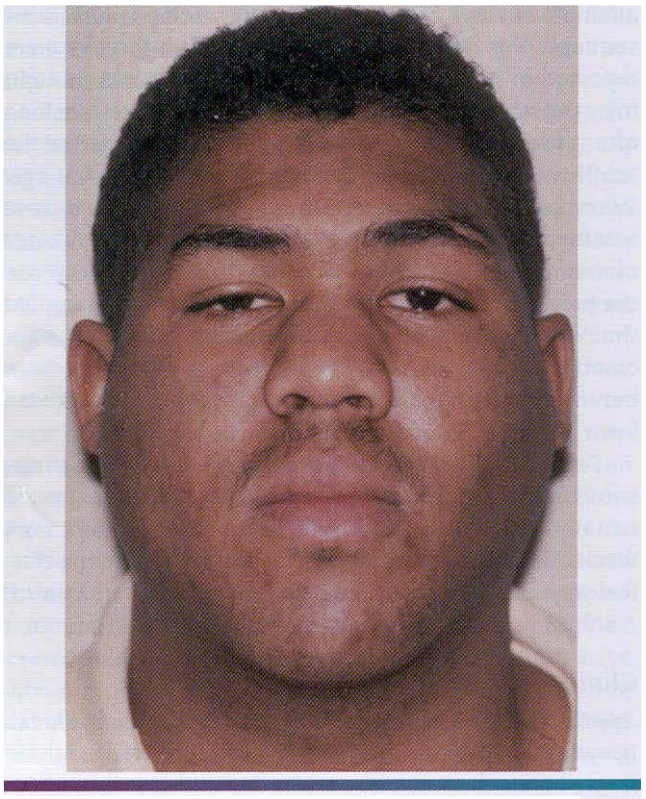


Figure 7-31 • Mumps. Bilateral parotid enlargement. (From Neville BW, Damm DO, White DK: *Coloratlas of clinical oral pathology*, ed 2, Baltimore, 1999, Williams & Wilkins.)

such as orchitis or meningitis, may occur in the absence of salivary gland Involvement, thereby making diagnosis difficult in nonepidemic settings. Mumps-related mortality is exceedingly rare and most frequently associated with mumps encephalitis.

The most frequently reported oral manifestation is redness and enlargement of Wharton's and Stenson's salivary gland duct openings. In addition, involvement of the sublingual gland may produce bilateral enlargements of the floor of the mouth.

Diagnosis

The diagnosis of mumps can be made easily from the clinical presentation when the infection is occurring in an epidemic fashion: *however,* isolated cases must be differentiated from other causes. Saliva, urine, or cerebrospinal fluid specimens can be obtained for culture. The most frequently used confirmatory measures are demonstration of mumps-specific IgM or a fourfold rise of mumps-specific IgG titers when measured during the acute phase and about 2 weeks later.

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. As with measles and rubella, the best results come from prior vaccination, thereby preventing the infection.

HUMAN IMMUNODEFICIENCY VIRUS AND ACQUIRED IMMUNODEFICIENCY SYNDROME

During the last two decades, more articles have been written on human immunodeficiency virus (HIV) and its related disease states than any other infectious process. A complete bibliography alone would be easily thicker than this chapter. Entire texts dedicated to HiV infection and acquired immunodeficiency syndrome (AiDS) are available and should be consulted for more detailed information.

AiDS came into the limelight in 1981. By 1992, 8 million people worldwide were thought to have been infected by HiV, with more than 5 million progressing to AIDS. Estimations at that time suggested the United States had between 1 and 1.5 million inhabitants infected with HIV. From the beginning of the epidemic to the dawn of the new century, 733,374 cases of AiDS have been reported in the United States to the Centers for Disease Control; of these individuals, 430,441 are dead. At the time of publication of the first edition of this text, the infection was thought to be nearly 100% fatal. Through treatment advances, the annual incidence of AIDS and related deaths have been dropping since 1996. This therapy is changing the face of HIV infection, with affected individuals demonstrating extended survival (resulting in an increased percentage of the population living with the virus).

In infected individuals, the virus can be found in most bodily fluids. HIV has been recovered from serum, blood, saliva, semen, tears, urine, breast milk, ear secretions, and vaginal secretions. The most frequent routes of transmission are sexual contact, parenteral exposure to blood, or transmission from mother to fetus during the perinatal period. Infection also has been documented to be caused by artificial insemination, breast-feeding from infected mothers, and organ transplantation. Although heterosexual transmission is increasing, most of the adults infected in the United States *have* been homosexual or bisexual men, intravenous drug abusers, hemophiliac patients receiving factor VIII before 1985.

recipients of blood products. or heterosexual contacts with one of the other high-risk groups.

Researchers have debated the infectiousness of oral fluids. HIV has been found to be present in oral fluids. but saliva appears to reduce the ability of HIV to infect its target cells. lymphocytes. Reports of transmission by oral fluids are rare, and it appears this is not a signifi- **cant source for the transmission of AIDS. In spite of this, anecdotal reports have documented the transmission of** AiDS during breast-feeding from the oral fiuids of post- partum infected infants to their previously noninfected mothers. In addition, rare examples have been documented reporting the transmission of HIV infection by contamination of the oral fluids during cunnilingus or repeated passionate kissing. Although rare, these anecdotal reports point out that oral fluids can be infectious **and are not completely protective against oral introduc-** tion of HIV. In summary. the best safety against infection is avoidance of all body fluids of infected patients.

Initially. in the United States. AIDS was thought to be a disease that primarily affected whites and male homo- **sexuals. Although men having sex with men remains the** largest single risk factor. the nature of the epidemic is shifting (Figure 7-32). When compared with the cumu- **lative data, more recent reports demonstrate a growing** proportion of patients with AIDS occurring in blacks and Hispanics (Figure 7-33). Since 1996. blacks have outnumbered whites in new AIDS diagnoses and HIv-relatcd deaths. Although the raw numbers are worrisome. the annual rates per 100.000 population dramatically highlight the ethnic shift (Figure 7-34). The proportion of women also is increasing steadily (23% in 1999). with a greater percentage infected heterosexually rather than through intravenous drug use.

The primary target cell of HIV is the CD4+ helper T lymphocyte. The DNA of HIV is incorporated into the DNA of the lymphocyte and. thus. is present for the life of the cell. In most viral infections. host antibodies that **are protective against the organism usually are formed.** In people with HIV infection, antibodies are developed **but are not protective. The virus may remain silent. cause** cell death. or produce syncytiai fusion of the cells. which **disrupts their normal function. A subsequent decrease in** l-hclper cell numbers occurs. with a resultant loss in **immune function. The normal response to viruses, fungi,** and encapsulated bacteria is diminished.

On introduction of the HIV. an indefinite percentage of those infected will have an acute self-limited viral syndrome. This is followed by an asymptomatic stage. which averages 8 to 10 years. The length of the asymptomatic period is variable and may be affected by the nature of **the virus. the host immune reaction, or external factors** that may delay or accelerate the process. Almost inevitably. the finai symptomatic stage develops.

Clinical Features

HIV infection initially may be asymptomatic or an acute response may be seen. The acute viral syndrome that occurs typically develops within I to 6 weeks after exposure in 50% to 70% of infected patients. The symptoms **bear some resemblance to those of infectious mono-** nucleosis (e.g.. generalized lymphadenopathy. sore throat, fever, maculopapular rash. headache. myalgia. arthralgia. diarrhea. photophobia. peripheral neuropathies). Oral changes may include mucosal erythema **and focal ulcerations.**

The acute viral syndrome clears within a few weeks; during this period, HIV infection usually is not considered or investigated. A variable asymptomatic period follows. Some patients have persistent generalized lymphadenopathy. which may later resolve. In some patients (before development of overt AIDS). there is a period of chronic fever. weight loss. diarrhea. oral candidiasis. herpes zoster, and/or oral hairy leukoplakia. This has been termed AIDS-related complex (ARC).

The presentation of symptomatic. overt AIDS is highly variable and often is affected by a person's prior expo- **sure 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 50% of the cases. pneumonia **caused by the protozoan** *Pneumocystis cannit* **is the pre-** senting feature leading to the diagnosis. Other infections of diagnostic significance include disseminated cytomeg- **alovirus (CMV) infection, severe herpes simplex virus** (HSV) infection. atypical mycobacterial infection. cryptococcal meningitis. and central nervous system (CNS) **toxoplasmosis. Persistent diarrhea is commonplace and** may be bacteriai or protozoal in origin. Clinically significant neurologic dysfunction is present in 30% to 50% **of** patients. **and the most common manifestation is a pro-** gressive encephalopathy known as AIDS-dementia **complex.**

Certain neoplastic processes also are associated with AIDS. Clinical descriptions of these cancers are presented in the portion of this text dealing with the oral manifestations of HIV infection. A vascular malignancy. Kaposi's **sarcoma (KSL which otherwise is rare in the United** States. has been reported in about 15% to 20% of **patients with AIDS. This cancer appears associated with** a sexually transmitted agent other than HIV: human herpesvirus type 8. AIDS-associated KS occurs primarily in homosexuals, but KS has been reported in homosexuals without HIV infection. This should remind clini-

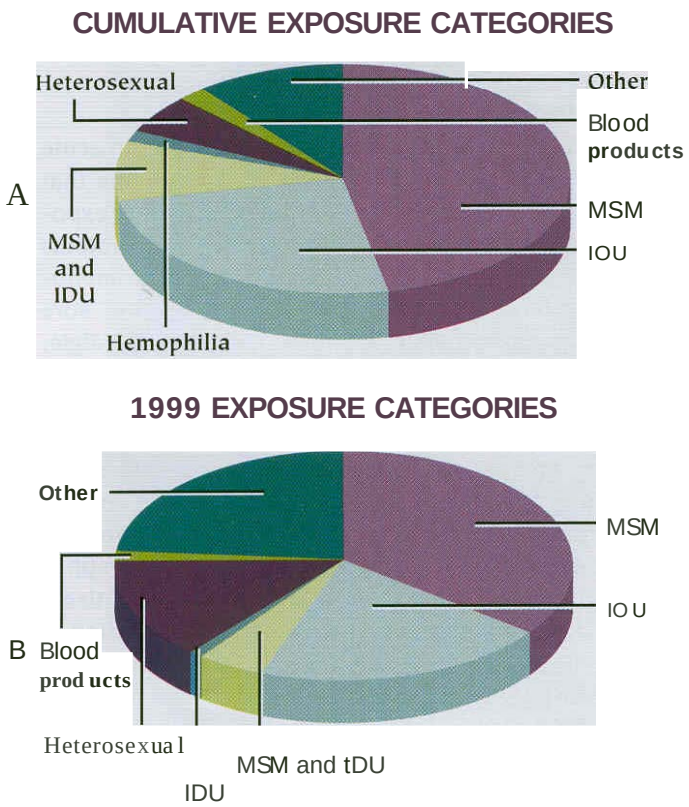


Figure 7-32 • A, Pie chart demonstrating the prevalence of the risk factors in patients documented with AIDS in the United States since the advent of the epidemic. B, Pie chart demonstrating the prevalence of the risk factors in patients documented with AIDS in the United States in 1999. Note the altered frequency of the MSM and heterosexual factors. *MSM,* Men having sex with men; *IOU,* injectable drug use.

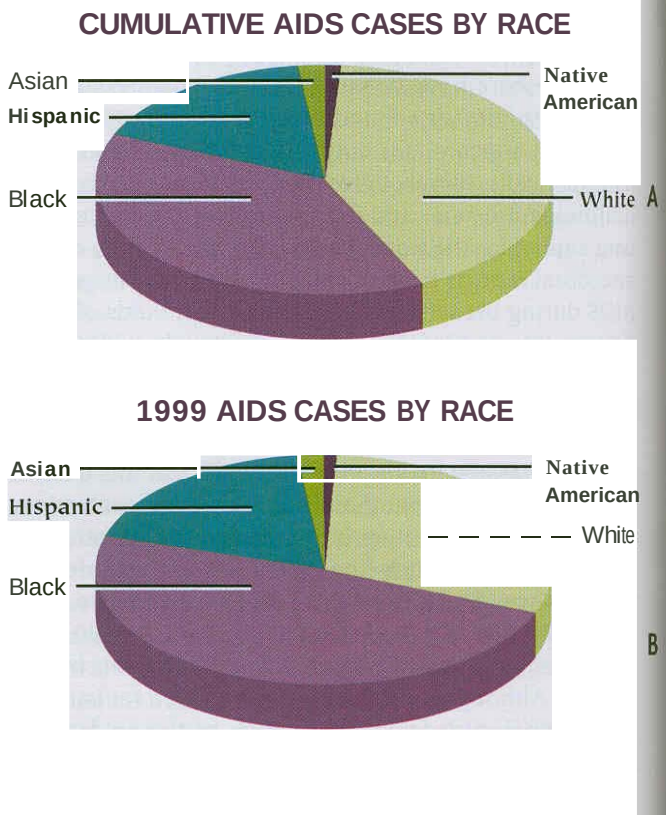


Figure 7-33. A, Pie chart demonstrating the prevalence of patients with AIDS by race in the United States since the advent of the epidemic. B, Pie chart demonstrating the prevalence of patients initially diagnosed with AIDS by race in the United States in 1999. Note the significant increased frequency occurring in blacks and Hispanics.

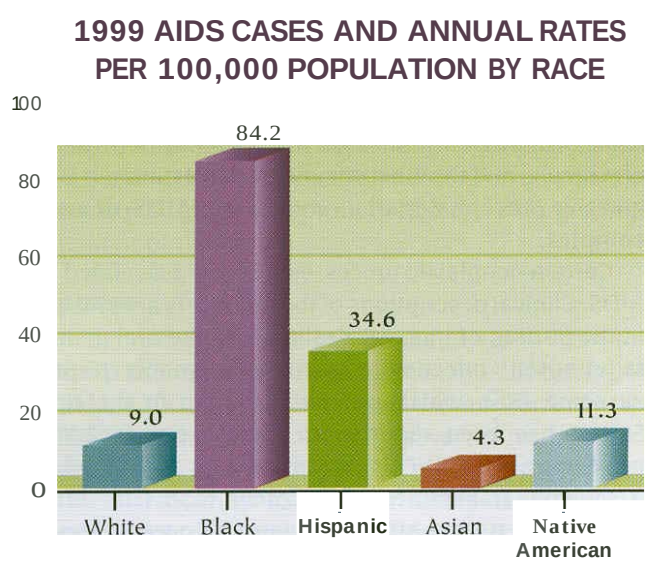


Figure 7-34 • Rates of AIDS per 100,000 population by race in the United States in 1999.

cians that homosexuals with KS should not be labeled "HIV-infected" until there is serologic proof. The prevalence of KS in HIV-infected patients has been decreasing and may be the result of the use of condoms, which may be preventing the transmission of herpesvirus 8.

Non-Hodgkin's lymphoma is the second most common malignancy. It is frequently found in extranodal sites, especially the CNS. Other cancers, including oral squamous cell carcinoma, have been documented in patients infected with HIV, but the association between AIDS and these cancers is not as strong.

A list of oral manifestations of AIDS is presented in Table 7-1. The discussion here concentrates primarily on the clinical presentations. (For detailed information on the histopathology, diagnosis, and treatment of each condition, see the text covering the individual disease.) When the infections are treated differently in HIV-infected patients, these variations are presented here. The most common manifestations are presented first, followed by a selection of the less frequently encountered disorders.

Table 7-1 *Oral Manifestations of Acquired Inlllllllodeficieucy Syndrome (AIDS)*

	MORE COMMON	LESS COMMON
Infections		
Fungal	Candidiasis	Aspergillosis
	HIV-related gingivitis	Histoplasmosis
		Cryptococcosis
		Geotrichosis
Bacterial	HIV-associated periodontitis	*Mycobacterium avium-intracetiuiare*
	NUG	*Klebsiella pneumoniae*
		Enterobacter cfoacae
		Escherichia coli
		Salmonella enteritidis
		Cat-scratch disease
		Sinusitis
		Exacerbation of periapical inflammatory disease
		Submandibular cellulitis
Viral	HSV	HPV
	VZV	CMV
	EBV	
Neoplasms	KS	Non-Hodgkin's lymphoma
		Squamous cell carcinoma
Lymphadenopathy	Cervical	
Neurologic		Trigeminal neuropathy
		Facial palsy
Miscellaneous		Aphthous ulcerations
		Necrotizing stomatitis
		Toxic epidermolysis
		Delayed wound healing
		Thrombocytopenia
		Xerostomia or siccalike syndrome
		HIV-related embryopathy
		Hyperpigmentation
		Granuloma annulare
		Exfoliative cheilitis
		lichenoid reactions

eM\!, Cytomegalovirus: fB\!, Epstein-Barr virus: *HI\!,* human tmmunodeftctency virus; HPV. human papllllomavtrus: *HSV.* herpes simples virus; *KS.* Kaposi's sarcoma; NUG, necrotizing ulcerative gingivitis; *VZv.* varicella-zoster virus.

(Modified from Scully C, Laskaris G, Pindborg J, et al: Oral manifestations of *HIV* infection and their management: I. More common lesions. *Oral Surg Oral Med Oral Pathol* 71:158-166. 1991.)

This list of common oral manifestations may change because of the impact of modern therapy on the disease. Current antiretroviral therapy has produced a significant decrease in the prevalence of HIV-related oral manifestations. with an altered ranking of the most commonly encountered pathoses. In one study. therapy appeared to decrease the frequency of oral candidiasis. hairy leukoplakia. destructive periodontal diseases. and KS; however. It increased the prevalence of HIV-associated salivary gland disease and human papillomavirus (HPV)-associated mucosal alterations.

Common oral and maxillo!aciall1lalli{estaliolls of IIIV infection

Persistent generalized lymphadenopathy. After seroconversion. HIV disease often remains silent except *tor* persistent generalized lymphadenopathy (PGL). The prevalence of this early clinical sign varies: however, in several studies it approaches 70%. PGL consists of lympha-

denopathy 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 (Figure 7-35).

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 exam**ination reveals florid follicular hyperplasia. Although not as predictive as oral candidiasis or hairy leukoplakia, PGI does warn of progression to AIDS; almost one third of affected and untreated patients will have diagnostic features of AIDS within 5 years.

Candidiasis. **Oral candidiasis is the most common** intraoral manifestation of HIV infection and often is the presenting sign that leads to the initial diagnosis (Figure 7-36). Its presence in a patient infected with HIV is not diagnostic of AIDS but appears to be predictive for the subsequent development 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;

- **Pseudomembranous**
- Erythematous
- Hyperplastic
- Angular cheilitis

The first two variants constitute most of the cases (see page 189), Although infrequently seen in Immunocom**petent patients, chronic multifocal oral involvement is common in patients who are infected with HIV.**

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 often is deficient (Figure 7-37).

Treatment is much more difficult in patlcnts with AIDS. Nystatin often is ineffective. Topical clotrimazole is associated with an improved response and typically produces a clinical cure rate that equals that of the systemic azoles, In spite of this success, topical therapy is associated with a high recurrence rate. The systemic azoles (t.c.. fluconazole, ketoconazolc, itraconazolc) produce longer **disease-free intervals but are associated with** another set of problems, Itraconazole and kctoconazole require gastric acidity for adequate absorption, and all three agents **are associated with a number of drug interactions.** In addition, Widespread use of systemic azoles has led to an increased prevalence of drug-resistant candidiasis.

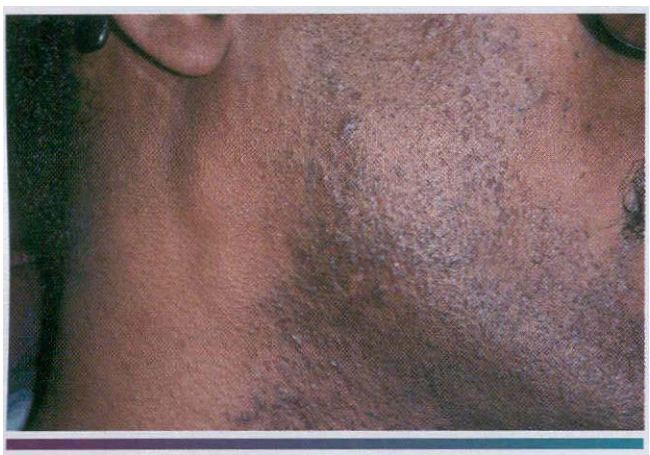


Figure 7-35 . HIV-associated lymphadenopathy. Enlarged cervical lymph nodes in a patient with persistent generalized lymphadenopathy (PGl).

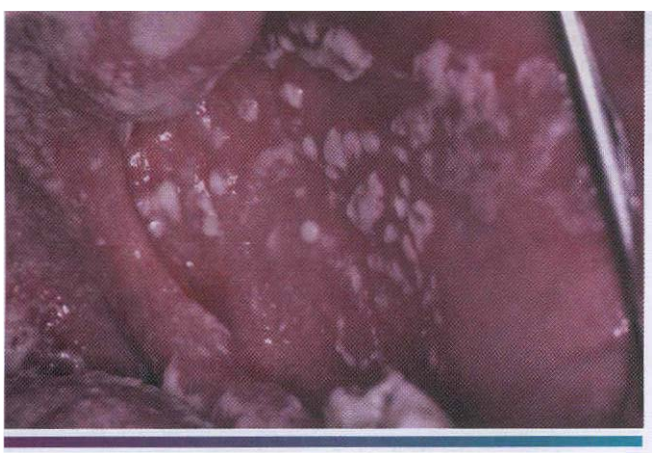


Figure 7-36 . HIV-associated candidiasis. Extensive removable white plaques of the left buccal mucosa.

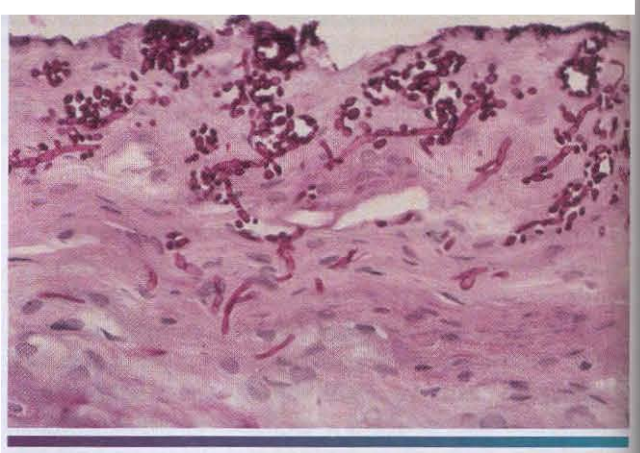


Figure 7-37 • HIV-associated candidiasis. Periodic acid-Schiff (PAS) stain of histopathologic section exhibiting numerous fungal organisms embedded in superficial keratin.

In patients who are receiving effective antiretroviral therapy and have a CD4 + count exceeding 50 ccIls/ rnrn' plus no signs of esophageal involvement. topical clotrimazole **is the treatment of choice. Systemic therapy is** recommended for patients not receiving effective antiretroviral therapy or for those with either esophageal involvement, a CD4 + count below 50, or a high viral **load. Itraconazolc in an oral solution has been shown to** be particularly effective in a swish-and-swallow method. Patients failing systemic azotetherapy are candidates for intravenous amphotericin B if the patient's health supports its use. Topical amphotericin B is available, but little research exists on its relative effectiveness. Prophylactic antifungal therapy is not recommended unless frequent **and severe recurrences are present.**

IiIV-associated periodontal disease. Three patterns of **periodontal disease are associated strongly with HIV infection:**

- Linear gingival erythema
- **Necrotizing ulcerative gingivitis**
- **Necrotizing ulcerative periodontitis**

Linear gingival erythema initially was termed *HiV-"Iated 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 (Figure 7-38). In addition, the alveo**lar mucosa and gingiva may demonstrate punctate or** diffuseerythema in a significant percentage of the cases. This form of gingivitis typically does not respond to improved plaque control and often exhibits a greater degree of erythema than would be expected for the amount of plaque in the area. Although some investigators **believe linear gingival erythema occurs from an** abnormal host immune response to subgingival bacteria, most believe this pattern of gingivitis represents an **unusual pattern of candidiasis. In many instances, linear** gingival erythema resolves after professional plaque removal. improved oral hygiene, and use of chlorhexidine rinses. Cases resistant to initial therapy typically respond to systemic antifungal medications such as flu**conazole or ketoconazole.**

Necrotizing ulcerative gingivitis (NUG) (see page **140) refers to ulceration and necrosis of one or more** interdental papillae with no loss of periodontal attachment. Patients with NUG have Interproximal gingival necrosis, bleeding, pain, and halitosis (Figure 7-39l.

Necrotizing ulcerative periodontis (NUP) was previously termed *HIV-associated periodontitis;* however, it has not been deemed to be specific for HIV infection. NUP is **characterized by gingival ulceration and necrosis asso**ciated 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 peri**odontitis. Edema, severe pain, and spontaneous hemor**rhage are common and often lead affected patients to seek care. Deep pocketing usually is not seen because extensive gingival necrosis typically coincides with loss of the adjacent alveolar bone (Figure 7-40l. Loss of more than 6 mm of attachment within a 6-month period is not **unusual. H1V-associated periodontitis does not respond** to conventional periodontal therapy.

The treatment of NUG and NUP revolves around debridement, antimicrobial therapy, immediate follow**up** care, **and long-term maintenance. The initial removal of necrotic tissue is necessary. combined with povidone-**iodine irrigation. The use of systemic antibiotics usually **is not necessary. but metronidazole has** been **administered to patients with extensive involvement that is asso**ciated with severe acute pain. All patients should use chlorhexidine mouth rinses initially and for long-term

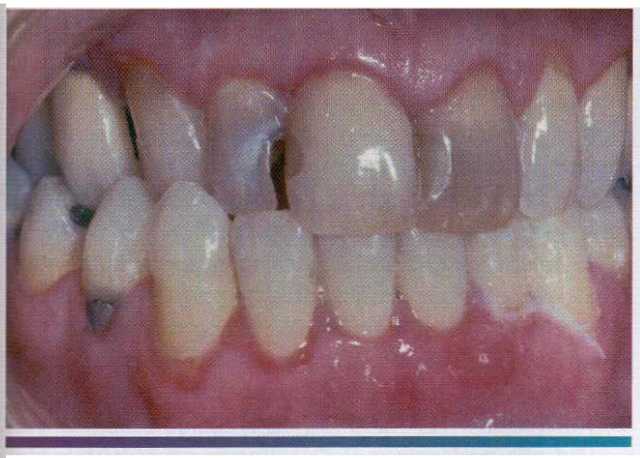


Figure 7-38 • HIY-associated gingivitis. Band of erythema involving the free gingival margin.

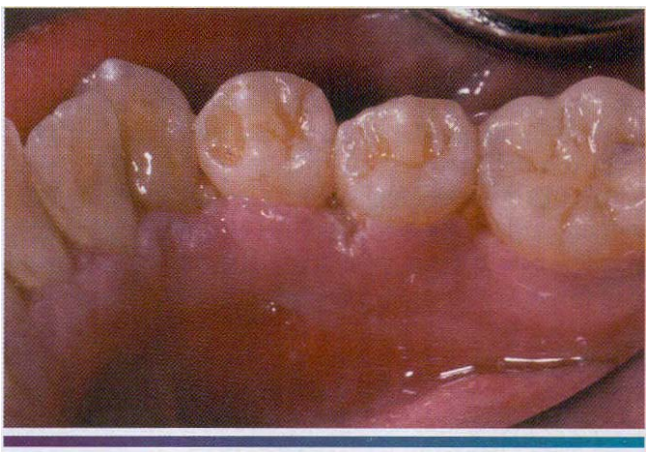


Figure 7-39 . HIY-associated necrotizing ulcerative gingivitis (NUG). Necrotic interdental papillae of the lingual mandibular gingiva.

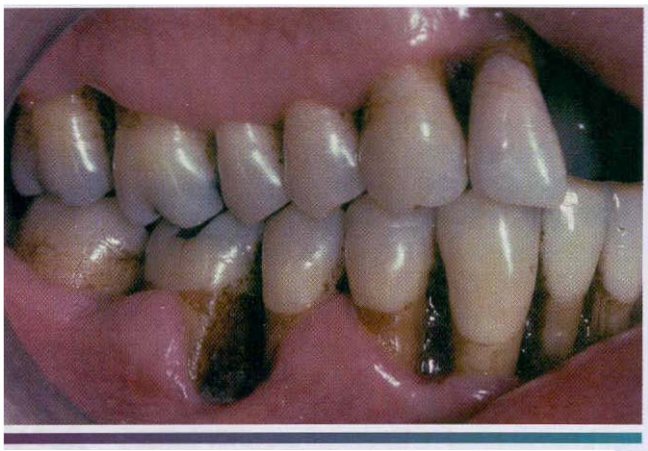


Figure 7-40 • HIV-associated periodontitis. Extensive loss of periodontal support without deep pocketing.

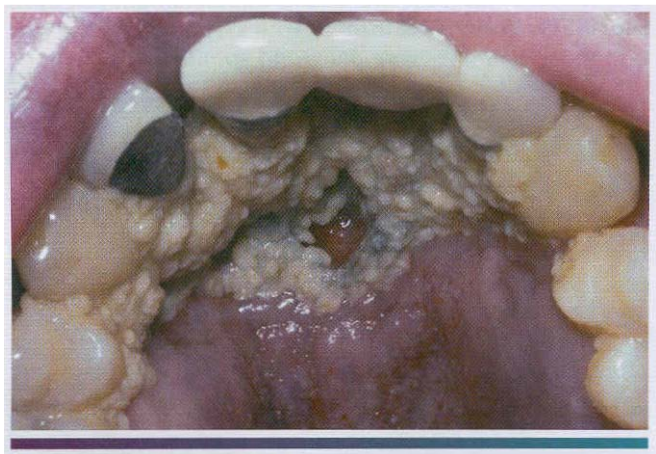


Figure 7-41 • HIV-associated necrotizing stomatitis. Massive necrosis of soft tissue and bone of the anterior maxilla.

maintenance. After initial debridement. follow-up 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. The process clinically resembles noma (see page 178) and may involve predominantly soft tissue or extend into the underlying bone, resulting in extensive sequestration (Figure 7-41), Although this process initially was thought to be an extension of NUP, **necrotizing stomatitis has arisen on the oral mucosa sep**arate from the gingiva (not overlying bone),

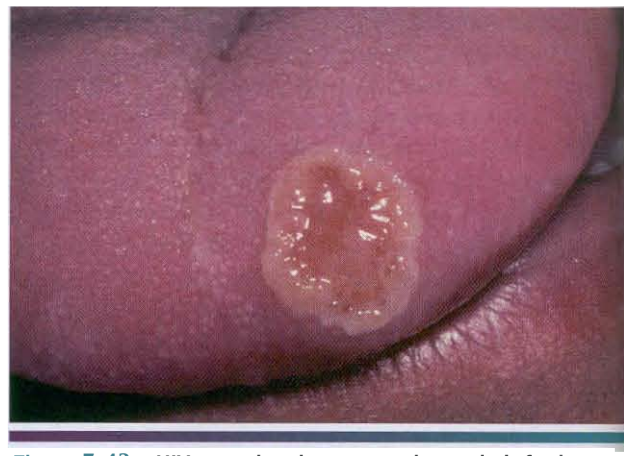


Figure 7-42 • HIV-associated recurrent herpetic infection. Mucosal erosion of the anterior dorsal surface of the tongue on the left side. Note the yellowish circinate border.

In the absence of gingival involvement, the clinical features of necrotizing stomatitis are nonspecific and mandate biopsy. In many instances, the areas of soft tissue ulceration and necrosis demonstrate infection with one of more agents, such as herpes simplex virus (HSVI. cytomegalovirus (CMV), and Epstein-Barr virus (EBV). On occasion, evaluations for HSV, CMV, and EBV are negative, leading one group to suggest that some lesions may represent an unusual immune reaction to the HIV. Upon biopsy. these ulceronecrotic lesions often demonstrate leukocytoclasia, histiocytic vasculitis. and an inflammatory infiltrate with numerous large atypical histiocytes.

Herpes simplex virus (HSV). Recurrent HSV infections occur in about the same percentage of HIV-infected patients as they do in the immunocompetent population (10% to 15%); however, the lesions are more widespread, occur in an atypical pattern, and may persist for months (Figure 7-42). The prevalence of HSV lesions increases significantly once the CD4+ count drops below 50. Herpes labialis may extend to the facial skin and exhibit extensive lateral spread. Persistence of active sites of HSV infection for more than 1 month in a patient infected with HIV is one accepted definition of AIDS. The clinical presentations of recurrences in immunocompromised patients and appropriate therapy and maintenance have been discussed in the text on herpesvirus (see page 217).

As mentioned in the discussion of necrotizing stomatitis. evaluation for HSV should be performed in all persistent oral ulcerations in HIV-infected individuals. In these ulcerations. investigators have discovered HSV in 10% to 19% (with an additional 10% to 28% exhibiting co-infection by HSV and CMV),

Varicella-zoster virus (VZV). Recurrent VZV infection (herpes zoster) is fairly common in HIV-infected patients.

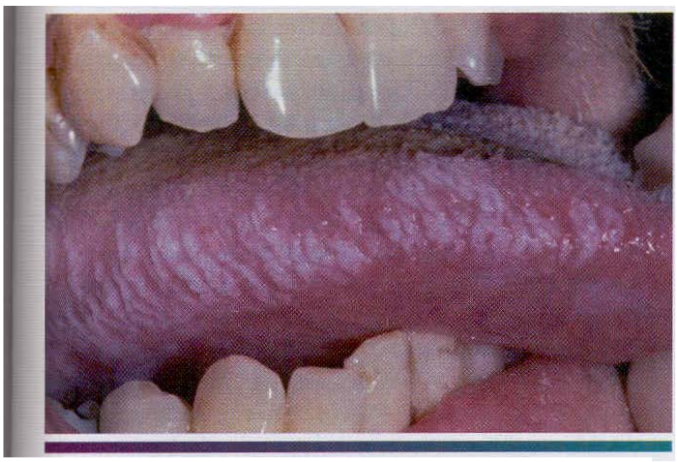


Figure 7-43 • HIV-associated oral hairy leukoplakia (OHL). Vertical streaks of keratin along the lateral border of the tongue.

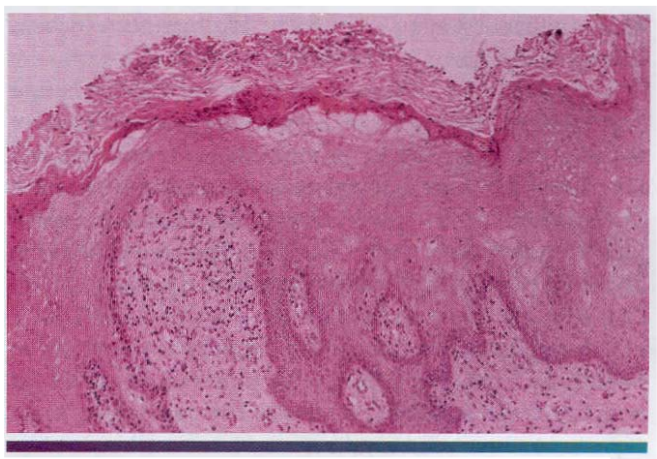


Figure 7-44 • HIV-associated oral hairy leukoplakia (OHI). Oral mucosa exhibiting hyperparakeratosls with surface corrugations.

but the course is more severe, with increased morbidity and mortality rates. Many of these patients are younger than age 40. in contrast to cases in immunocompetent patients that usually arise later in life. In the early stages of HIV-related immunosuppression, herpes zoster usually is confined to a dermatome but persists longer than usual. in full-blown AIDS, herpes zoster usually begins in a classic dermatomal distribution; *however,* subsequent cutaneous dissemination is not unusual. When present intraorally. the involvement often is severe and occasionally leads to bone sequestration and loss of teeth. Associated pain typically is intense. Although peroral antiviral medications are beneficial in immunocompetent patients, intravenous *acyclovir* is recommended for *severe* herpes zoster in the absence of an intact immune system.

Epstein-Barr virus fEBV). Although EBV is thought to be 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). This lesion has a somewhat distinctive (but not diagnostic) pattern of hyperkeratosis and epithelial hyperplasia that is characterized by white mucosal lesions that do not rub off.

Most cases of OHL occur on the lateral border of the tongue and range in appearance from faint white vertical streaks to thickened and furrowed areas of leukoplakia, exhibiting a shaggy keratotic surface (Figure 7-43). The lesions may become extensive and cover the entire dorsal and lateral surfaces of the tongue. Rarely, involvement also has been observed on the buccal mucosa. soft palate. pharynx, or esophagus.

Histopathologically, OHL exhibits thickened parakcrattn, which demonstrates surface corrugations or thin projections (Figure 7-44). The epithelium is hyperplastic

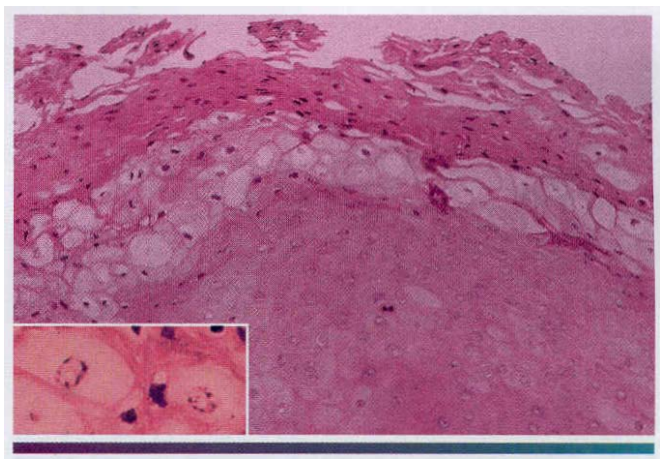


Figure 7-45 • HIV-associated oral hairy leukoplakia (OHL). Oral epithelium exhibiting hyperparakeratosis and layer of "balloon cells" in the upper spinous layer. Inset reveals high-power magnification of epithelial cells that demonstrate nuclear beading.

and contains a patchy band of lightly stained "balloon cells" in the upper spinous layer (Figure 7-45). Close examination of the superficial epithelium *reveals* scattered cells with nuclear clearing and a characteristic pattern of peripheral margination of chromatin termed *nuclearbeading* (see Figure 7-45. *inset).* The nuclear alterations arc created by *extensive* EBV replication that displaces the chromatin to the nuclear margin. Dysplasia is not noted. Heavy candidal infestation of the parakeratin layer is typical, and the normal inflammatory reaction to the fungus usually is absent.

In the routine management of HIv-infected patients, the clinical features typically are sufficient for a pre*sumptive* diagnosis. When definitive diagnosis is necessary, demonstration of EBV within the lesion is required and can be achieved by *in situ* hybridization, PCR.

immunohistochemistry, Southern blotting, or electron microscopy (Figure 7-46l.

Treatment of OHL usually is not needed, although **slight discomfort or aesthetic concerns may necessitate** therapy. Acyclovir or desiclovtr produces rapid resolu**tion. but recurrence is expected with a discontinuation** of therapy. Topical treatment with retinoids or podo**phyllum resin has resulted in temporary remissions. In** addition, HIV therapy with zidovudine appears to affect *EBV* and result in significant regression.

Although rare instances of OHL have been reported in **immunocompetent individuals. most cases arise in** immunocompromised persons. OHL also has been **reported in heart. kidney, liver. and bone marrow trans**plant recipients, but its presence in the absence of a known cause of immunosuppression strongly suggests **HIV infection. Discovery of OHL in "normal" patients** mandates a thorough physical evaluation to rule out **immunocompromised status. The presence of OHL in HIV-infected patients is a signal of severe immune suppression and more advanced disease.**

Kaposi's sarcoma (KS). KS is a multifocal neoplasm of vascular endothelial cell origin. Before AIDS, KS was rare in North America and was found classically in patients over the age of 60 (see page 484). Since the beginningo! **the HIV epidemic, however, most cases have been seen** in association with AIDS. Human herpesvirus type 8 (HHV-8) is noted within the tumor and thought to be involved in the neoplasm's development.

KS begins with single or, more frequently. multiple lesions of the skin or oral mucosa. The trunk. arms, head, **and neck are the most commonly involved anatomic sites** (Figure 7-47). Oral lesions are seen in approxtmatelv 50% of affected patients and arc the initial site of involvement in 20% to 25%. Although any mucosal site may be involved, the hard palate, gingiva, and tongue are affected most frequently (Figures 7-48 and 7-49). When present on the palate or gingiva, the neoplasm can invade bone and create tooth mobility. The lesions begin as fiat, brown or reddish purple zones of discoloration that do not blanch with pressure. With time, the involved areas may develop into plaques or nodules (Figure 7-50). Pain, bleeding, and necrosis may become a problem and necessitate therapy (Figure 7-51.

A biopsy is required to make the definitive diagnosis, **although a presumptive diagnosis is sometimes made** from the clinical presentation and history. It must be remembered **that similar clinical lesions can occur in** HIV-infected patients who exhibit bacillary angiomatosis, the multifocal vascular proliferation associated with the cat-scratch bacillus (sec page 183).

KS is a progressive malignancy that may disseminate widely to lymph nodes and various organ systems. Extensive systemic therapy often further depresses the

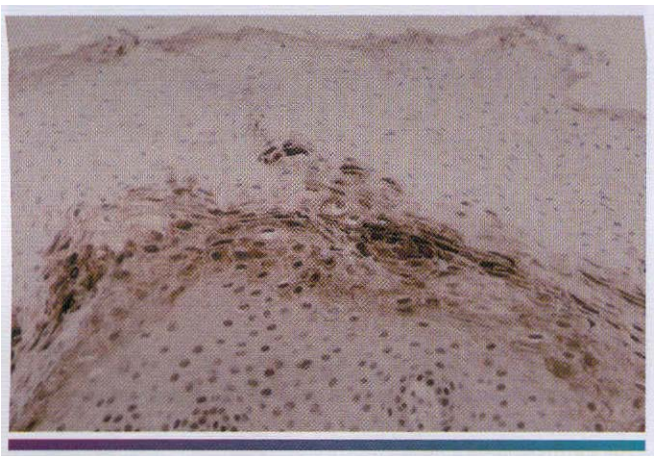


figure 7-46. **HIV-associated oral hairy leukoplakia (OHl). Immunoperoxidase evaluation for Epstein-Barr virus revealing positive reaction within numerous epithelial cells.**

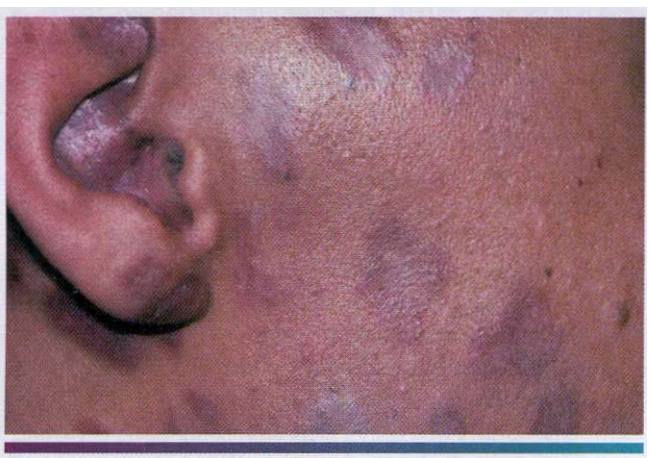


Figure 7-47. HIV-associated Kaposi's sarcoma (KS). Multiple purple macules on the right side of the face.

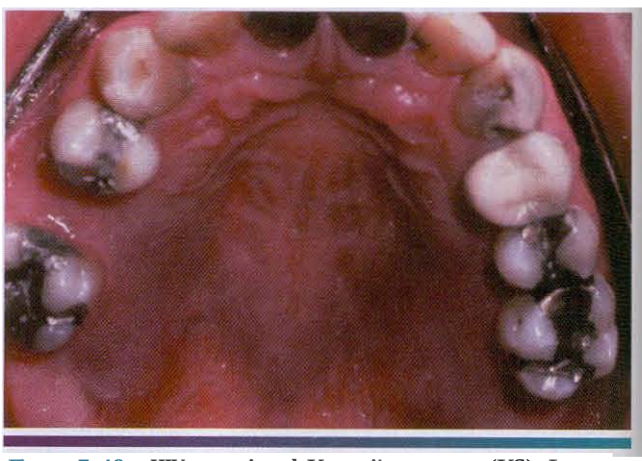


Figure 7-48 • HIV-associated Kaposi's sarcoma (KS). Large zones of KS exhibiting as a flat. brownish, and M-shaped discoloration of the hard palate.

immune system, thereby increasing the susceptibility of the patient to infection and other cancers. Achievement of permanent cure has been elusive, although most patients with AIDS-related KS die of other complications. such as oppo rtuni stic infections. Therefore. treatment objectives usually are palliative. KS responds to radiation or systemic chemotherapy (singly or in combination), such as vinblastine, vincristine. etoposide, bleomycin, Adriamycin, actinomycin D, doxorubicin, or alpha-interferon.

Oral lesions frequently are a cause of major morbidity, as a result of pain, bleeding, and functional interferences. Intralcsional injection of oral lesions with vinblastine is effective and may be repeated if required. Intralcslonal injection of a sclerosing agent, sodium tetradccyl sulfate, has been effective for problematic intraoral lesions less than 2.5 cm in diameter. Problematic lesions also may be removed by surgical excision, cryotherapy, laser ablation, or electrosurgery. Concerns exist about the use of the latter two methods because of aerosolization of viral particles that may place the surgical team at risk.

Significant regression of KS has been noted in a number of patients receiving antiretroviral therapy such as indinavlr, rltonavlr, or saquinavir. It is not known if this response is due to an improvement in the immune system of the host or a direct antiviral effect against HHV-8.

Less common oral and maxillolacial manifestations of HIV infection

Aphthous ulcerations. Lesions that are similar clinically to aphthous ulcerations occur with increased frequency in patients infected with HIV. All three forms (minor, major, and herpetiform) are seen: surprisingly, however, almost two thirds of the patients have the usually uncommon herpetiform and major variants (Figure 7-52). As immunosuppression becomes more profound, major aphthous ulcerations demonstrate an increased prevalence.

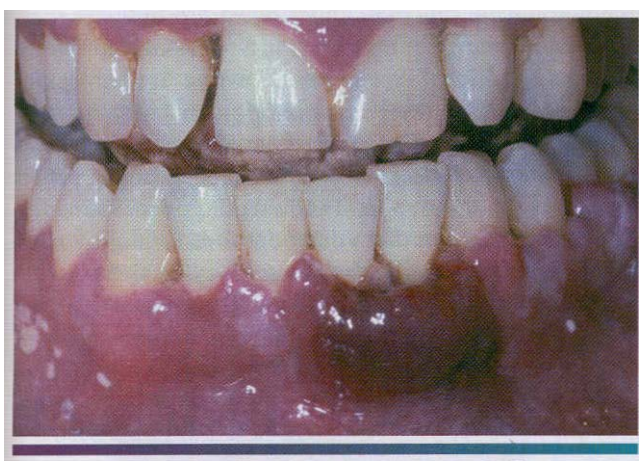


Figure 7-49 . HIV-associated Kaposi's sarcoma (KS). Raised. dark-red enlargement of the mandibular anterior facial gingiva on the left side.

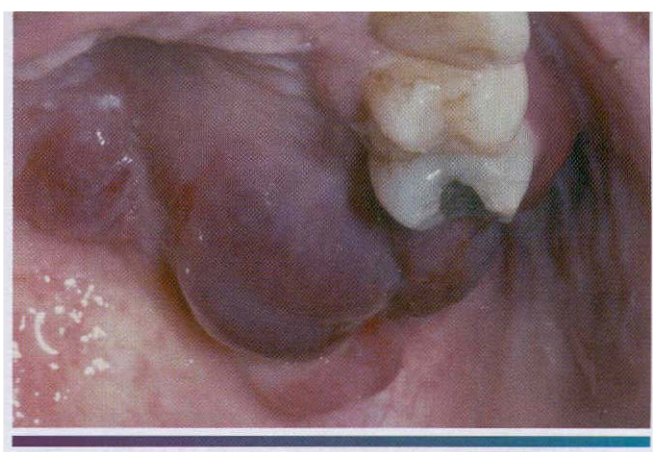


Figure 7-50 . HIV-associated Kaposi's sarcoma (KS). Diffuse. reddish-blue nodular enlargement of the left hard palate.

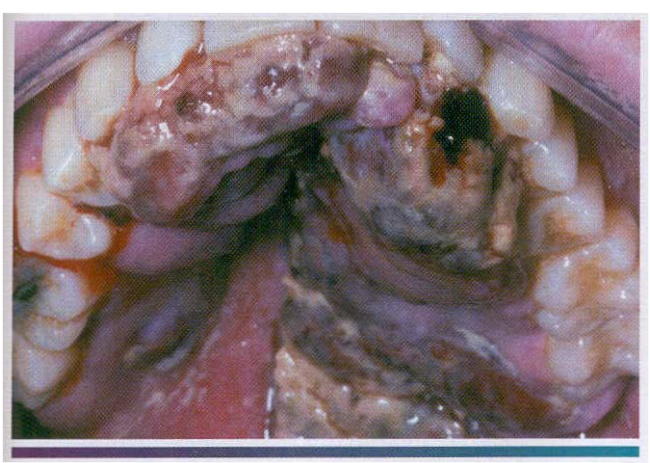
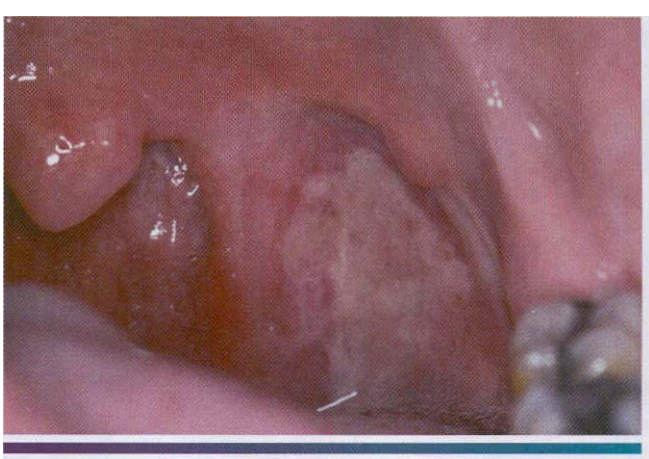


Figure 7-51 • HIV-associated Kaposi's sarcoma (KS). Diffuse. reddish-blue gingival enlargement that demonstrates widespread necrosis.



Figure]-52 • HIV-associated aphthous ulceration. Large superficial ulceration of the posterior soft palate.

Treatment with potent topical or intralesional corticosteroids has been successful in a number of patients. **Not all lesions respond. and recurrences are common.** Secondary candidiasis may be a complication of therapy. Systemic corticosteroids also may prove beneficial but typically are avoided in an attempt to prevent further **immune depression. For lesions nonresponsive to top**ical steroids, thalidomide has been found to be advantageous in many patients. Thalidomide must be used cautiously for only a short term because of its ability to enhance the production of HIV. In a limited number of patients, granulocyte colony stimulating factor has produced rapid and sustained resolution of aphthous ulcerations that were resistant to therapy with topical corticosteroids, cyclosporine, and thalidomide.

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 (Figure 7-53). In such cases, biopsy often reveals another cause, such as HSV, CMV, deep fungal infection, or neoplasia. (For further information on aphthous ulcerations and the pathogenesis of these lesions in patients infected with HIV, see page 285).

Human papillomavirus (HPV). HPV is responsible for **several facial and oral lesions in immunocompetent patients. the most frequent of which are the verruca vul**garis *(common* wart) (see page 317) and oral squamous papilloma (see page 316). An increased prevalence of HPV-related lesions is noted in HIV-infected patients, and most are located in the anogenital areas. Oral involvement also may be seen. Although usual types of HPV may be present in intraoral lesions, HIV-infected **patients often demonstrate more unusual variants** such as HPV-7 (associated with butcher's warts) or HPV-32 (often noted in Heck's disease) (see page 320).

The oral lesions usually are multiple and may be located on any mucosal surface. The labial mucosa, tongue, buccal mucosa, and gingiva are frequent sites. The lesions may exhibit a cluster of white, spikelike projections, pink cauliflower-like growths, or slightly elevated sessile papules (Figure 7-54).

Histopathologically, the lesions may be sessile or papillary and covered by acanthotic or even hyperplastic stratified squamous epithelium (Figure 7-55). The affected epithelium often demonstrates vacuolization of numerous epithelial cells (i.e., kollocytosis) and occasionally may exhibit mild variation in nuclear size (Figure

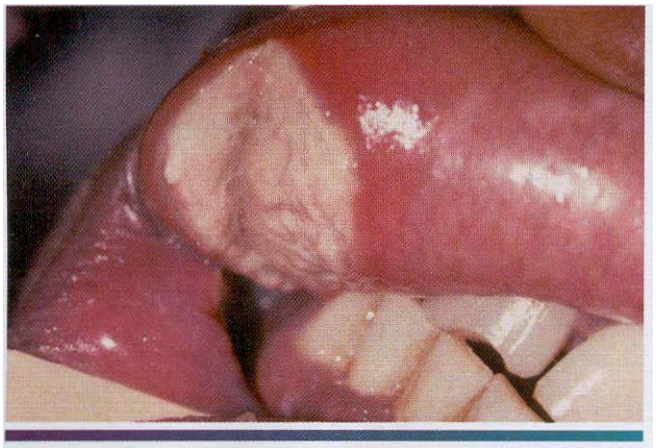


Figure 7-53 • HIV-associated ulceration. Atypical mucosal ulceration that mandates biopsy and may be attributable to a variety of causes.

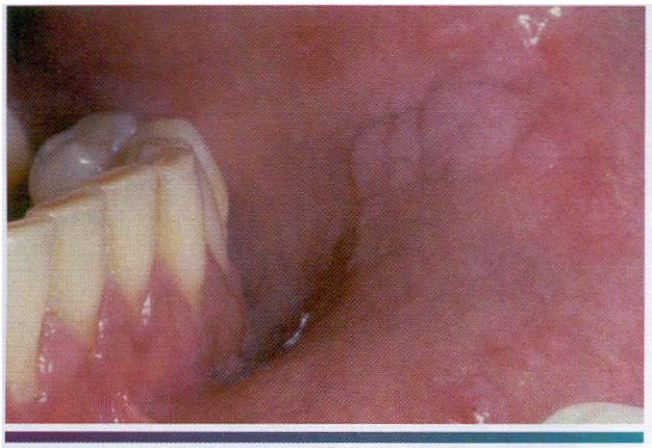


Figure 7-54. HIV-associated human papillomavirus (HPV) infection. Multiple elevated and sessile papules of labial mucosa.

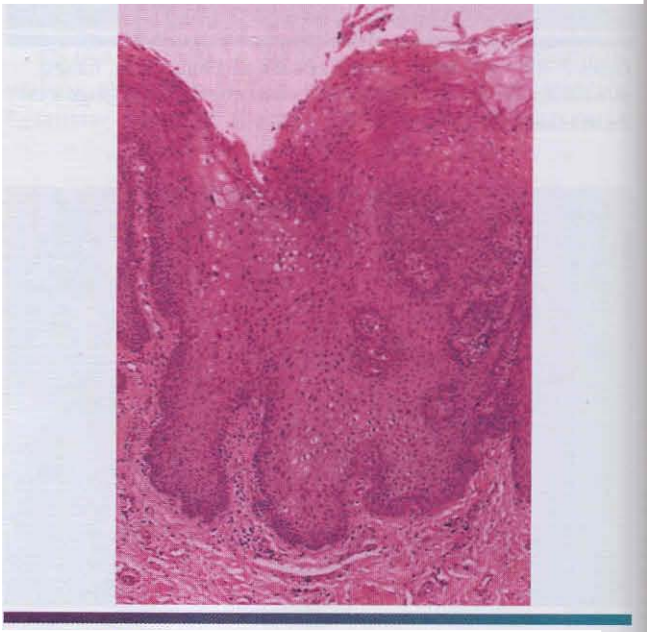


Figure 7-55 • HIV-associated human papillomavirus (HPV) infection. Oral mucosa exhibiting acanthosis and mild nuclear pleomorphism.

]-56), Immunohistochemistry or DNA in situ hybridization often is used to confirm the presence and type of HPV within histopathologic specimens (Figure 7-57).

Dysplasia has been noted within HPV-related lesions in patients with AIDS and mandates close observation of affected patients for development of squamous cell carcinoma. **The treatment of choice is surgical removal; however, recurrences are common, especially in patients** with significant immune deficiency. Other therapeutic modalities that have been used include topical podophyllin. interferon. cryosurgery. laser ablation, and electrocoagulation. If one of the latter two choices is used. the surgical team must be wary of the resultant plume that may contain infectious HPV.

Histoplasmosis. **Histoplasmosis. the most common** endemic respiratory fungal infection in the United States, is produced by *Histoplasma capsulatum* (see page 197). In healthy patients. the infection typically is subclinical and self-limiting, but clinically evident infections do 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. In **patients** with AIDS, diagnosis of 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 blood-borne 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 in the jaws has been reported, the most common oral **presentation of histoplasmosis is a chronic. indurated** mucosal ulceration with a raised border (Figure 7-58). The oral lesions may be singular or multiple. and any area of the oral mucosa may be Involved.

Microscopically. the small fungal organisms are visible within the cytoplasm of histiocytes and multinucleated giant cells. These phagocytic cells may be present in sheets or in organized granulomas (Figure 7-59). The therapy of choice for disseminated histoplasmosis has **been intravenous amphotericin B. but itraconazole has been shown to be effective with fewer adverse reactions** and better patient compliance. Ketoconazole is another alternative. but its hepatotoxicity makes this approach a less desirable form of therapy.

Molluscum ***contagiosum.*** **Molluscum** contagtosum **is an** infection of the skin caused by a poxvirus (see page 323). The lesions are small. waxy. dome-shaped papules that often **demonstrate a central depressed crater. In immuno-**

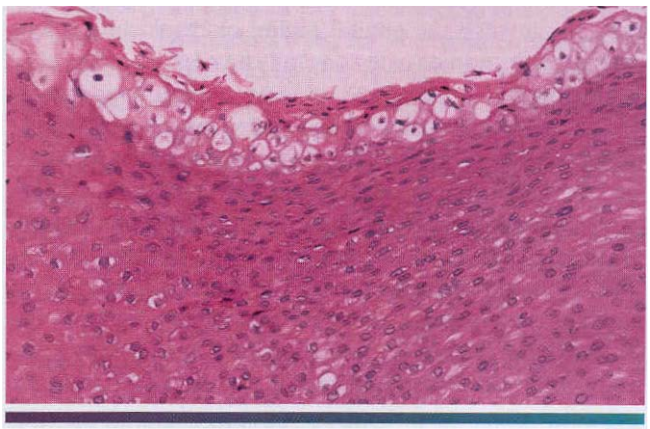


Figure 7-56 . HIV-associated human papillomavirus (HPV) infection. Oral mucosa exhibiting extensive koilocytosis in the superficial spinous cell layer.

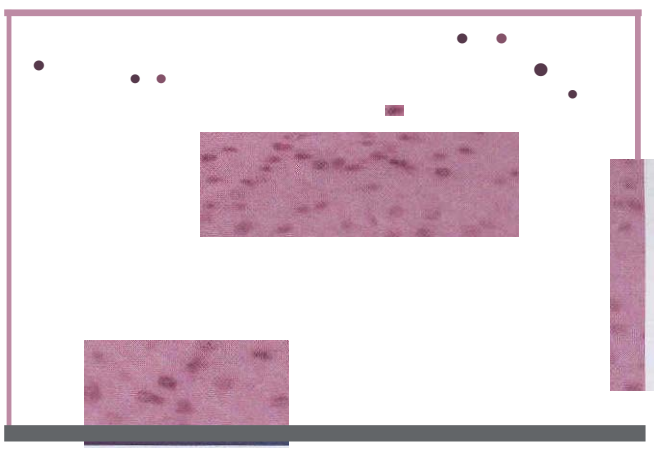


Figure 7-57 . HIV-associated human papillomavirus (HPV) infection. DNA *in situ* hybridization of oral mucosal biopsy that reveals diffuse cellular positivity for HPV.

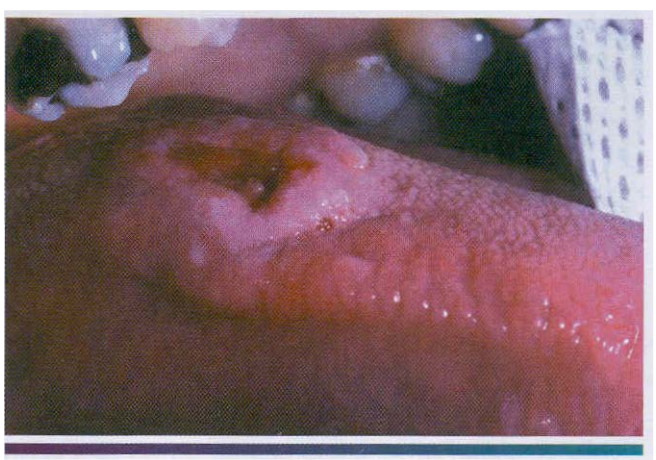


Figure 7-58 . HIV-associated histoplasmosis. Indurated **ulceration with a rolled border on the dorsal surface of the tongue on the right side.**

competent individuals, the lesions are self-limiting and typically involve the genital region or trunk. tn patients with AIDS, hundreds of lesions may be present, with many exhibiting little tendency to undergo spontaneous resolution. and some occasionally obtaining large size. Approximately 5% to iO% of HIV-infected patients are affected. and the facial skin commonly is involved (Figure 7-60).

Histopathologically. the surface epithelium forms several hyperplastic downgrowths. This involuting epithelium contains numerous large, intracytoplasmic inclusions known as molluscum bodies (Figure 7-61). In the center of the lesion, the keratin layer often disintegrates and releases the adjacent molluscum bodies. hence the central crater.

Local therapy (e.g.. curettage. cryosurgery, cautery) usually is painful and often disappointing because of frequent recurrences. Several separate reports have documented resolution of Widespread and recalcitrant lesions after successful initiation of highly active antiretroviral therapy. It is not known if these responses are secondary to immune reconstitution or the antiviral effects of the therapy.

Thrombocytopenia. Thrombocytopenia has been reported in nearly 10% of patients with HIV infection and may occur at any time during the course of the disease. Some reports show that megakaryocytes have CD4 molecules and may be an additional target for the HIV virus. Cutaneous lesions are present in most cases, but oral lesions do occur with petechiae, ecchymosis, or spontaneous gingival hemorrhage.

H/V-associated salivary gland disease. HIv-associated salivary gland disease also can arise anytime during infection. Clinically obvious salivary gland disease is noted in approximately 5% of HIV-infected patients, with a greater prevalence noted in children. The main clinical sign is salivary gland enlargement, particularly affecting the parotid. Bilateral involvement is seen in about 60% of the patients with glandular changes and often is associated with cervical lymphadenopathy.

As a result of a genetically influenced alteration of the immune response to *HIV* infection, some patients develop diffuse infiltrative lymphocytosis syndrome (DILS), which is associated with a more favorable prognosis of their HIV infection. Affected individuals reveal *COB* lymphocytosis and lymphadenopathy along with salivary gland enlargement. Although the parotid is

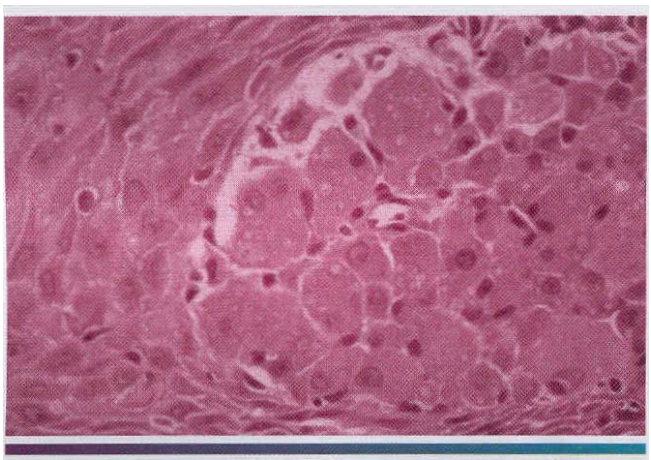


Figure 7-59 . HIV-associated histoplasmosis. Mucosal biopsy in which the connective tissue is filled with numerous enlarged histiocytes. Numerous small. clear-appearing fungal organisms are located within the cytoplasm of the histiocytes.

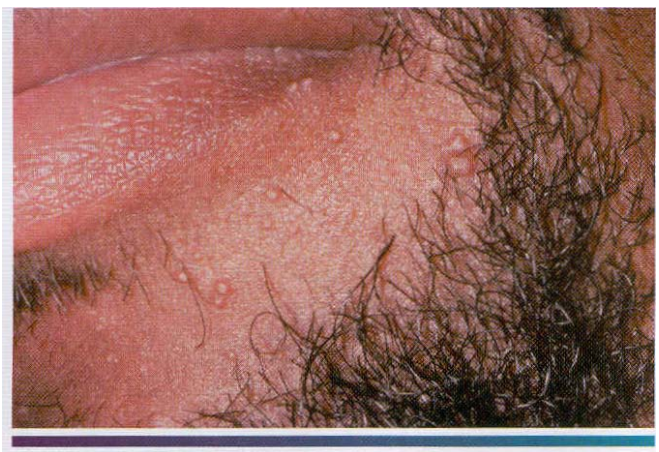


Figure 7-60 • HIV-associated molluscum contagiosum. Numerous perioral papules.

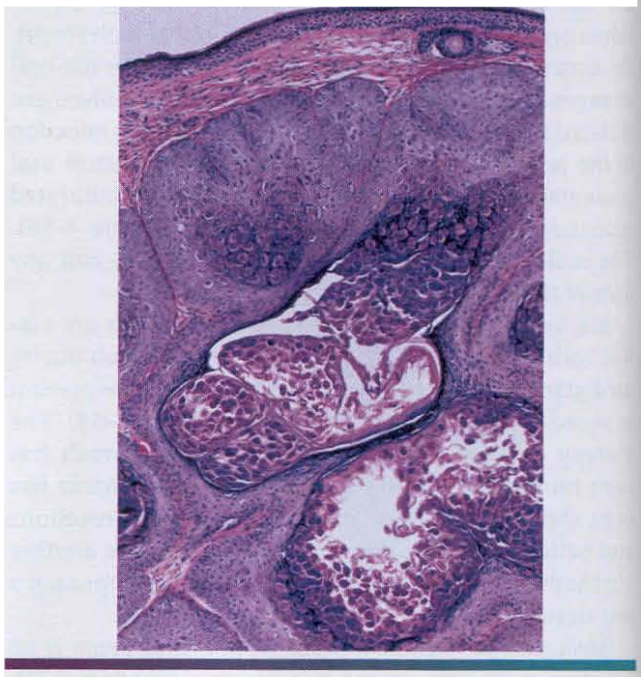


Figure 7-61 • HIV-associated molluscum contagiosum. Downgrowth of surface epithelium exhibiting numerous "molluscum bodies."

affected most commonly, minor gland involvement is possible. The glandular involvement arises from CD8-lymphocytic infiltration and often is followed by lymphoepithelial cyst formation in the parotid.

The most widely accepted therapy for OILS is oral prednisone or antiretroviral therapy, although some patients *have* been treated with parotidectomy or radiation therapy. Affected patients exhibit an increased risk for s-cell lymphoma; observation with histopathologic monitoring by fine-needle aspiration is prudent. Associated xerostomia is variable and treated in a manner similar to that of cases associated with non-HIV disease (i.e., maintenance of good oral health and the use of slalogogues and saliva substitutes).

Hyperpigmenration. 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) may cause the increased melanin pigmentation. Adrenocortical destruction has been reported from *several* of the infections associated with AIDS, 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 the HIV infection.

Lymphoma. Lymphoma is the second most common malignancy in HIV-infected individuals. This neoplasm occurs in approximately 3% of those with the *virus*, a prevalence 60 times greater than the normal population. Most are non-Hodgkin's B-ceil lymphomas, but reports of T-cell and Hodgkin 'S lymphomas exist. A relationship between EBV and non-Hodgkin's lymphomas has been documented, and many investigators *believe* these tumors arise from a combination of EBV, antigenic stimulation, and immune dysfunction.

Lymphoma in patients with AiDS is typically exhibited in extranodal locations, with the CNS being the most common site. Oral lesions may occur and most often present as a soft tissue enlargement of the palate or gin*giva* (Figure 7-62). Intraosseous *involvement* also has been documented, and it 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 frequently are noted and represent clues to the diagnosis.

The treatment usually is combination chemotherapy, and radiation is reserved for local control of the disease. These malignancies are *aggressive*, and *survival* usually is measured in months from the date of *discovery*. Although highly *active* antiretroviral therapy has reduced dramatically the prevalence of opportunistic infections and Kaposi's sarcoma in HIV-infected patients, a major decrease in lymphoma has not been documented. It appears that non-Hodgkin's lymphoma will become increasingly more important as a cause of morbidity and mortality in patients infected with HIV.

Oral squamous cell carcinoma. Squamous cell carcinoma of the oral cavity, pharynx, and larynx has been reported in HiV-infected patients. These neoplasms are associated with the same cancer risk factors as the general population but tend to occur at a younger age. Similar clinical presentations and anatomic distribution of these carcinomas are noted (Figure 7-63). It appears HIV infection may accelerate the development of squamous cell carcinoma, possibly because of Impaired immune surveillance.

Treatment of squamous cell carcinoma is not significantly different for HIV-Infected patients and consists of

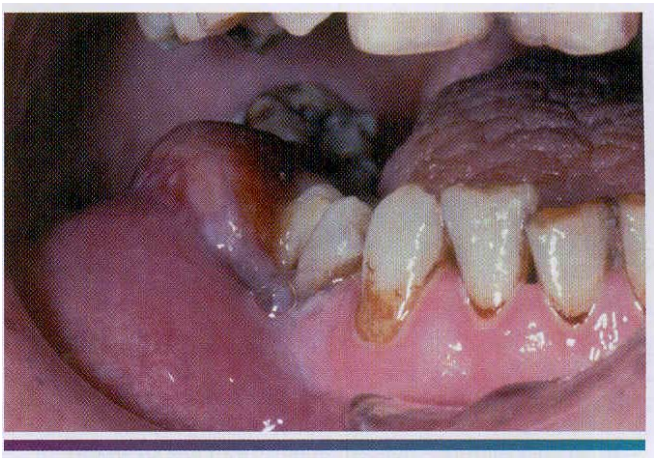


Figure 7-62 • **HIV-associated lymphoma. Erythematous and ulcerated soft tissue enlargement of the posterior mandibular gingiva and mucobuccaJ fold on the right side.**

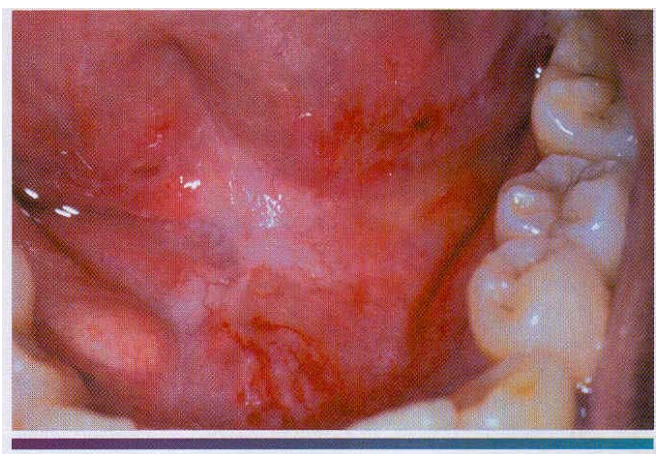


Figure 7-63 • **HIV-associated squamous cell carcinoma. Multifocal erythroplakic and erosive appearing lesions of the floor of the mouth. Multifocal or diffuse involvement is not rare in HIV-infected patients. (Courtesy of Dr. Catherine Flaitz.)**

surgical resection. radiation therapy. or combined radiation and chemotherapy. Clinical staging can be problematic because of HIv-related cervical lymphadenopathy. In these cases, cross-sectional CT or MRI can 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 squamous cell carcinoma are diagnosed with advanced disease and exhibit a less favorable prognosis.

Diagnosis

Confirmation of HIV infection can be made by viral culture or by detection of HIV antibodies or antigens. The standard screening tool is the enzyme immunoassay (EIA) for antibodies to HIV. This test can have false-positive results or cross-reactions: therefore. it should be repeated and followed by the more accurate Western blot antibody assay. Other alternatives include radioimmunoprecipitation (RIPAl, rapid latex agglutination assay. and dot-blot immunobinding assay. All of these evaluations are used to detect antibodies to HIV.

In an attempt to improve the safety of the blood supply. a few assays have been approved by the FDA to detect viral antigens before development of anti-HIV antibodies. These tests are not used widely and include the p24 antigen capture assay and polymerase chain reaction (PCR) for detection of HIV DNA that may be integrated into the host DNA. This latter method may be used to identify someone who was infected recently or HIV carriers who otherwise have negative antigen or antibody findings.

The diagnosis of AIDS is indicated if the patient has laboratory evidence of HIV infection combined with documentation of less than 200 CD4 + T lymphocytes per microliter or a CD4 + T-lymphocyte percentage of total lymphocytes of less than 14. In addition. the diagnosisof AIDS can be made in an HIv-Infected person if one of the indicator diseases listed in Box 7- 1has been documented.

Box 7-1 *Indicator* ***Diseases Used ill the*** *Oiagnosls* ***of*** *Acquired immunodeficiency* ***Syndrome***

1. Candidiasis of bronchi, trachea, or lungs
2. Candidiasis. esophageal
3. Cervical cancer, invasive
4. Coccidioidomycosis, disseminated or extrapulmonary
5. Cryptococcosis. extrapulmonary
6. Cryptosporidiosis, chronic intestinal (> 1 month's duration)
7. Cytomegalovirus disease (other than liver, spleen, or nodes)
8. Cytomegalovirus-induced retinitis (with loss of vision)
9. Encephalopathy, HIV-related
10. Herpes simplex: chronic ulcer or ulcers (> 1 month's duration) or bronchitis. pneumonitis, or esophagitis
11. Histoplasmosis, disseminated or extrapulmonary
12. Isosporiasis, chronic intestinal (> 1 month's duration)
13. Kaposi's sarcoma
14. lymphoma, Burkitt's (or equivalent term)
15. lymphoma, immunoblastic (or equivalent term)
16. lymphoma. primary. of brain
17. *Mycobacterium avium* complex or M. *kansasii,* disseminated or extrapulmonary
18. *Mycobacterium tuberculosis,* any site (pulmonary or extrapulmonary)
19. Mycobacterium. other species or unidentified species, disseminated. or extrapulmonary
20. *Pnevmocystis carinii* pneumonia
21. Pneumonia. recurrent
22. Progressive multifocal leukoencephalopathy
23. *Salmonella* septicemia, recurrent
24. Toxoplasmosis of brain
25. Wasting syndrome as a result of AIDS

Treatment and Prognosis

As mentioned prevtouslv, HIV infection initially was considered fatal; however, the introduction of highly active antiretroviral therapy (IIAART) has altered the course of the epidemic, The annual incidence of AIDS and related deaths in the United States dropped for the first time in 1996 and has continued to do so since that time. Three types of medications are available (Box 7-2). Initial regimens consist of two nucleoside reverse transcriptase inhibitors and one or two protease inhibitors, Alternatively. two nucleoside reverse transcriptase inhibitors and a nonnucleoside reverse transcriptase inhibitor can be used.

The current therapeutic approaches have driven HIV to undetectable levels in many patients. with a resultant clinically significant reconstitution of the immune system. With the current antiretroviral medications. total HIV eradication would take at least a decade and presently is not a realistic goal. Although no cure exists. survival

Box 7-2 *Antiretrovim ! T/ucral'Y*

1. Nucleoside reverse-transcriptase inhibitors
   - Abacavir; didanosine, lamivudine, stavudine, zalcitabine. or zidovudine
2. Nonnucleoside reverse transcriptase inhibitors
   - Delavlrdlne. efavirenz. or nevirapine
3. Protease inhibitors
   - Amprenavir; indinavir; nelflnavh; ritonavir; or saquinavir

times are increasing as a result of earlier diagnosis and improved therapy.

Although antiretroviral therapy is effective for many patients, it is expensive. In addition, this treatment often isassociated with significant adverse reactions, may not be effective in ail patients, or may fail after a period of initial success. Work is proceeding toward the development of a safe and effective vaccine against HIV infection. but complex issues slow the progress. Advances in therapy and prevention of HIV infection occur daily; however, the best defense against the disease is prevention of the initial infection.

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CHAPTER 8

Physical and Chemical Injuries

CHAPTER OUTLINE

LINEA ALBA

linea alba ("white line") is a common alteration of the buccal mucosa that is most likely associated with pressure, frictional irritation, or sucking trauma from the facial surfaces of the teeth. In one study of 256 young men. the alteration was present in 13%. 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 is usually bilateral. It may be scalloped and is located on the buccal mucosa at the level of the occlusal plane of the adjacent teeth (Figure 8-1). The line varies in prominence and is usually restricted to dentulous areas. It often is more pronounced adjacent to the posterior teeth.

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 BUCCARUM (CHRONIC CHEEK CHEWING)

Morsicatio buccarum is a classic example of medical terminology gone astray; it is the scientific term for chronic cheek chewing. *Morsicatio* comes from the Latin word *morsus*. or bite. Chronic nibbling produces lesions

that are most frequently located on the buccal mucosa; however. the labial mucosa (morstcatlo labiorurn) 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 buccarum has been found In people who are under stress or who **exhibit psychologic conditions. Most patients arc aware** of their habit. although many deny the self-inflicted **injury or perform the act subconsciously. The occurrence is twice as prevalent in women and three times more** prevalent after age 35. At any given time, one in every 800 adults has active lesions.

Clinical Features

Most frequently. the lesions in patients with morsicatio are found bilaterally on the 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 are infrequently combined with **intervening zones of erythema. erosion, or focal traumatic** ulceration (Figures 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.

The altered mucosa is typically located in the mid-portion of the anterior buccal mucosa along the occlusal plane. **large lesions may extend some distance aboveor** below the occlusal plane in patients whose habit involves pushing the cheek between the teeth with a finger.

Histopathologic Features

Biopsy reveals extensive hyperparakcratosts that often **results in an extremely ragged surface with numerous projections of keratin. Surface bacterial colonization** is typical (Figure 8-4). On occasion, clusters of vacuolated cells are present in the superficial portion of the prickle

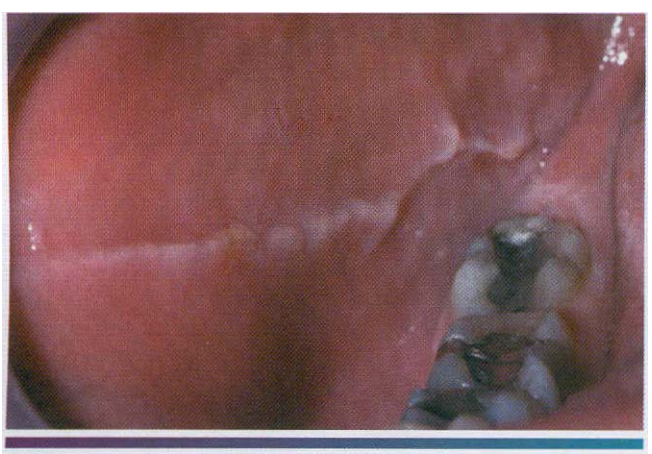


Figure 8-1 • Linea alba. White line of hyperk.eratosis on the right buccal mucosa at the level of the occlusal plane.

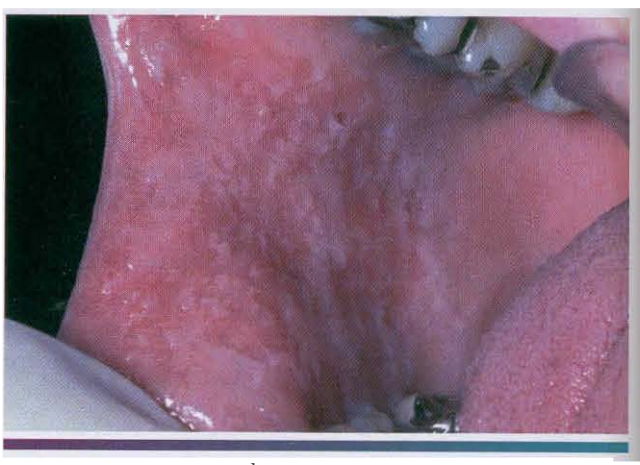


Figure 8-2 • Morsicatio buccarum. **Thickened. shredded areas of white hyperkeratosis of the right buccal mucosa.**

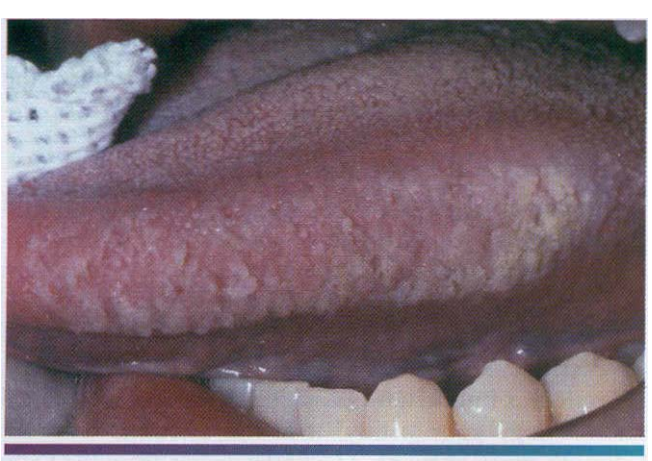


Figure 8-3 • Morsicatio linguarum. Thickened, rough areas of white hyperkeratosis of the lateral border of the tongue on the left side.

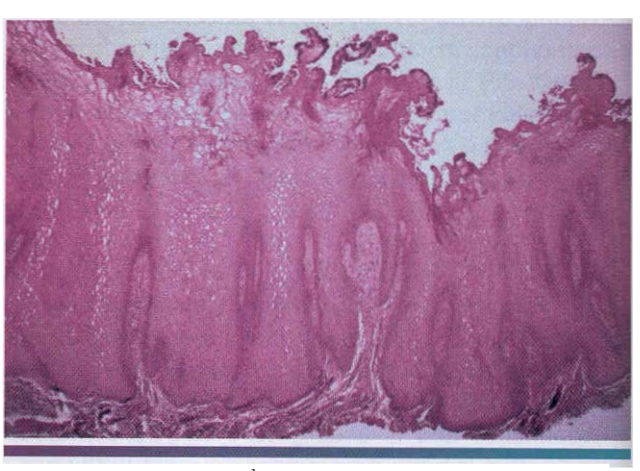


Figure 8-4 • Morsicatio buccarum. **Oral mucosa exhibiting greatly thickened layer of** parakeratin **with ragged surface** colonized **by bacteria.**

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) (see page 241) or to uremic stomatitis (see page 735). A similar histopathologic pattern is noted in patients who chronically chew betel quid and has been termed betel chewer's mucosa (see page 350). Similarities with linea alba and leukoedema also may be seen.

Diagnosis

In most cases the clinical presentation of morsicatio buccarum 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. In patients at high risk for HIV infection with isolated involvement of the lateral border of the tongue, further investigation is desirable to rule out HIV-associated OHL.

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 who desire treatment, an oral acrylic shield that covers the facial surfaces of the teeth may be constructed to eliminate the lesions by restricting access to the buccal and labial mucosa. Several authors also have suggested psychotherapy as the treatment of choice, but no extensive well-controlled studies have indicated benefits from this approach.

TRAUMATIC ULCERATIONS

Acute and chronic injuries of the oral mucosa are frequently observed. Injury can result from mechanical damage, such as contact with sharp foodstuffs or accidental biting during mastication, overzealous toothbrushing, talking, or even sleeping. Some are self-induced and clinically obvious or subtle and difficult to diagnose. Damage also may result from thermal, electrical, or chemical burns. (Oral mucosal manifestations of such burns are discussed later in the chapter.)

Acute or chronic trauma to the oral mucosa may result in 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. 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 instances, an eosinophilic ulceration is not associated with trauma, demonstrates an inflammatory infiltrate that suggests a neoplastic process, and has been termed atypical eosinophilic ulceration (atypical histiocytic granuloma). Although the term *atypical histiocytic granuloma* was initially coined, several subsequent investigations have shown that the atypical cells often are T-lymphocytes, not histiocytes. The true nature of this alteration is controversial. Although the lesions may undergo spontaneous remission after incisional biopsy, recurrence unrelated to trauma is common. Some investigators have suggested this pattern of eosinophilic ulceration represents the oral counterpart of a cutaneous lymphoproliferative disorder of T-cells that 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

Some intraoral injuries are intentional and used to attract attention (Figure 8-5), but the majority of injuries are unintentional from a variety of causes. 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 (Figure 8-6). Lesions of the gingiva, palate, and mucobuccal fold may occur from other sources of irritation. Overzealous toothbrushing can create linear erosions along the free gingival margins (Figure 8-7). Although these areas may superficially resemble a number of the chronic vesiculoerosive processes, thorough questioning of the patient often leads to the appropriate diagnosis. 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 (Figure 8-8).

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

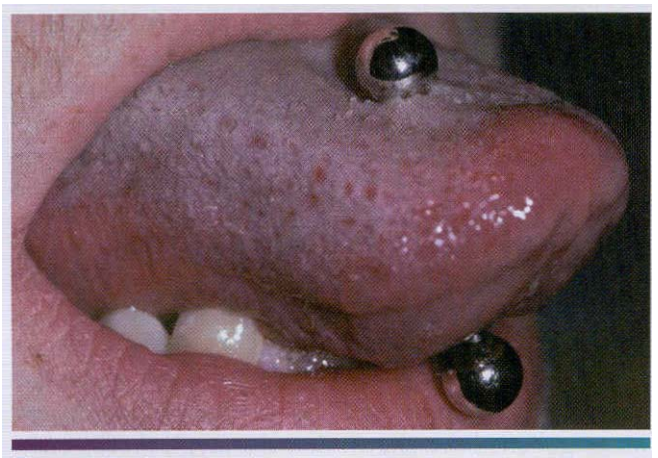


Figure 8-5 • **Intentional injury. Tongue pierced with a jewelry item known as a** "dumbbell" **(a most appropriate name!).**

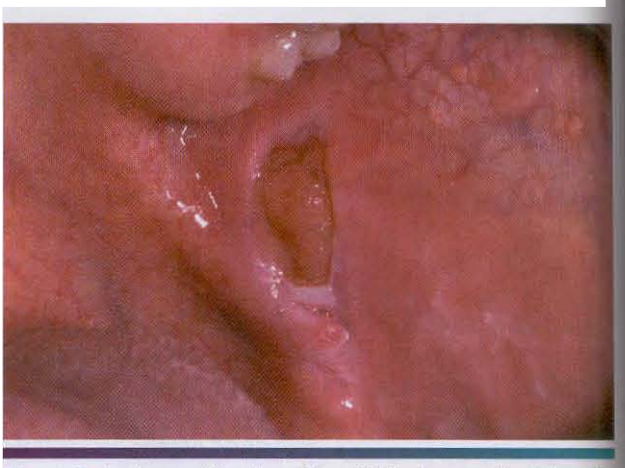


Figure 8-6 • **Traumatic ulceration.** Well-circumscribed ulceration of the posterior buccal mucosa on the left side.

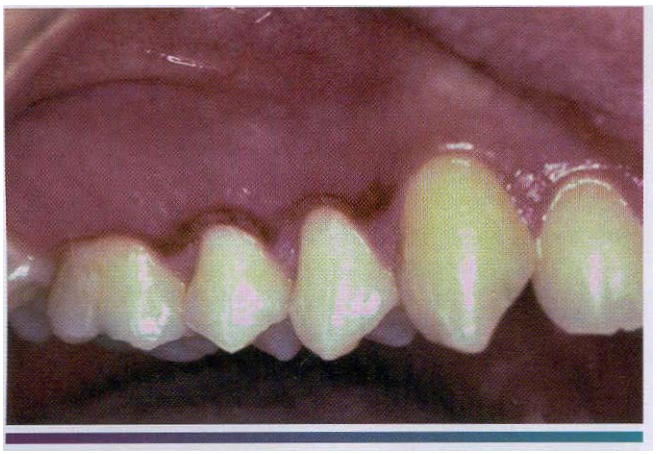


Figure 8-7 • **Traumatic erosion. Linear gingival erosion caused by overzealous toothbrushing.**

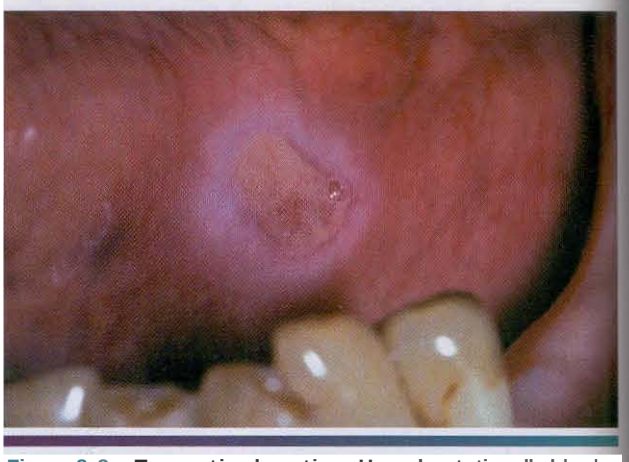


Figure 8-8 • **Traumatic ulceration. Hyperkeratotic rolled border encircling mucosal ulceration of the ventral surface of the tongue.**

simple traumatic ulcerations: however, on occasion. underlying proiifcrative granulation tissue can result in a raised lesion similar to a pyogenic granuloma (see page 447) (Figure 8-9).

Riga-Fede disease typically appears between I week and I year of age. The condition often develops in association with natal or neonatal teeth (see page 72). The **anterior ventral surface of the tongue is the most common** site of involvement, although the dorsal surface also may be affected (Figure 8-10). *Ventral* lesions contact the adjacent **mandibular anterior incisors; lesions on the dorsal surface are associated with the maxillary incisors.**

The atypical eosinophilic ulceration occurs in older people, with most cases developing in patients over age 40. Surface ulceration is present, and an underlying 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 (Figure 8-11).

Histopathologic Features

Simple traumatic ulcerations are covered by a flbnnopurulent membrane that consists of fibrin intermlxedwith neutrophils. The membrane is of variable thickness. 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 prolifera-

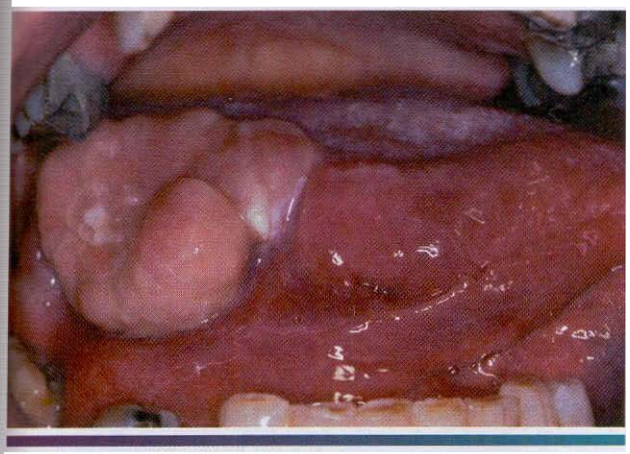


Figure 8-9 • **Traumatic granuloma.** Ulceration of lateral border of the tongue on the right side. The surface of the ulcer developed proliferative granulation tissue that resembles a pyogenic granuloma.

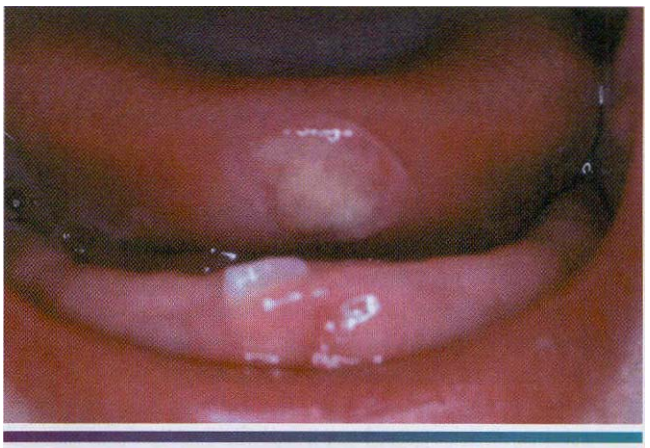


Figure 8-10 • **Riga-Fede disease.** Newborn with traumatic ulceration of anterior ventral surface of the tongue. Mucosal damage occurred from contact of tongue with adjacent tooth during breast-feeding.

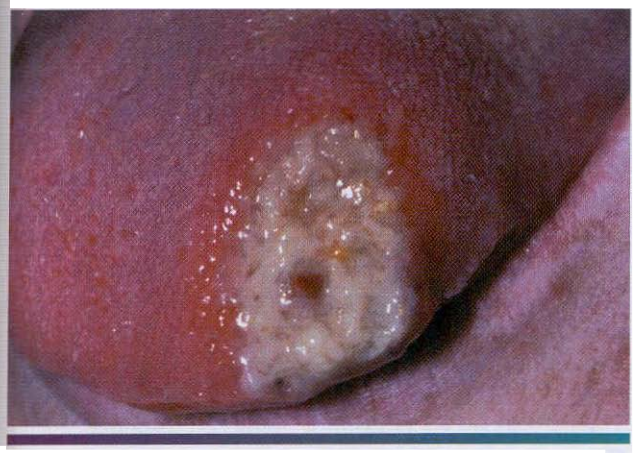
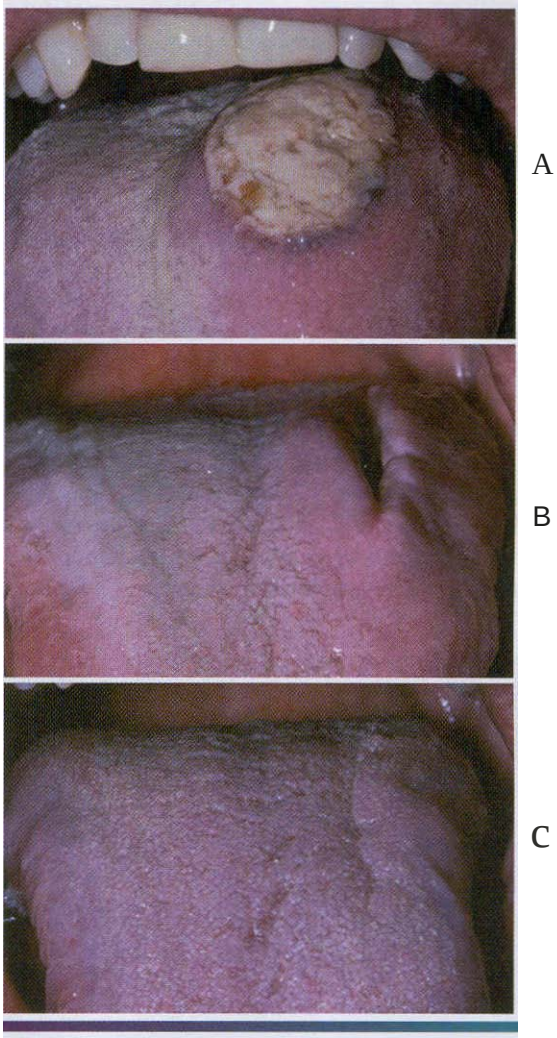


Figure 8-11 • **Atypical histiocytic granuloma.** Large ulceration of the anterior dorsal surface of the tongue.



A

B

C

Figure 8-12 • **Eosinophilic ulceration. A,** Initial presentation of a large ulceration of the dorsal surface of the tongue. **S,** Significant resolution noted 2 weeks after incisional biopsy. **C,** Subsequent healing noted 4 weeks after biopsy.

non 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 eoslnophils. Although an associated immunohistochemical profile has been rarely reported. investigators have shown the large cells to be l-lymphocytes, the majority of which react with CD30 (Ki-II. This same marker also reacts with the proliferative cells noted in a group of nonaggressive cutaneous lymphomas.

Treatment and Prognosis

For traumatic ulcerations that have an obvious source of Injury. the irritating cause should be removed. Dyclonine Hel or hydroxypropyl cellulose films can be applied for temporary pain relief. If the cause is not obvious or if a patient does not respond to therapy. biopsy is indicated. Rapid healing after a biopsy is typical even with large eosinophilic ulcerations (Figure 8- 12). 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-Pede disease. The teeth should be retained if they are stable. Grinding the incisal margins, 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.

Patients with atypical eosinophilic ulcerations should be thoroughly evaluated for evidence of lymphoma elsewhere. Although recurrence is frequently seen, no dissemination of the process has been documented, and all ulcerations reportedly have healed after initial incisional biopsy. 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 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. The microwave oven has been associated with an increased frequency of thermal burns because of its ability to produce a food that is cool on the exterior but extremely hot in the interior.

Clinical Features

Most electrical burns occur in children younger than 4 years of age. The lips are most frequently affected, and the commissure is commonly involved. Initially, the burn appears as a painless, charred, yellow area that exhibits little to no bleeding (Figure 8-13). Significant edema often 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 closely monitored. 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 infrequently reported and typically resolves over several weeks to months.

The injuries related to thermal food burns usually appear on the palate or posterior buccal mucosa (Figure 8-14). The lesions appear as zones of erythema and ulceration that often exhibit remnants of necrotic epithelium at the periphery.

Treatment and Prognosis

For patients with electrical burns of the oral cavity, tetanus immunization, if not current, is required. A prophylactic antibiotic, usually penicillin, is given by most clinicians to prevent secondary infection in severe cases. The primary problem with oral burns is contracture of the

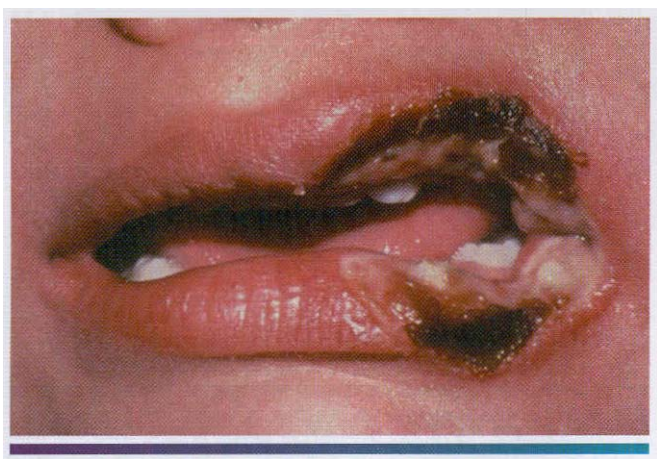


Figure 8-13 • Electrical burn. Yellow charred area of necrosis along the left oral commissure. (Courtesy of Dr. Patricia Hagen.)

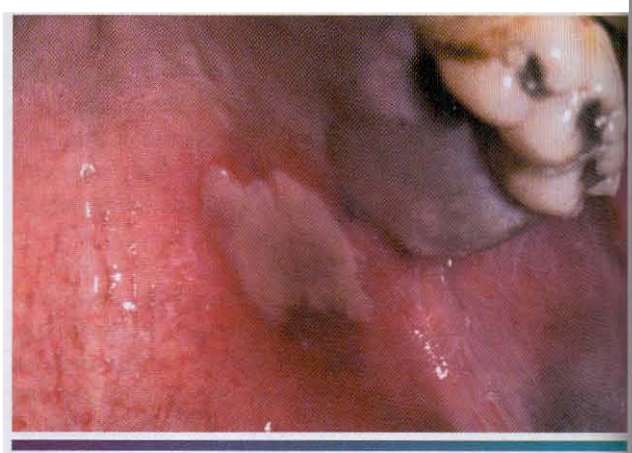


Figure 8-14 • Thermal food burn. Area of yellow epithelial necrosis of the posterior soft palate on the left side. Damage was due to attempted ingestion of hot pizza.

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.

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.

Certain patients, typically children or those under psychiatric care, may hold medications within their mouths rather than swallow them. A surprising number of medications are potentially caustic when held in the mouth long enough. Aspirin and two psychoactive drugs, chlorpromazine and promazine, are well-documented examples.

Over-the-counter medications for mouth pain can compound the problem. Mucosal damage has been documented from many of the topical medicaments sold as treatments for toothache or mouth sores. Products containing phenol, hydrogen peroxide, or eugenol have produced adverse reactions in patients.

Health care practitioners 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 (Figure 8-15). 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 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 (Figure 8-16).

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 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 one report, an application of a silver nitrate stick to a small aphthous ulceration led to a necrotic defect that exceeded 2 × 2 cm and had to be surgically debrided.

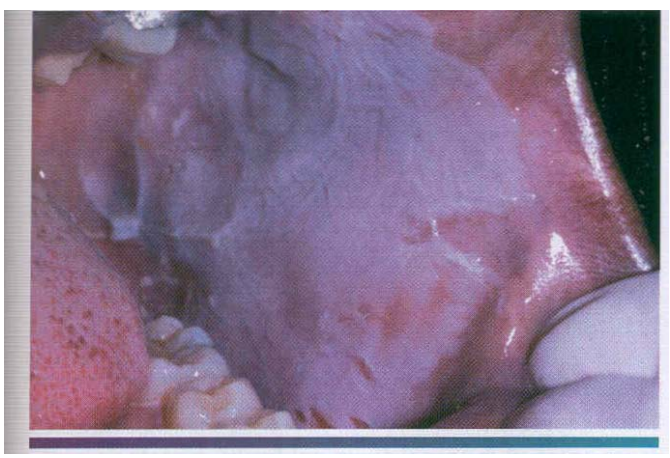


Figure 8-15 • Aspirin burn. Extensive area of white epithelial necrosis of the left buccal mucosa caused by aspirin placement in an attempt to alleviate dental pain.

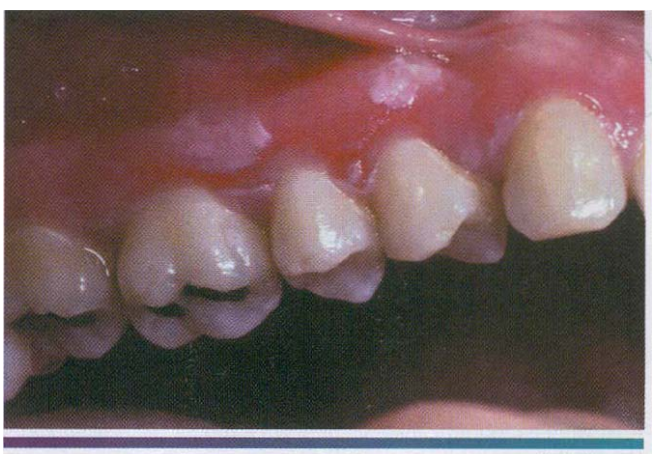


Figure 8-16 • Hydrogen peroxide burn. Extensive epithelial necrosis of the anterior maxillary gingiva secondary to interproximal placement of hydrogen peroxide with cotton swabs.

Phenol. Phenol has occasionally 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 (Figure 8-17).

A prescription therapy containing 50% sulfuric acid. 4% sulfonated phenol, and 24% sulfonated phenolics 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.

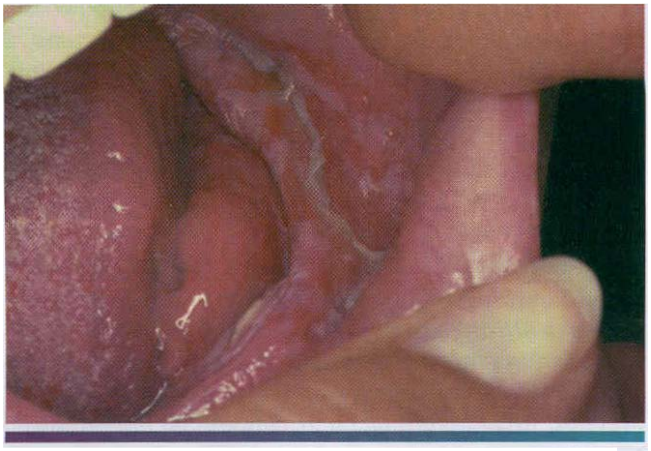


Figure 8-17 • Phenol burn. Extensive epithelial necrosis of the mandibular alveolar mucosa on the left side. Damage resulted from placement of an over-the-counter, phenol-containing, antiseptic and anesthetic gel under a denture. (Courtesy of Dr. Dean K. White.)

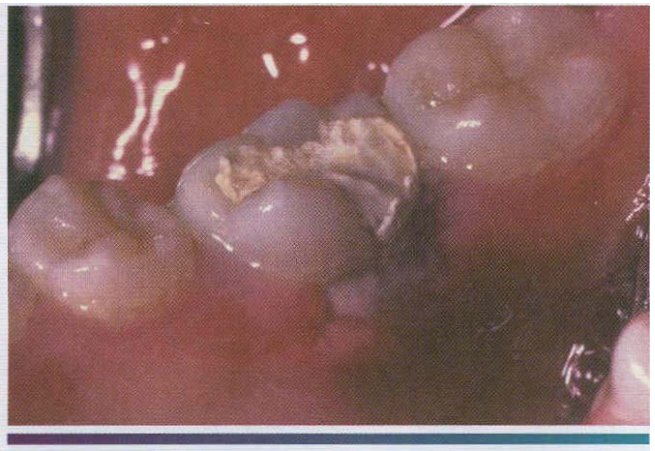


Figure 8-18 • Formocresol burn. Tissue necrosis secondary to leakage of endodontic material between a rubber dam clamp and the tooth.

*Endodontic **materials.*** Some endodontic materials are dangerous because of the possibility of soft tissue damage (Figure 8-18) or their injection into hard tissue with resultant deep spread and necrosis. Because of the difficulty of obtaining profound anesthesia in some patients undergoing root canal therapy, some clinicians have used 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. In addition. extrusion of filling material containing paraformaldehyde into the periapical tissues has led to significant difficulties, and its use should be discouraged. Sodium hypochlorite produces similar results when injected past the apex. The chances of tissue damage can be reduced by:

- Using a rubber dam;
- Avoiding excessive pressure during application; or
- Keeping the syringe needle away from the apex.

Clinical Features

The caustic agents previously discussed 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. fibrinopuruient membrane. Mucosa bound to bone is keratinized and more resistant to damage, whereas the nonkeratinized movable mucosa is destroyed more quickly.

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) (Figure 8-19).

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 coagula-

live necrosis of the epithelium, with only the outline of ihe individual epithelial cells and nuclei remaining IFigure 8-20). 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 inflam**matory cells.

Treatment and Prognosis

The best treatment of chemical injuries is prevention of **exposure of the oral mucosa to caustic materials. When** using potentially caustic drugs (e.g.. aspirin, chlorpro**mazine), the clinician must instruct the patient to swal**low 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.

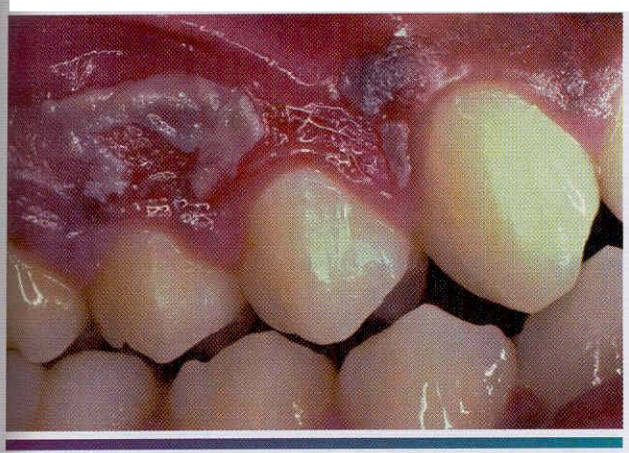


Figure 8-19 • Cotton roll burn. Zone of white epithelial necrosis and erythema of the maxillary alveolar mucosa.

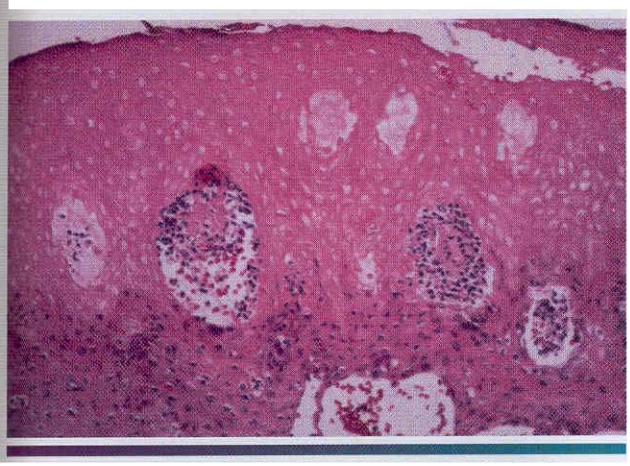


Figure 8-20 . Chemical-related epithelial necrosis. Oral mucosa exhibiting superficial coagulative necrosis of the epithelial cells.

Superficial areas of necrosis typically resolve completely without scarring within tO to 14 days after discontinuation of the offending agent, For temporary pro**tection, some clinicians have recommended coverage with** a protective emollient paste or a hydroxypropyl cellulose film. Topical dyclonine HCl provides excellent but tem**porary pain relief. When large areas of necrosis are present. such as that related to the use of silver nitrate** or accidental intrabony injection of offending materials, **surgical debridement 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 (c.g., oral epithelium) are especially susceptible. The mouth is a common site (and one of the most visible) 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. Each year almost 400,000 patients in the United States suffer acute or chronic oral side effects **from anticancer treatments. With the advancement of** medical practice, these complications are becoming more **common as more patients have longer survival times and as intense therapies. such as bone marrow transplanta**tion, **become more commonplace.**

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 **doses.**

Painful acute mucositis and dermatitis are the most frequently encountered side effects of radiation, but sev**eral 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 (hypogeusla)
- **Osteoradionecrosis**
- **Trismus**
- **Chronic dermatitis**
- Developmental abnormalities

Hemorrhage. Intraoral hemorrhage is typically secondary to thrombocytopenia, which develops from bone **marrow suppression. Intestinal or hepatic damage, how-**

ever, 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 (Ole). 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. 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 will resolve slowly 2 to 3 weeks after cessation of treatment. Oral mucositis associated with chemotherapy typically involves the nonkeratinized surfaces (l.e.. buccal mucosa, ventrolateral tongue, soft palate, 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 soon is 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 (Figures 8-21 to 8-23). 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 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.

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 I 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. Upon 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. Symptomatic dry mouth appears most strongly associated with a decrease in palatal mucous secretions, with the loss of parotid serous secretion exerting a less noticeable effect. 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 (Figure 8-24). The decay is predominantly cer-

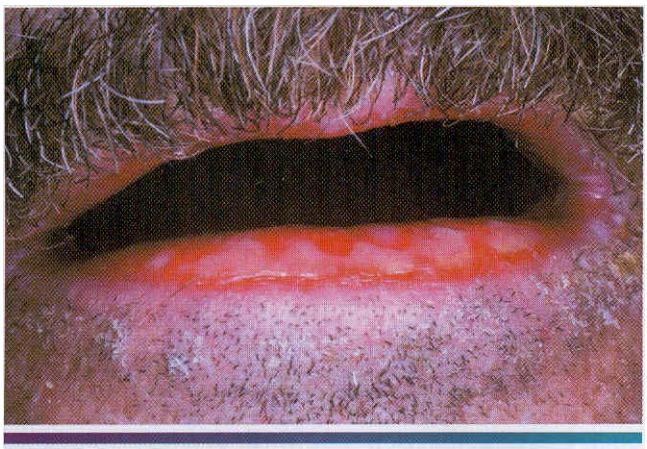


Figure 8-21 • Chemotherapy-related epithelial necrosis. Vermilion border of the lower lip exhibiting epithelial necrosis and ulceration in a patient receiving systemic chemotherapy.

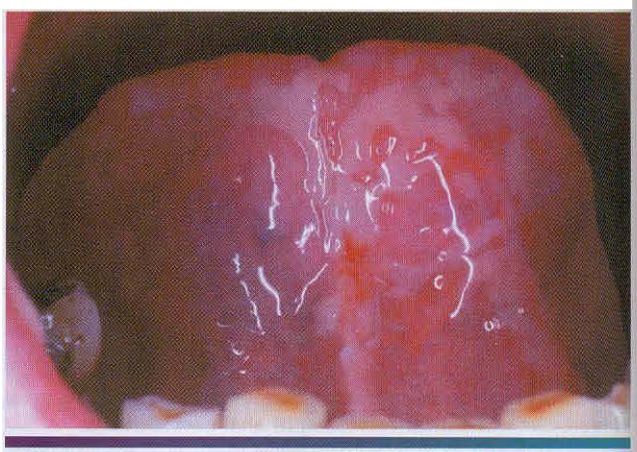


Figure 8-22 • Chemotherapy-related epithelial necrosis. Large, irregular area of epithelial necrosis and ulceration of the anterior ventral surface of the tongue in a patient receiving systemic chemotherapy.

vical **in location and secondary to xerostomia (not a** direct effect of the radiation).

Loss of taste. **In patients who *receive* significant radi-**ationto the oral cavity, a substantial loss of all four tastes (hypogcusra) often develops within several weeks. Although these senses 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 753).

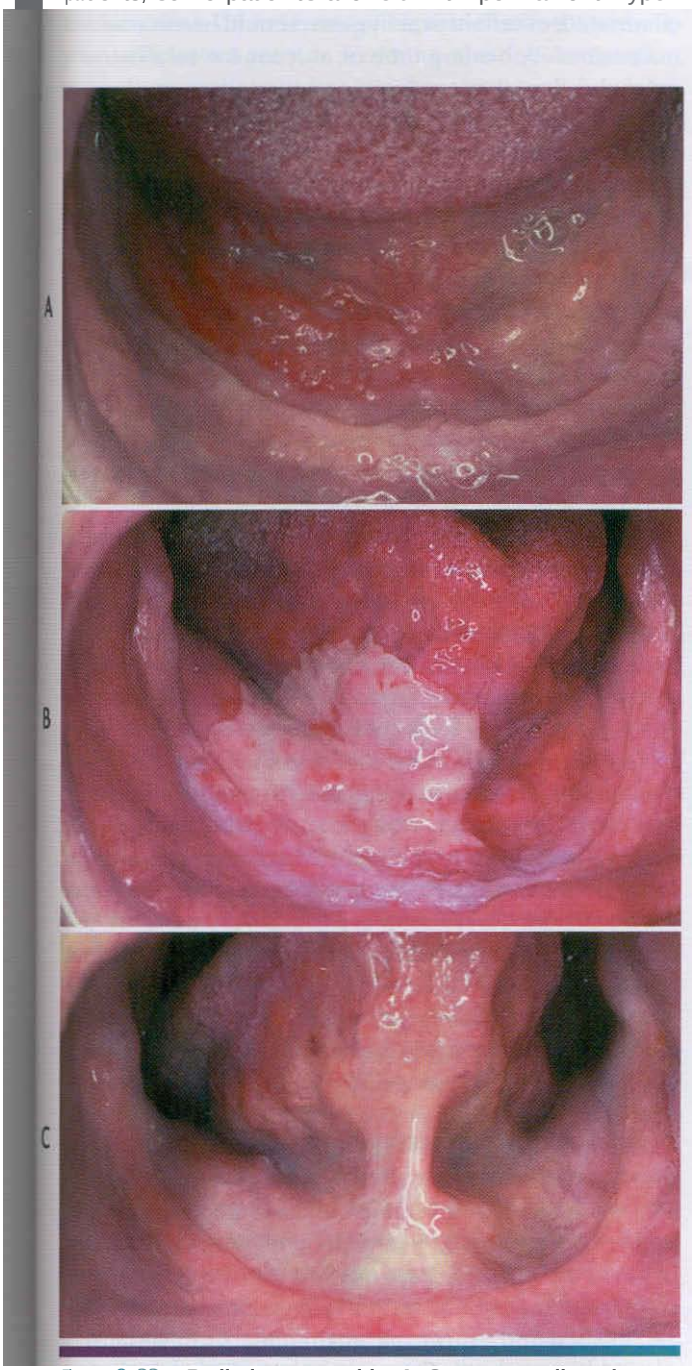


Figure 8-23 • **Radiation mucositis. A, Squamous cell carcinoma before radiation therapy. Granular erythroplakia of the floor of the mouth on the patient's right side. B, Same lesion after initiation of radiation therapy. Note the large, irregular area of epithelial necrosis and ulceration of the anterior 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.**

Osteoradionecrosis. **Osteoradionecrosis is one of the most serious complications of radiation to the head and** neck but is seen less frequently today because of better **treatment modalities and prevention. The current prevalence** rate is less than 4%, whereas the frequency approached 15% less than 20 years ago. Although the risk is low, it increases dramatically if a local surgical procedure is performed within 21 days of therapy initiation or between 4 and 12 months after therapy. Radia**tion of bone results in permanent damage to the** osteocytes and microvasculature system. The altered bone becomes hypoxic, hypovascular, and hypocellular. Ostcoradionecrosis **is the result of** nonhealing. **dead bone; infection is not necessarily present.**

Although most instances arise secondary to local trauma, a minority appears spontaneous. The mandible is involved most frequently, although a few cases have involved the maxilla (Figure 8-25). 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 (Figure 8-261. Intractable pain, **cortical perforation. fistula formation.** surface ulceration, and pathologic fracture may be present (Figure 8-27).

The radiation dose is the main factor associated with bone necrosis, although the volume of bone irradiated and the proximity of the maximal dosing both exert an effect. The risk of bone necrosis increases in the presence of the following:

- Teeth
- **Bone trauma**
- Periodontal disease
- **Concurrent chemotherapy**

Postradiation dental extractions should be avoided and **are a known risk factor for osteoradionecrosis. Surgery** performed during the first 4 months after radiation

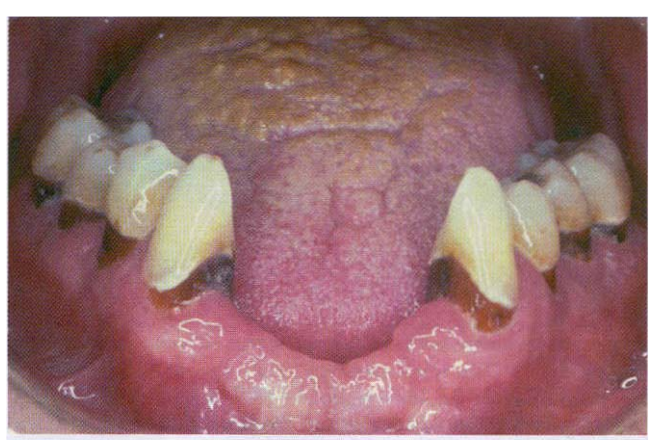


Figure 8-24 • **Xerostomia-related caries. Extensive cervical caries of mandibular dentition secondary to radiation-related xerostomia.**

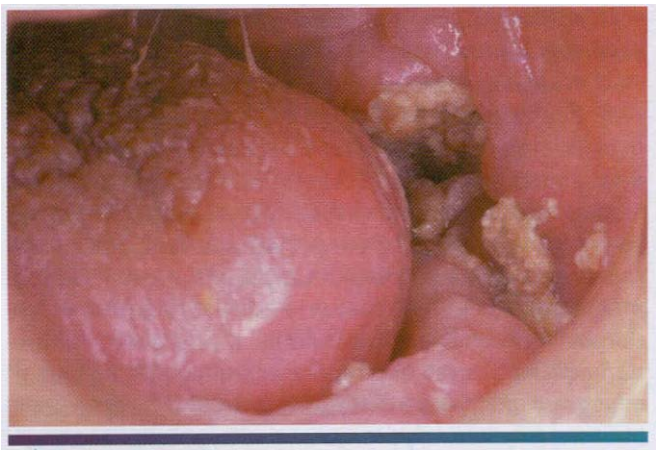


Figure 8-25 • Osteoradionecrosis. Ulceration overlying left body of the mandible with exposure and sequestration of superficial alveolar bone.

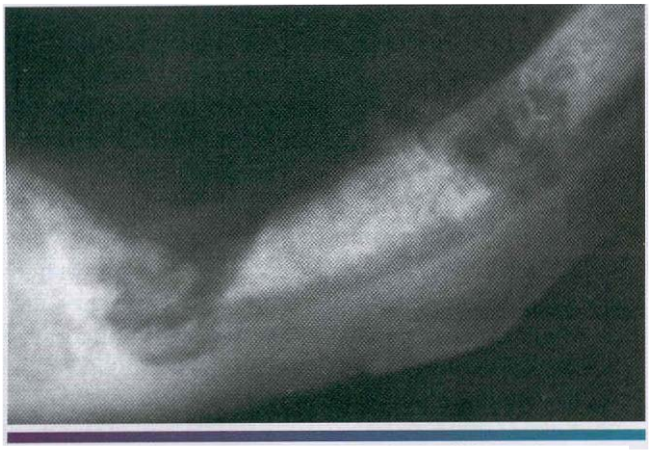


Figure 8-26 • Osteoradionecrosis. Multiple ill-defined areas of radiolucency and radiopacity of the mandibular body.

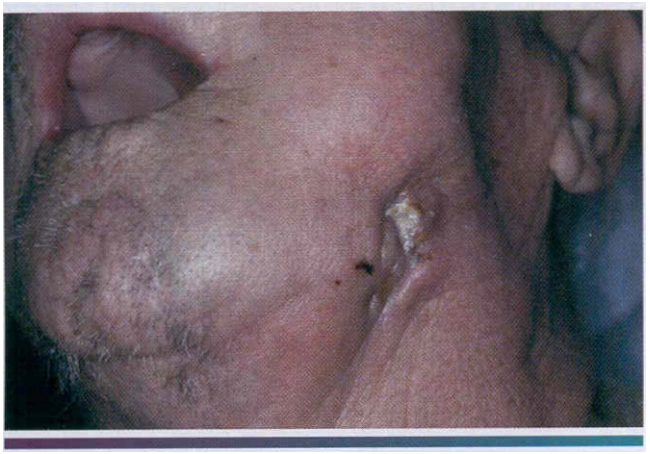


figure 8-27 • Osteoradionecrosis. Same patient as depicted in Figure 8-25. Note fistula formation of the left submandibular area resulting from osteoradionecrosis of the mandibular body.

therapy (the so-called "golden" period) is usually associated with normal healing. For the following 8 months, the risk of bone necrosis from trauma is at its highest but continues to a lesser extent for the life of the patient.

Prevention of bone necrosis is the best course of action. Before therapy, all questionable teeth should be extracted or restored, and oral foci of infection should be eliminated; excellent oral hygiene should be initiated and maintained. A healing time of at least 3 weeks between **extensive dental procedures and the initiation of radio-**therapy significantly decreases the chance of bone **necrosis. Extraction of teeth or any bone trauma is** contraindicated strongly during radiation therapy. If necessary, hyperbaric oxygen should be used before and after any procedure that may cause bone damage.

Any surgical procedures required after the 4-month golden period should be preceded and followed by intensive hyperbaric oxygen therapy. This technique has shown the ability to reverse many of the cellular alterations related to radiation therapy and restore the microvasculature to an acceptable level. By following the techniques pioneered by Marx, more than 95% of affected patients can be successfully treated.

***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

The most effective measure against oral complications of cancer therapy is establishment of good oral health. Before therapy, over 75% of patients with malignancies of the head and neck have not had routine dental care or maintained acceptable oral hygiene. Once oral health is established and cancer therapy initiated, efforts must be directed toward relieving pain, preventing dehydration, **maintaining adequate nutrition, eliminating foci of infec-**tion, and ensuring oral hygiene.

MflCosilis. In an attempt to decrease the severity, duration. and symptoms associated with oral mucositis. a large number of anesthetics, analgesics. antimicrobials. and coating agents have been tried with mixed reviews. These include topical allopurinol, antimicrobial lozenges (e.g., polymyxin. tobramycin. amphotericin B), attapulgite (Kaopectate), benzydamine. capsaicin, chamomila, chlorhexidine, diphenhydramine. dyclonine HCI. rnesalazme, milk of magnesia, povidone and iodine solution. protective emollient paste (Orabase), viscous lidocaine, silver nitrate, sucralfatc, or tretinoin. Systemic approaches include administration of azelastine. beta carotene. pentoxifyillne, indomethacin, or glutamine. No single method has proven to be consistently effective and widely accepted as standard therapy.

In many instances. periodic cleansing with a simple saline solution often proves to be most effective. Oral cooling (swishing ice chips before and during drug administration) is an inexpensive method that has been shown to reduce mucositis associated with systemic administration of chemotherapeutic drugs with a short hail-life, such as S-fluorouracil or melphalan. Systemic and topical granulocyte macrophage colony stimulating factor IGM-CSF) and granulocyte colony stimulating factor (G-CSF) appear to aid directly in the regeneration of oral mucosa and have shown promise in reducing the severity of mucositis. Finally. in a small study of patients receiving intensive radiation therapy. use of a high-dose betamethasone mouthwash was associated with a dramatic reduction in mucositis.

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 application should be instituted.

The problem of chronic xerostomia has been approached through the use of salivary substitutes and sialagogues. Because the mucous glands often demonstrate significant recovery after radiation. the sialagogues show promise because they stimulate the residual functional glands. Moisturizing gels. sugarless candies. and chewing gum are used. but the most efficacious product in controlled clinical studies has been systemic use of the cholinergic drug, pilocarpine. Although it is beneficial for many patients. pilocarpine is 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.

Other systemic salivary stimulants that are associated with a less dramatic influence on flow include bethanechol and anetholetrithione. Anetholetrithione appears to act by increasing the number of salivary gland receptors. Although somewhat effective when used alone, this medication has been combined with pilocarpine and achieved improvement in patients that failed to respond to the use of a single agent.

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 above the usual recommended daily doses appear to be beneficial.

Osteoradionecrosis. Although prevention must be stressed. cases of osteoradionecrosis do occur. Use of hyperbaric oxygen dramatically improves the outcome and is used in combination with antibiotics and local debridement of the infected necrotic bone. Once the diagnosis has been made. therapy must be immediate and aggressive to prevent greater destruction.

ANESTHETIC NECROSIS

Administration of a local anesthetic agent can, on rare occasions. be followed by ulceration and necrosis at the site of injection. This necrosis is thought 10 result 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 (Figure 8-28). A well-circumscribed area of ulceration develops at the site of injection. The ulceration often is deep, and. on occasion, healing may be delayed. One report has documented sequestration of bone at the site of tissue necrosis.

Treatment and Prognosis

Treatment of anesthetic necrosis is not usually required unless the ulceration fails to heal. Minor trauma, such as 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 agent without epinephrine is recommended.

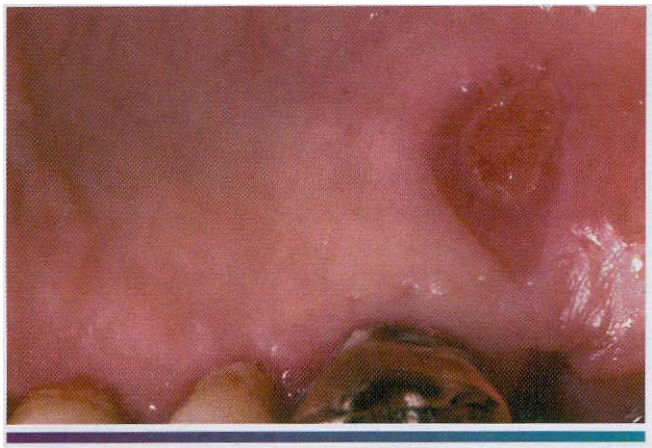


Figure 8-28 • Anesthetic necrosis. Mucosal necrosis of the hard palate secondary to palatal injection with a local anesthetic agent containing epinephrine.

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 appears 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, such as atopy. chronic candidal infection. actinic cheilitis. cheilitis glandularis. hypervitaminosis A. and photosensitivity. should be ruled out. In a review of 165 patients with AIDS. over 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 192); 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 (cheilocandldiasts).

In one review of 7S patients with chronic cheilitis. a thorough evaluation revealed that over one third represented irritant contact dermatitis (often secondary to chronic lip lieking). In 25% of the patients. the cheilitis was discovered to be an allergic contact mucositis lsee page 303). Atopic eczema was thought to be the cause in 19% of cases: the remaining portion was related toa 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 reststanne 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 eases feature chronic dryness, scaling. or cracking of the vermilion border of the lip (Figure 8-29). 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 (Figure 8-30). Although this pattern may be confused with perioral dermatitis (see page 304). the most appropriate name for this process is circumoral dermatitis. Both lips or justthe lower lip may be involved.

in patients with chronic cheilitis. development of fissures on the vermilion border is not rare. In a prevalence study of over 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 anda prevalence rate of approximately 0.6% . The maiority arises in young adults. with rare occurrence noted in children and the elderly.

Although the cause is unknown. proposed contributing factors include overexposure to sun, wind. and cold weather; mouth breathing; bacterial or fungal infections: and smoking. Application of lipstick or chapstick appears 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. Although highly variable. protecne moisturizing preparations are occasionally successful in resistant cases.

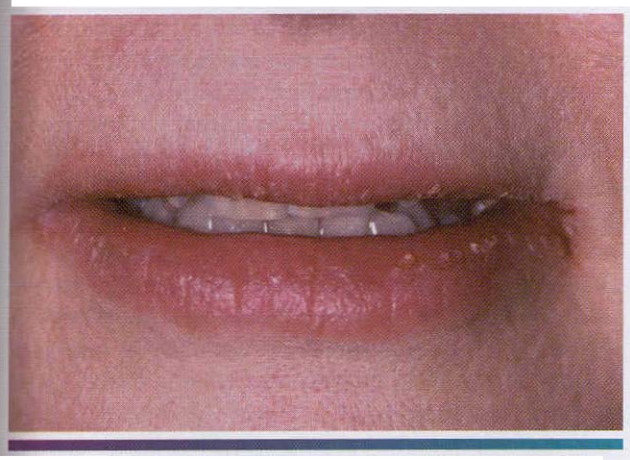


Figure 8-29 • Exfoliative cheilitis. Scaling and erythema of the vermilion border of the lower lip.

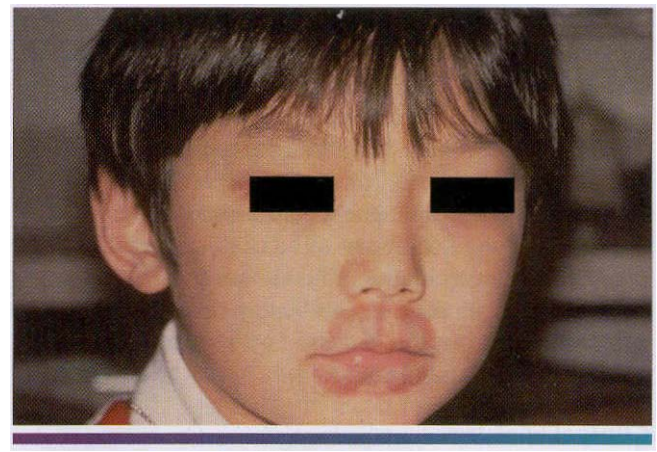


Figure 8-30 • Circumoral dermatitis. Crusting and erythema of the skin surface adjacent to the vermilion border in a child who chronically sucked on both lips.

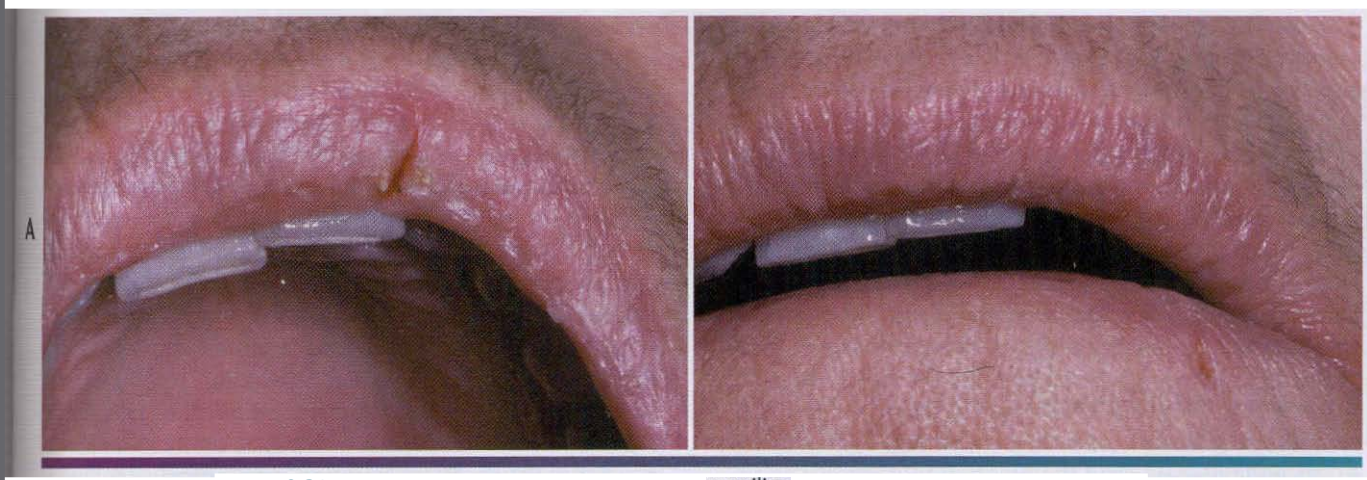


Figure 8-31 . Lip fissure. A. Chronic fissure of the vermilion border of the upper lip. B, Same site 2 weeks later, after use of hydrocortisone and iodoquinol cream.

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. further investigation is warranted in an attempt to discover the true source of the lip alterations.

In cases for which no cause can be found. therapeutic interventions often are not successful. Reports have documented lack of response 10 cryosurgery, antibiotics. anufungals. corticosteroids. vitamin supplements. petrolatum gels. sunscreens, and moisturizing preparations.

Hydrocortisone and iodoquinol (antibacterial and antimycotic) cream has been used to resolve chronic lip fissures in some patients (Figure 8-31). Other reported therapies include topical silver nitrate, salicylic acid. and various antibacterial and antifungal formulations. 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 successfully used,

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 over 2 em 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 (Figure 8-32). When considering a diagnosis of traumatic hemorrhage, the clinician should keep in mind that hemorrhages can result from nontraumatic causes. such as thrombocytopenia. disseminated intravascular coagulation (Ole), 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 bluish-black (Figure 8-33). As would be expected, traumatic lesions are located most frequently on the labial or buccal mucosa. Blunt facial trauma often is responsible, but such injuries as minor as cheek bitingmay produce a hematoma or areas of purpura. Mild pain may be present.

The hemorrhage associated with increased intrathoracic pressure is usually 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

No treatment is required if the hemorrhage is not related to systemic disease, and the areas should resolve spontaneously. Large hematomas may require several weeks to resolve. If the hemorrhage occurs secondary to an underlying disorder. 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 males and females, orogenital sexual activity almost is universal. For married heterosexual couples under 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.

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 are often asymptomatic and resolve without treatment in 7 to 10 days (Figure 8-34). Recurrences are possible with repetition of the inciting (excitingj) 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

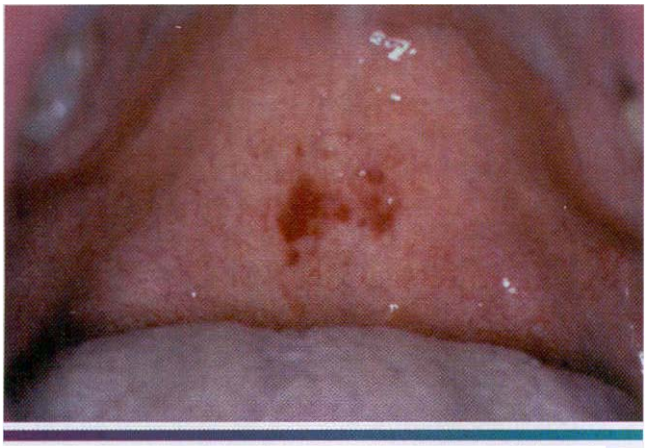


figure 8-32 • Petechiae. Submucosal hemorrhage of the soft palate caused by violent coughing.

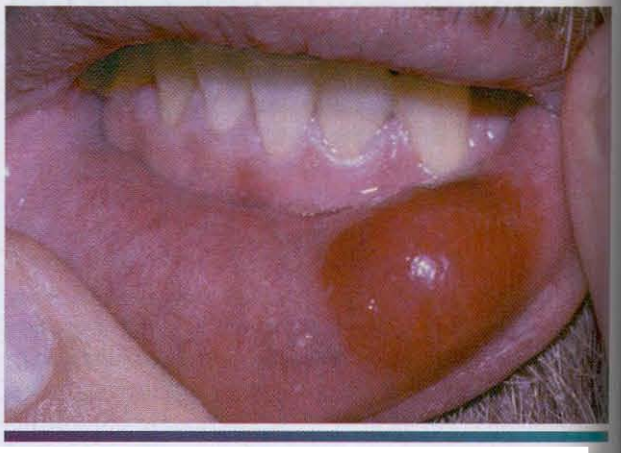


Figure 8·33 • Purpura. Submucosal hemorrhage of the lower labial mucosa on the left side secondary to blunt trauma.

position. The lesions resolve in 7 to 10days but may recur with repeated performances. Linear fibrous hyperplasia has been discovered in the same pattern in individuals who chronically perform the act (Figure 8-35).

Histopathologic Features

With an appropriate index of suspicion, biopsy is not usually required; however, a biopsy has been performed in some cases of paiatal lesions secondary to fellatio. These suction-related lesions reveal subepitheliai accumulations of red biood 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 usc 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 outdistancesthat 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, 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, linear areas of pig**mentation can be created in the gingival tissues as a** result of hygiene procedures (Figure 8-36). Amalgam from endodontic retrofill procedures can be left within the soft tissue at the surgical site (Figure 8-37). Finally, fine metallic particles can be driven through the oral mucosa from the pressure of high-speed air turbine drills.

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.** 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. oral health professionals also are responsible for a number of intentional tattoos for the purpose of demonstrating landmarks. repigmenting areas of vitiligo. cosmetically disguising disfigured areas. and judging tumor response to antineoplastic therapies. Injudicious intraoral use of these marking agents can cause diffusion of the pigment with discoloration of the adjacent skin surface.

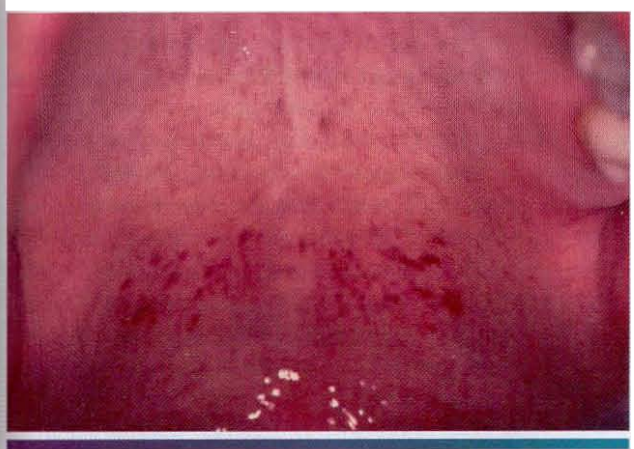


figure 8-34 • **Palatal petechiae from fellatio. Submucosal** hemorrhage of the soft palate resulting from the effects of negative pressure.

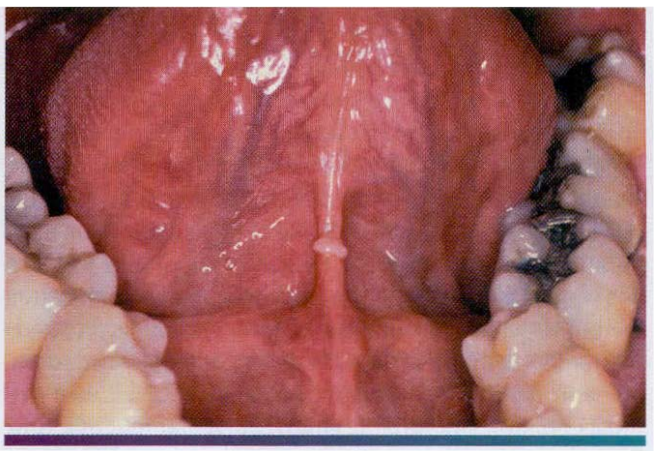


Figure 8-35 • **Fibrous hyperplasia from repeated cunnilingus. linear fibrous hyperplasia of the lingual frenum caused by repeated irritation from lower incisors.**

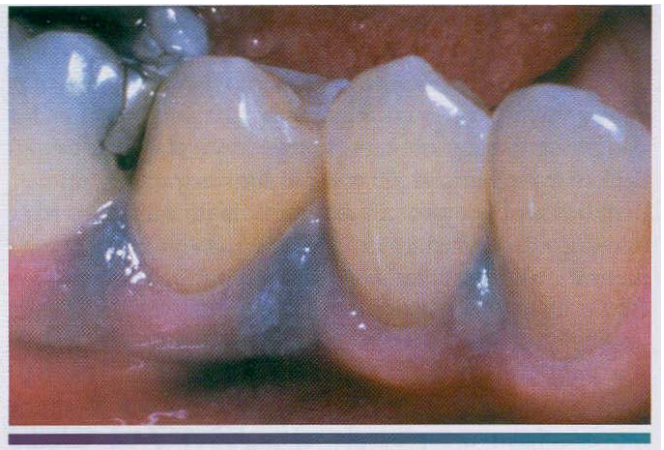


Figure 8-36 • Floss-related amalgam implantation. linear strips of mucosal pigmentation that align with the interdental papillae The patient used dental floss on the mandibular first molar immediately after the placement of the amalgam restoration. Because the area was still anesthetized. the patient impaled the floss on the gingiva. then continued forward using the amalgam-impregnated floss in the bicuspid area to create additional amalgam tattoos.

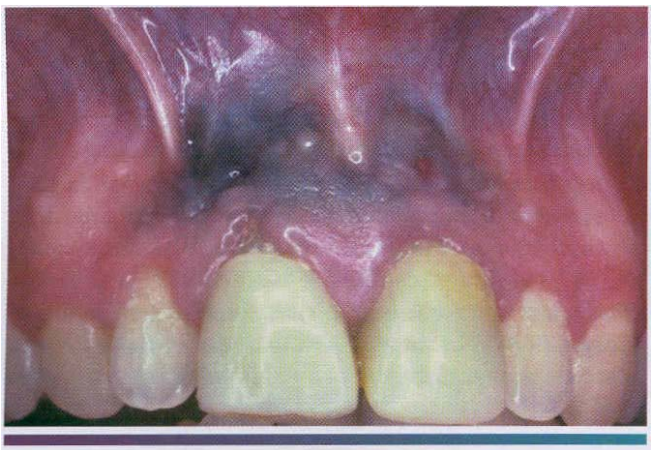


Figure 8-37 • Endodontic-related amalgam implantation. Multifocal areas of mucosal discoloration overlying the maxillary anterior incisors, which have been treated with apical retrofill procedures.

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 (Figure 8-38). Lateral spread may occur for several months after the implantation. In most cases. only one site is affected. although multiple tattoos in a single patient may be present. Any mucosal surface can be involved. but the **most common sites are the gingiva, alveolar mucosa, and** buccal mucosa (Figure 8-39).

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 (Figures 8-40 and 8-41). 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.

The pattern of accidental localized foreign body tattoo other than amalgam is diverse and depends on the associated trauma that impacted the material. Mucosal graphite implantation is rarely documented. but it most likely occurs with a higher frequency than indicated by the number of cases reported. Examples in the literature *have* been presented as grayish areas of mucosal discoloration of the hard palate. the most likely site for pencil-related trauma.

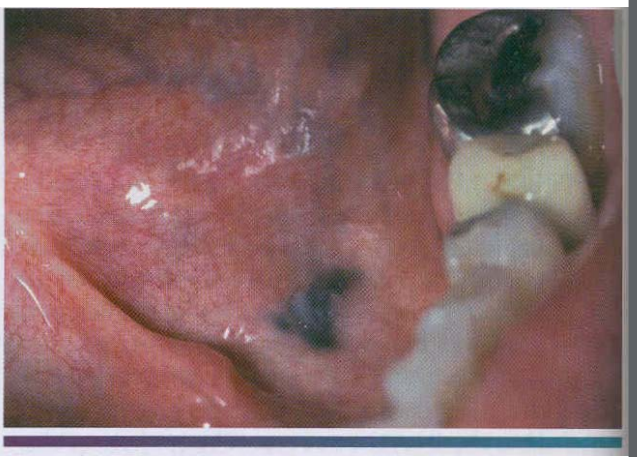


Figure 8-38 . Amalgam tattoo. Area of mucosal discoloration of the floor of the mouth on the patient's left side.

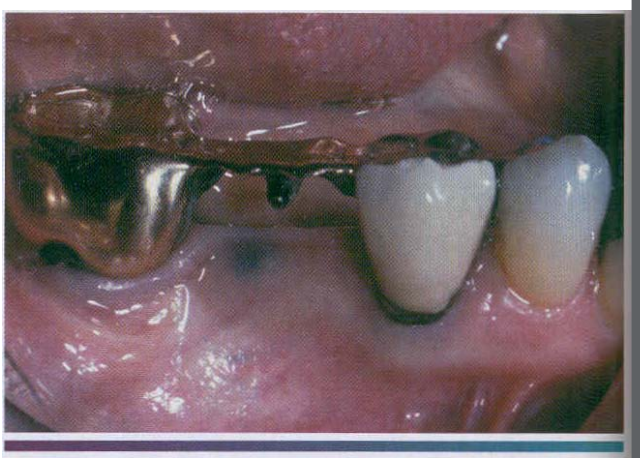


Figure 8-39 • Amalgam tattoo. Area of mucosal discoloration of the mandibular alveolar ridge immediately below the bridge pontic.

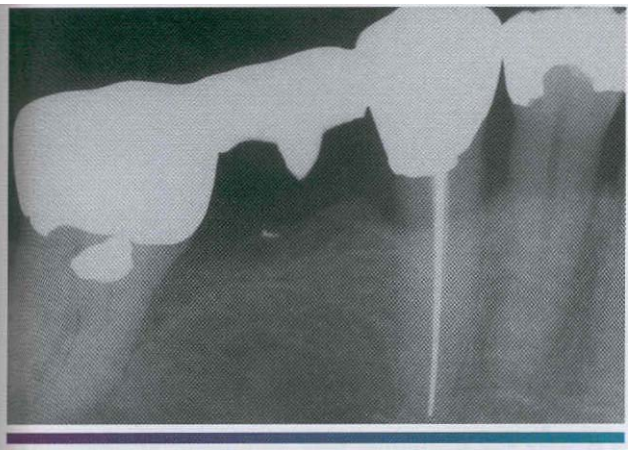


figure 8-40 • **Amalgam tattoo.** Radiograph of the same patient depicted in Figure 8-39. Note the radiopaque metallic fragment present at the site of mucosal discoloration.

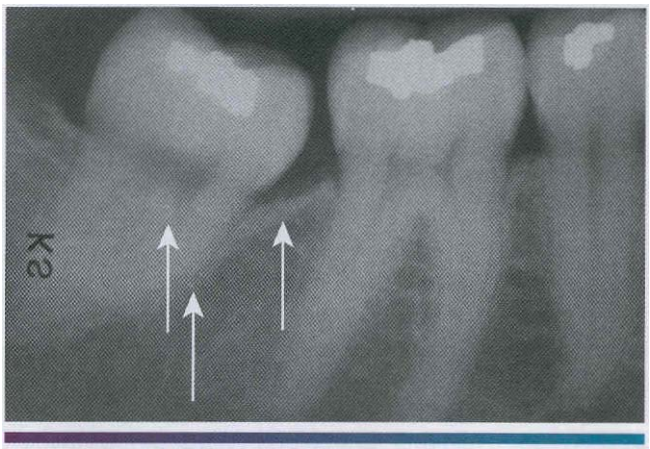


Figure 8-41 • Amalgam tattoo. Radiographic appearance of amalgam tattoo of lingual gingival mucosa adjacent to the mandibular third molar. Note the pinpoint radiopaque metallic fragments overlying the crestal and mesial portions of the root *(arrows)*.

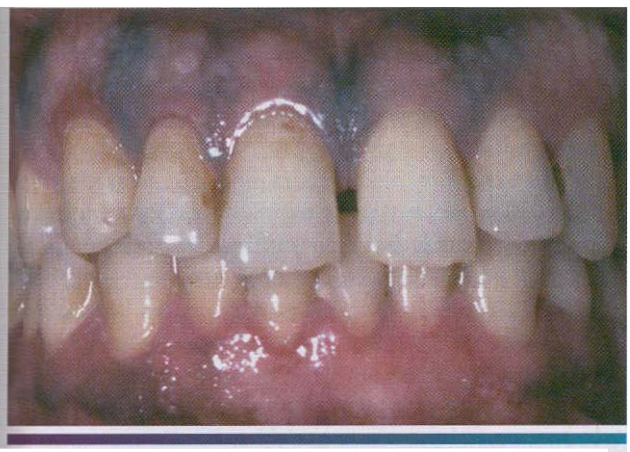


Figure 8-42 • **Intentional intraoral tattoos. Cultural tattoos of the anterior facial gingiva in an adult male from Eritrea.**

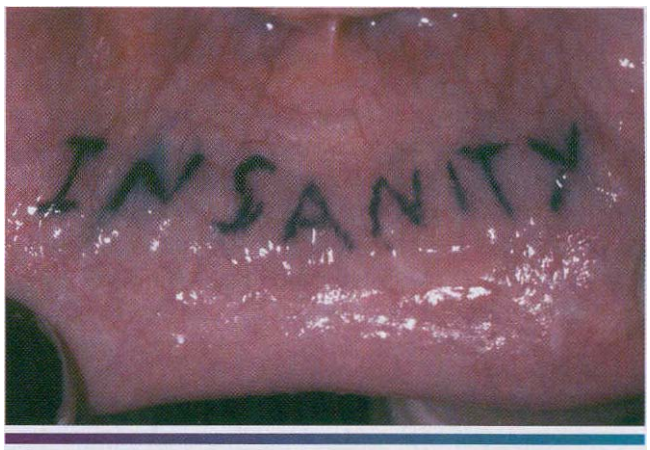


Figure 8-43 • Intentional intraoral tattoo. Amateur tattoo of the lower labial mucosa. (Courtesy of Dr. Edward Herschaft.)

The intentional intraoral tattoos that are not placed by health professionals occur most frequently on the anterior maxillary facial gingiva of individuals from east African countries (most commonly Ethiopia or Eritrea) and have been documented at institutions in the United States (Figure 8-42). In these cases, the anterior maxillary facial gingiva is given a heavy bluish-black discoloration. Occasionally, tattoos (usually blue or black) are placed on the labial mucosa of adults in the United States to convey a personal, often vulgar, message (Figure 8-43).

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, black, or dark-brown granules may be seen (Figure 8-44). The silver salts of the dental amalgam preferentially stain the reticulin fibers, especially those encircling nerves and vascular channels (Figure 8-45).

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** are typically associated with a more significant inflam**matory 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 micro**analysis can be used to identify the type *at* material present within areas of foreign-body tattoos.

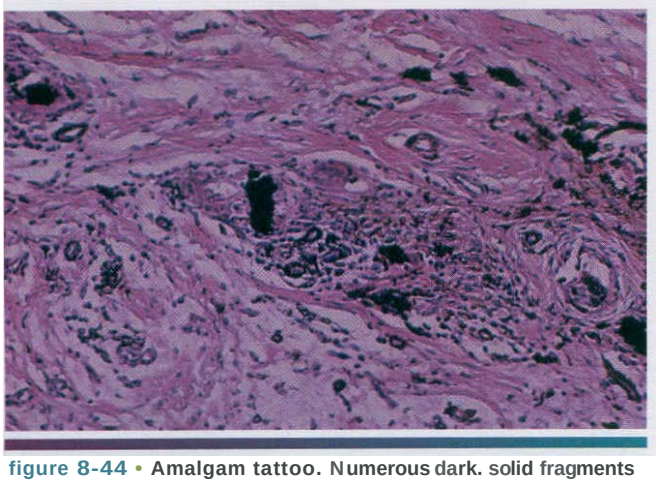


figure 8-44 • Amalgam tattoo. Numerous dark. solid fragments of amalgam are surrounded by a lymphohistiocytic inflammatory infiltrate.

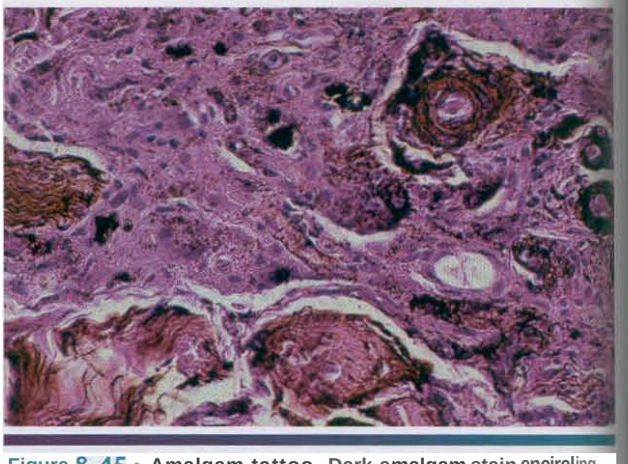


Figure 8-45 • Amalgam tattoo. Dark amalgam stain encircling numerous vascular channels.

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. biopsy may be needed to rule out the possibility of melanocytic neoplasia.

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. lead solder was not banned in plumbing until 1986. Homes built before then have the potential **for significant water contamination, and one of the pri**mary causes of lead intoxication in infants is formula preparation using tap water tainted by the metal.

Another significant source of lead poisoning in the young 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 compieted until 1995. These **sources of lead combined with previous industrial** emissions have resulted in areas of highly contaminated soils especially in urban areas. Despite the widespread publicity and significant efforts to restrict exposure to lead during childhood. significant risk remains.

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 aiso may be contaminated with lead. lead contamination in illicit alcohol has made the distinction between symptoms of lead intoxification and chronic alcohol abuse very difficult in certain sections of the American deep South.

Mercury. The danger of mercury exposure is wen 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 cathartic agents, and anthelmintic preparations. 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 hypersensitivity to mercury). The level of mercury that is released from amalgams does not appear sufficiently high to cause disease.

In spite of the knowledge gained decades ago. scattered problems still arise. Intoxication from chronic household exposure to mercury is still reported secondary to liquid mercury spills that have not been adequately cleaned up. Rare reports of occupation-related incidents in dental offices also occur. As late as 1990,

documented cases of mercury intoxication from paint fumes were reported from its incorporation as a preservative in household latex paint.

Silver. Systemic administration of silver was once common, especially in the treatment of gastrointestinal ulcerations; occasionally, silver intoxication resulted. Current examples of silver poisoning are usually restrtcted to industrial exposure or secondary to misuse of silver containing rncdicatlons or so-called supplements.

In a 1996 review, a number of colloidal silver proteins continued to be marketed in health food stores as essential mineral supplements for diseases such as cancer, diabetes, AIDS, and herpes. These products have no known physiologic function, and their continued use cannot be supported.

A number of silver nitrate and silver sulfadiazine formulations remain available by prescription. Use of these products should be minimized and used only under strict supervision. Well-documented examples of generalized argyria have been seen secondary to long-term treatment of aphthous ulcerations and denture sores with silver nitrate.

Bismuth *and arsenic,* In the United States, exposure to bismuth and arsenic is currently rare. The medical use of these metals has diminished dramatically; most current cases arise from occupational exposure. Bismuth was used in the past for treatment of venereal diseases and various dermatoses. Arsenic was used to treat many conditions, especially asthma and dermatoses such as psoriasis. 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. tn these cases, the side effects are well known and the patients are closely observed by their physician.

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 (organic or inorganic) 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.

Oral manifestations include ulcerative stomatitis and a gingival lead 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. Additional manifestations include the following:

- Tremor of the tongue on thrusting
- Advanced periodontal disease
- Excessive salivation
- Metallic taste

Mercury. Mercury poisoning also may be acute or chronic. With acute cases, abdominal pain, vomiting, diarrhea, thirst, pharyngitis, and gingivitis are typically present. With chronic cases, gastrointestinal upset and numerous neurologic symptoms occur. 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, Swift disease). The children have cold, clammy skin, especially on the hands, feet, nose, ears, and cheeks. An erythematous and pruritic rash is present. Severe sweating, increased lacrimation, irritability, insomnia, photophobia, hypertension, weakness, 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. Because mercury salts were formerly 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."

Silver. Systemic silver intoxication is known as argyria. Silver is disseminated throughout the body with substantial amounts accumulating as subepithelial deposits in the skin. These deposits result in a diffuse grayish-black discoloration that develops primarily in the sun-exposed areas. The 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 bluish-black discoloration.

Bismuth, Chronic bismuth exposure can result in a diffuse blue-gray discoloration of the skin. The conjunctiva and oral cavity also may be involved. A blue-gray line along the gingival margin similar to that seen from lead intoxication is the most common intraoral presentation. Bismuth combines with bacterial hydrogen sulfide to form

bismuth sulfide, which is locally irritating but not as destructive as mercuric sulfide. Associated ptyalism, burning, stomatitis, and ulceration may be seen.

Arsenic. In addition to widespread effects on numerous organ systems, significant dermatologic alterations frequently occur. Prolonged ingestion of arsenic often results in a diffuse macular hyperpigmentation. The discoloration is due to both the presence of the metal and an increased melanin production. In addition, palmar and plantar hyperkeratosis often is noted, as well as numerous premalignant skin lesions called arsenical keratoses. Development of basal cell carcinoma and cutaneous squamous cell carcinoma has been seen after years of exposure. Oral manifestations are rare 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 is often preceded by a warning signal: pruritus. Generalized exfoliative dermatitis with resultant alopecia and loss of nails can be seen.

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. A metallic taste often precedes development of the oral lesions and should be considered another warning signal. Therapy with gold can rarely 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 the past, two chelators, 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, and treatment is limited to supportive measures.

SMOKER'S MELANOSIS

Oral pigmentations are increased significantly in heavy smokers. In one investigation of more than 31,000 Caucasians, 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 (such as nicotine and the benzpyrenes) has been shown to stimulate melanin production by melanocytes that also are known to bind strongly to nicotine. It has been 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 who 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 (Figure 8-46). 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 it has been 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 330). 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 mod-

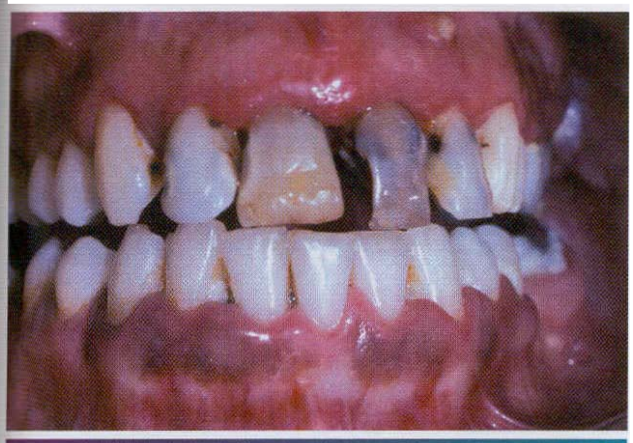


Figure 8-46 • Smoker's melanosis. Light, diffuse melanin pigmentation in a white female who is a heavy smoker. Pigmentary changes are limited to the anterior facial gingiva.

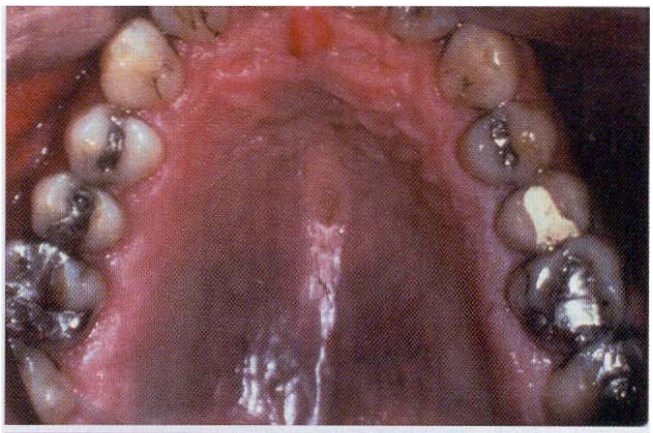


figure 8-47 • Chlorpromazine pigmentation. Diffuse grayish pigmentation of the hard palate.

ical 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 ruled out.

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 acquired immunodeficiency syndrome (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 associated with chemotherapeutic medications is most commonly reported with use of doxorubicin, busulfan, cyclophosphamide, or 5-fluorouracil. 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.

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.

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 (see Figure 2-35) and a broad zone of discoloration on the hard palate. Rare soft tissue pigmentation of the lips, tongue, eyes, and skin also has been reported.

The classic presentation of intraoral pigmentation from use of antimalarial medications or tranquilizers is a bluish-black discoloration limited to the hard palate (Figure 8-47). 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.

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 hyperpigrnentatlon.

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 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 are also occasionally discovered during histopathologic examination of nasopalatine duct cysts and maxillary gingivectomy specimens.

Despite the suggestion that the anterior maxillary lesions arc 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 is typically noted that may be associated with local enlargement (Figure 8-48). 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 may rarely be seen overlying the maxillary alveolar ridge or associated with anterior portions of the mandible. Because of significant associated symptoms and occasional enlargement. biopsy is frequently performed.

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 hyper-

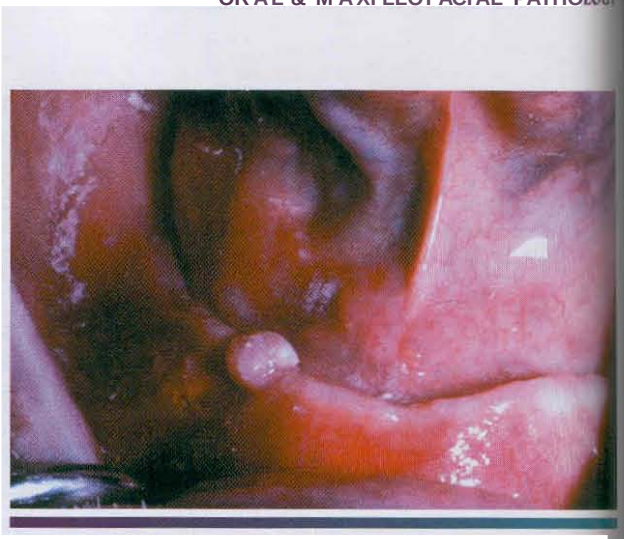


Figure 8-48 • Periosteal hyperplasia with osseous and chondromatous metaplasia. Tender. elevated nodule along the thin crest of the mandibular alveolar ridge. (Courtesy of Dr. *Steven* Tucker]

cellularity, pleomorphism, nuclear hyperchromatism, and occasional binucleatcd or multinucleated cells (Figure 8-49). 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 supplernented 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. the continued injury to the site occasionally results in recurrence of the lesion.

SPONTANEOUS SEQUESTRATION (TRAUMATIC SEQUESTRATION)

Spontaneous sequestration of cortical bone not related to systemic disease, infection, or a major traumatic event is uncommon. Most instances arise along the lingual surface of the mandible and often are associated with concurrent loss of the overlying oral mucosa.

The blood supply of the peripheral cortical plate is thought to be delivered by the periosteal rnicrovasculature, Investigators have suggested that loss of the overlying mucosa and periosteum could result in superficial infection. reactive periostitis, and sequestration. One oral surgeon had a full-thickness excision of half of his anterior palatal mucosa performed to investigate the degree of wound contraction and redevelopment of the rugee. Upon removal of the overlying soft tissue. most of the exposed cortical plate ultimately became necrotic and sequestrated. Other possible causes for this pattern of

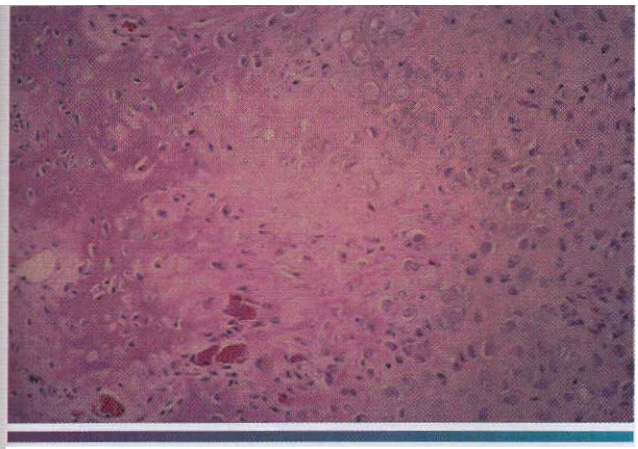


Figure 8-49 • Osseo us and chondromatous metaplasia. High-power photomicrograph demonstrating cellular woven bone and metaplastic cartilage.

sequestration include surgical trauma, traumatic injury. excessive occlusal forces, local vascular disruption. or bone exposure secondary to mucosal denudation from processes such as chemical burns.

In most instances. the sequestration arises without a history of preceding trauma and is frequently noted in patients with prominent exostoses. The association is so strong that some authors believe that those patients who are genetically predisposed to bony exostoses also exhibit a predilection to develop spontaneous sequestration.

Clinical and Radiographic Features

The most frequently affected area is the lingual surface of the mandible adjacent to the molars and along the crest of the mylohyoid ridge (Figure 8-50). The overlying mucosa typically demonstrates a focai 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.

The mylohyoid ridge is often 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.

A similar pattern of focal ulceration with underlying sequestrum also is reported occasionally along the surface of mandibular tori and less commonly in association with palatal tori. Analogous to those cases along themylohyoid ridge. most patients cannot recall any significant preceding trauma or history of recent dental procedures.

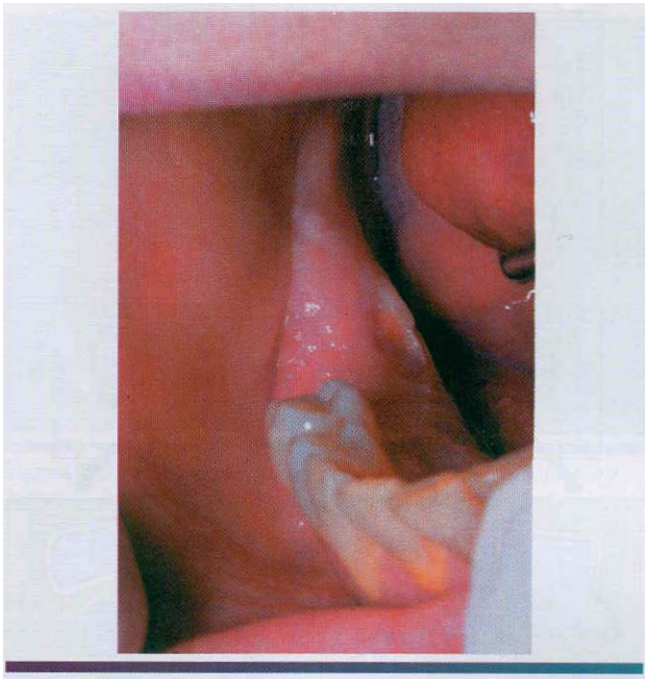


Figure 8-50 • Spontaneous sequestration. Linear ulceration and exposed bone of the posterior lingual surface of the mandible on the right side.

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.

ANTRAL PSEUDOCYSTS

Antral pseudocysts are common findings on panoramic radiographs. They appear as dome-shaped. faintly radiopaque lesions arising from the floor of the maxillary sinus. In the past, these sinus changes were incorrectly termed sinus mucoceles because previous investigators thought the lesions resulted from mucus extravasation similar to that seen in salivary glands of soft tissue. In fact. it appears that no comparable mucus extravasation occurs in the maxillary sinus.

***Antral** pseudocyst. Antral pseudocyst* is the best term for the dome-shaped lesion of the sinus floor. The process usually consists of an inflammatory exudate (serum. not mucin) that has accumulated under the maxillary sinus mucosa and caused a sessile elevation (Figure 8-51). The exudate is surrounded by connective tissue,

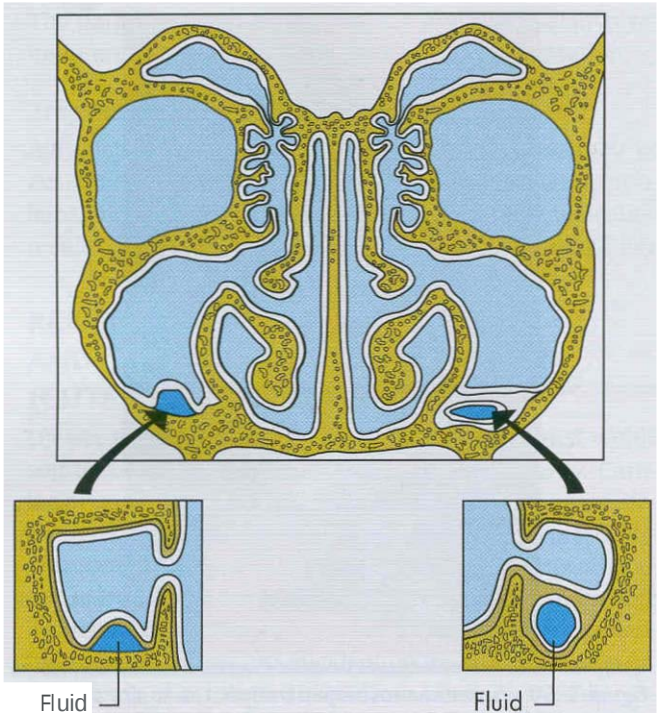


Figure 8-51 • Antral pseudocyst and true sinus mucocele. An antral pseudocyst is an accumulation of serum beneath the sinus lining. A sinus mucocele is an epithelium-lined cystic structure separate from the sinus.

and the epithelial lining of the sinus is superior to the fluid. Reviews of large numbers of radiographs have determined the prevalence, which varies from 1.5% to 14% of the population. The cause of the inflammatory infiltrate has not been definitively determined, but in a radiographic review, most 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 subperiosteal 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 infections or irritation from dry, forced-air heating. Although allergies have been proposed as a cause, no increased prevalence has been noted during the time of peak pollen exposure.

Sinus ***mucoceles.*** True sinus mucoceles are accumulations of mucin that are completely encased by epithelium. They occur in two situations.

One type of sinus mucocele occurs after trauma or surgery to the sinus; this type is best known as a surgical 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 mucin is secreted (see Figure 8-51). 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.

The second type of sinus mucocele arises from an obstruction of the sinus ostium, thereby blocking normal drainage. This blocked sinus then acts like a separate cystlike structure lined by epithelium and filled with mucin.

Sinus mucoceles enlarge in size as the intraluminal pressure increases and can distend the walls of the sinus and erode through bone, often clinically mimicking malignancy of antral origin.

Postoperative maxillary cysts appear to be uncommon in the United States and Europe but are reported more frequently in Japan. 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 are relatively rare and account for less than 10% of paranasal sinus mucoceles.

Retention cysts. Retention cysts of the maxillary sinus arise from the partial blockage of a duct of the seromucous glands or from an invagination of the respiratory epithelium. The mucin is surrounded by epithelium, and no extravasation occurs. Most retention cysts are located around the ostium or within antral polyps. The majority is small, not evident clinically, and discovered during histopathologic examination of antral polyps.

Clinical and Radiographic Features

Many symptoms have been attributed to sinus mucoceles; however, because of the confusion between pseudocysts and true mucoceles, it is unclear which symptoms are associated with pseudocysts and which are related to true sinus mucoceles. Most pseudocysts are asymptomatic; although it is rare, affected patients may exhibit facial fullness or report paresthesia, pain, or soreness upon palpation. As true sinus mucoceles enlarge and expand bone, symptoms may develop and vary according to the location and the degree of expansion and destruction.

Radiographically, the pseudocyst classically appears as a dome-shaped and slightly radiopaque lesion on the intact floor of the maxillary sinus (Figure 8-52). When the maxillary sinus is involved by a true sinus mucocele, the entire sinus will be cloudy. As the lesion enlarges, the walls of the sinus may become thinned and eventually eroded. Surgical ciliated cysts are spheric lesions that are separate from the sinus and lack the dome-shaped appearance of pseudocysts (Figure 8-53). As these postoperative cysts enlarge, they, too, can lead to perforation

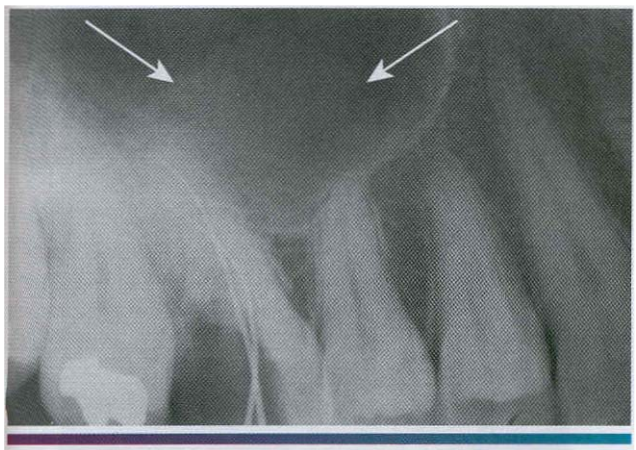


Figure 8-52. Antral pseudocyst. Dome-shaped radiopacity within the maxillary sinus *(arrows)*.

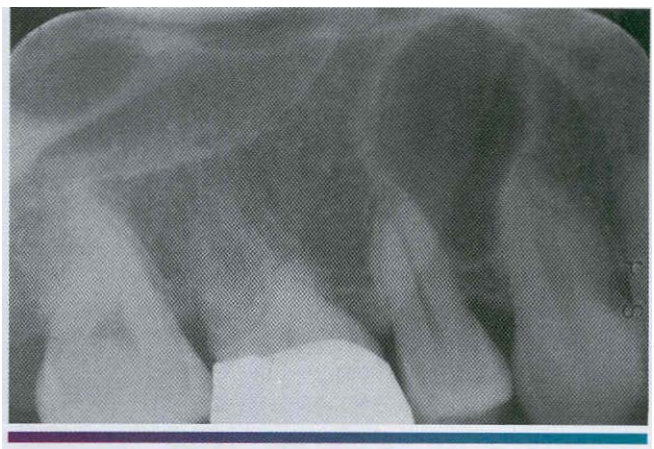


Figure 8-53 • Surgical ciliated cyst. Well-defined radiolucency between vital maxillary bicuspids. (Courtesy of Dr. Patrick Coleman}

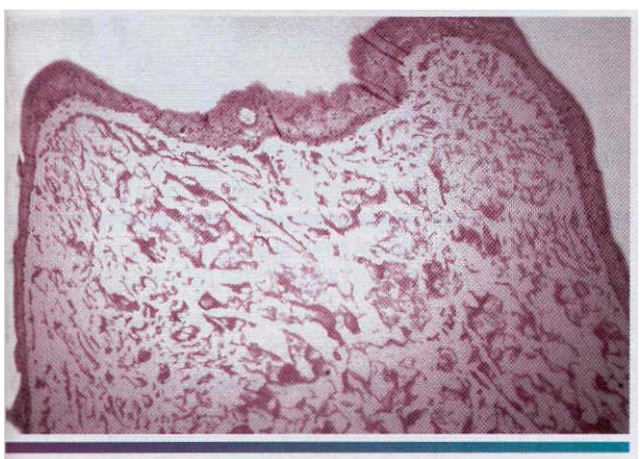


Figure 8-54 • Antral pseudocyst. low-power photomicrograph demonstrating pool of serum surrounded by loose connective tissue.

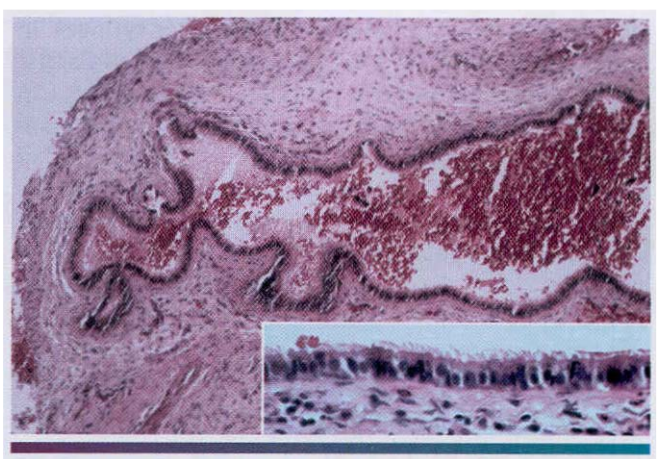


Figure 8-55 • Surgical ciliated cyst. True cyst lined by respiratory epithelium. Inset provides high-power *view* of the ciliated pseudostratified columnar epithelium that lines the cyst.

of the sinus walls. Retention cysts rarely reach a size that would produce detectable radiographic changes.

Histopathologic Features

Antral pscudocysts demonstrate a central inflammatory exudate that consists of serum occasionally intermixed with inflammatory cells. Surrounding the exudate is a wall of loose fibrous connective tissue that reveals variable inflammation (Figure 8-54). Collections of cholesterol clefts and scattered small dystrophic calcifications may be seen. True sinus mucoceles and surgical ciliated cysts are true cystic structures lined by ciliated pseudostratified columnar epithelium. squamous epithelium with mucous cells. or metaplastic squamous epithelium (Figure 8-55). A sinus retention cyst shows focal dilatation 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

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 should be performed on any radiographically diagnosed lesion that produces significant expansion or is associated definitively with symptoms such as headache.

Because sinus mucoceles and surgical ciliated cysts are expansile and destructive lesions. the traditional therapy for these pathoses is assured surgical removal. Numerous investigators also have shown that sinus rnucocclcs arising from ostial obstruction often do not require surgical excision and 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, 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. On occasion, cervicofacial emphysema has resulted from compressed air being accidentally forced into small intraoral lacerations located away from the field of operation. Conservative surgical flap design without extension into fascial planes and limited use of air-driven handpieces during surgical procedures may minimize the chance of occurrence.

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 (such as in glassblowers and wind instrument players). Stensen's 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 (Figure 8-56). Pain is usually minimal, and crepitus is easily detected with gentle palpation. Subsequently, the enlargement increases and spreads because of secondary inflammation and edema. Variable pain, facial erythema, 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.

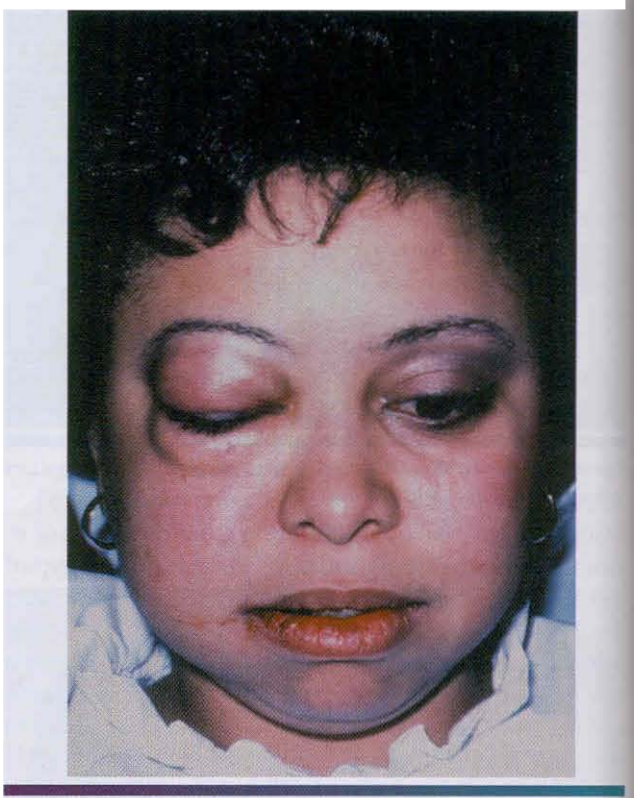


Figure 8-56 • Cervicofacial emphysema. Periorbital and facial enlargement caused by use of an air-driven handpiece during third molar removal.

Significant spread into the mediastinum can result in dysphonia, dysphagia, or dyspnea. Cardiac auscultation often reveals crepitus synchronous with the heart beat (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 upon gentle palpation. Milking the parotid duct produces a frothy, air-filled saliva, rather than the typical clear, waterlike secretion.

Treatment and Prognosis

Broad-spectrum antibiotic coverage is recommended in all dental related cases of cervicofacial emphysema. The body gradually removes the entrapped air over a 2- to 5-day period. Most cases spontaneously resolve without significant difficulty. 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 may occasionally result in a unique foreign-body reaction, known as myospherulosis. The resultant histopathologic pattern is most unusual and was initially thought 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. The inilial report described involvement of the arms, legs, and gluteal and scapular regions. 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 occasionally reported in a paranasal sinus after a surgical procedure in which a petroleum gauze packing was used.

The involved area may exhibit swelling or be discovered as an asymptomatic and circumscribed radiolucency in a previous extraction site (Figure 8-57). In some cases, pain and purulent drainage have resulted. On exploration of the lesion, a black, greasy, tarlike material is found.

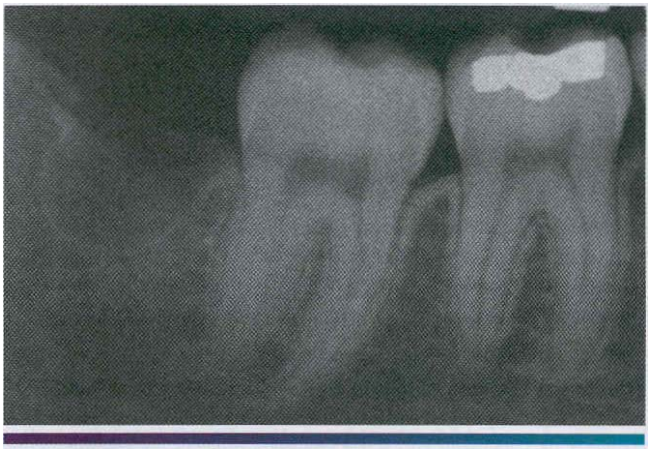


Figure 8-57 • Myospherulosis. Radiolucency has persisted after extraction of the mandibular third molar. An antibiotic ointment was placed at the time of initial surgery. (Courtesy of Dr. Tony Traynham.)

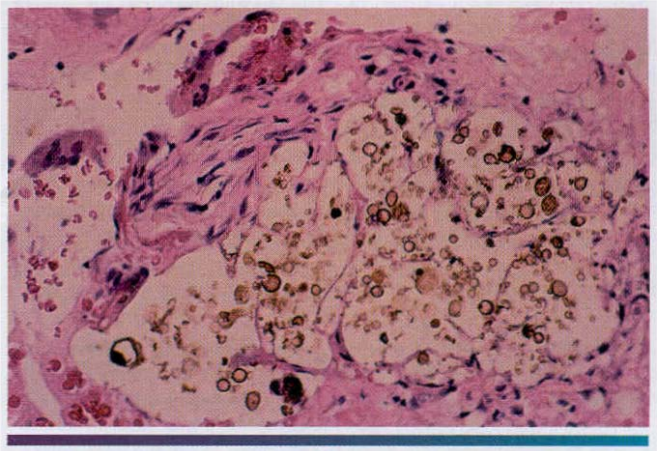


Figure 8-58 • Myospherulosis. High-power photomicrograph exhibiting multiple cystlike spaces containing numerous brown-stained spherules.

Histopathologic Features

The histopathologic pattern is unique; it is the result of a tissue interaction with both the petroleum base and the antibiotic, typically tetracycline. 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 (Figure 8-58). 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 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 is occasionally 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 antimicrobials.

A similar clinical and radiographic pattern has been seen in association with the use of powdered tetracycline in a polymer dressing. Although somewhat different histopathologically, this formulation also leads to a granulomatous foreign-body reaction. Because of complications associated with both formulations, the practice of applying topical antibiotics to oral wounds should be approached with caution, and other methods of delivery should be considered. If topical antibiotics are used, they should be accompanied by close follow-up to ensure appropriate clinical and radiographic evidence of healing of the surgical site.

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CHAPTER 9

Allergies and Immunologic Diseases

CHAPTER OUTLINE

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%. The hypotheses of its pathogenesis are numerous. **As soon as one investigator claims to have** discovered the definitive cause, a subsequent report discredits the discovery. Different subgroups of patients appear to have different causes for the occurrence of aphthae. These factors suggest a disease process that is triggered by a variety of causative agents, each of which iscapable of 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. Analysis of the peripheral blood in patients with aphthae shows a decreased ratio of CD4+ to CD8+ T lymphocytes, increased T cell-receptor $\gamma\delta$+ cells, and increased tumor necrosis factor-a. When developing aphthae have been investigated locally, a heavy inflammatory infiltrate is noted, and approximately 80% of the cells in the affected mucosa and underlying lamina propria are T lymphocytes. Although some investigators suggest the process may involve an antibody-dependent cellular cytotoxicity, **most believe the destruction is due to a direct** T lymphocyte-mediated cytotoxicity. 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 subgroupsl):

- Allergies
- Genetic predisposition
- Nutritional deficiencies
- Hematologic abnormalities
- **Hormonal influences**
- infectious agents
- **Trauma**
- Stress

When all the various subgroups are combined, the various causations cluster into three categories:

1. Primary immunodysregulation
2. Decrease of the mucosal barrier
3. Increase in antigenic exposure

One or more of these three factors may be involved in subgroups of patients.

Recurrent aphthous stomatitis demonstrates a definite tendency to occur along family lines. In addition, several investigators support genetic predisposition: these clinicians have associated certain histocompatibility antigen (HLA) types with subgroups of patients with aphthous stomatitis. HLA-B12, B51, and Cw7 are some of the numerous types that have been mentioned; as expected, however, these findings are not present consistently. Interestingly, the predominantly mucocutaneous form of Behcet's syndrome (Behcet's disease) (see page 290) exhibits significant aphthouslike oral ulcerations and also has been associated with HLA-B12. Two other disorders-Crohn's disease (see page 733) and celiac disease-have been associated with certain HLA types and exhibit an increased frequency of aphthouslike ulcerations.

Stress, with its presumed effects on the immune system, directly correlates with the presence of aphthous stomatitis in some groups. In studies of professional students, recurrences clustered around stressful periods of the academic year; conversely, periods of vacation were associated with a low frequency of lesions.

Aphthouslike ulcerations have occurred in patients with systemic immunodysrcgulations. Patients with cyclic neutropenia (see page 801) occasionally have cycles of aphthouslike ulcerations that correspond to the periods of severe immunodysregulation. Resolution of the neutropenia terminates the cycle of ulcerations. In addition, patients with acquired immunodeficiency syndrome (AIDS) have an increased frequency of severe aphthous stomatitis (see page 243). This is not surprising when one considers the relatively increased percentage of CD8+ cells, which occurs as a result of the reduction in CD4+ T lymphocytes in that disease.

The mucosal barrier appears to be important in the prevention of aphthous stomatitis and might explain the almost exclusive location of aphthous stomatitis on nonkeratinized mucosa. Numerous factors that can decrease the mucosal barrier increase the frequency of occurrence; conversely, those associated with an increased mucosal barrier have been correlated with decreased ulcerations. Certainly, trauma can decrease the mucosal barrier locally and has been associated with aphthae. In addition to their effects on the hematologic system, most of the nutritional abnormalities associated with aphthae (e.g., B12, folate, and iron deficiencies) also cause a decreased relative thickness of the oral mucosa. Although the effects of tobacco byproducts on the immune system are unclear, the use of tobacco products has been associated with increased keratinization of the oral mucosa and a decreased frequency of aphthae. In a small subset of female patients, a negative association was reported between the occurrence of aphthae and the luteal phase of the menstrual cycle, a period of mucosal proliferation and keratinization. In addition, these same patients often experience ulcer-free periods during pregnancy.

An antigenic stimulus appears to be the primary initiating factor in the immune-mediated cytotoxic destruction of the mucosa in many patients. Numerous antigens have been explored; as expected, however, no one answer is true in all subgroups of patients. Microbiologic agents, such as the L forms of streptococci, herpes simplex virus (HSV), varicella-zoster virus (VZV), adenovirus, and cytomegalovirus (CMVI. have been implicated. It is known that patients can exhibit herpesvirus within the epithelium without having a productive infection, and small subgroups of patients have attacks of aphthous stomatitis that coincide with asymptomatic viral shedding and elevated viral titers. Finally, other investigators have discovered subgroups of patients who respond well to a strict elimination diet or the removal of specific foods found to be allergenic by patch testing.

An increased prevalence of aphthouslike ulcerations has been noted in a variety of systemic disorders (Box 9-1). These ulcerations are typically 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.

Box 9-1 *Systemic Disorders Associated With Recurrent Aphthous Stomatitis*

- Behcet's syndrome
- Celiac disease
- Cyclic neutropenia
- Nutritional deficiencies
- IgA deficiency
- Immunocompromised conditions, including HIV disease
- Inflammatory bowel disease
- MAGIC syndrome (mouth and genital ulcers with inflamed cartilage)
- PFAPA syndrome [periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis)
- Reiter's disease
- Sweet's syndrome
- Ulcus vulvae acutum

The three clinical variations of aphthous stomatitis arc:

1. Minor
2. Major
3. Herpetiform

Minor aphthous ulcerations are the most common and represent the form present in up to 80% of those affected. Major aphthous ulcerations (also known historically as **Sutton's disease or periadenitis mucosa** necrotica recurrens [PMNRJ) occur in approximately 10% of the patients. 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 Behcet's syndrome as an additional variation of aphthous stomatitis. but this multisystem disorder *is* **more complex and is considered later in this** chapter.

Clinical Features

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. The lesions may be preceded by prodromal symptoms of burning. itching. or stinging. with the development of an erythematous macule. The macule develops an ulceration that is covered by a yellowish-**white. removable fibrinopurulent membrane and is encir**cled by an erythematous halo (Figure 9-I). Classically. **the ulcerations measure between 3 and 10 mm in diam**eter and heal without scarring in 7 to 14 days (Figure 9-2). From one to five lesions may be present during each episode. and the pain often is out of proportion for the size of the ulceration. The buccal and labial mucosae are the most commonly involved sites, followed by the ventral surface of the tongue. mucobuccal fold. floor of the mouth. and soft palate (Figure 9-3). 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 nonkeratinizcd** epithelium. Development of minor aphthae usually begins in childhood or adolescence. and the recurrence rate is highly variable. ranging from one ulceration every few years up to two episodes per month. Females arc affected more frequently than males.

Major *aphthous ulcerations*. Major aphthous ulcerations are larger than minor aphthae and demonstrate the longest duration per episode. The number of lesions **is usually intermediate between that seen in the minor**

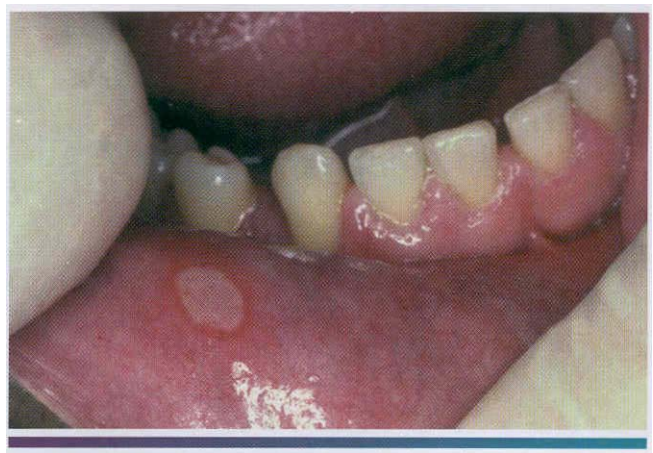

Figure 9-1 • Minor aphthous ulceration. Erythematous *halo* **encircling a yellowish ulceration of the lower labial mucosa. (Courtesy of Dr. Dean K. White.)**

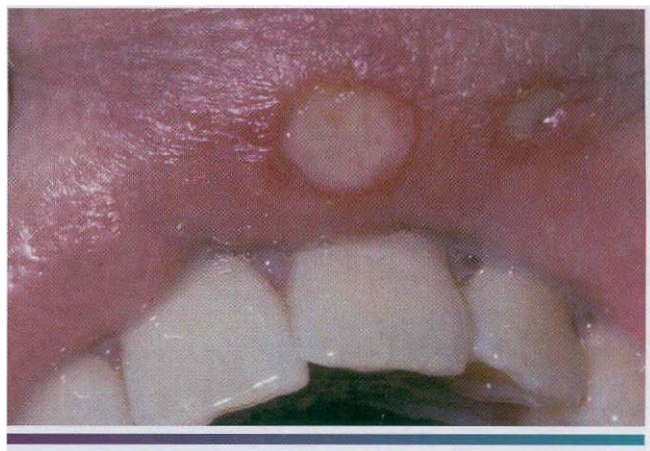

Figure 9-2 • Minor aphthous ulcerations. Two ulcerations of different sizes located on the maxillary labial mucosa.

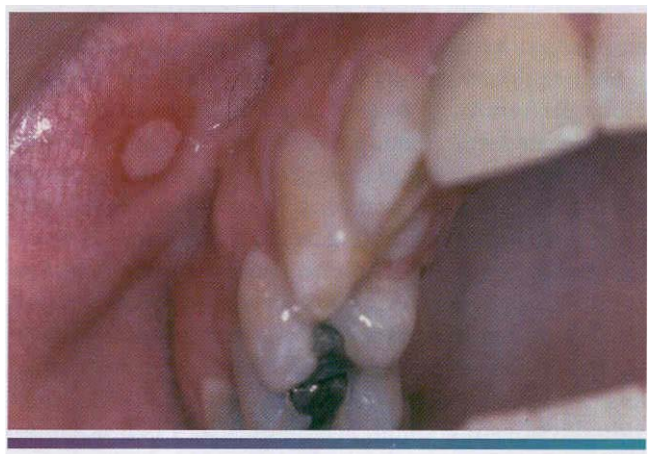

Figure 9-3 • Minor aphthous ulceration. Single ulceration of the anterior buccal mucosa.

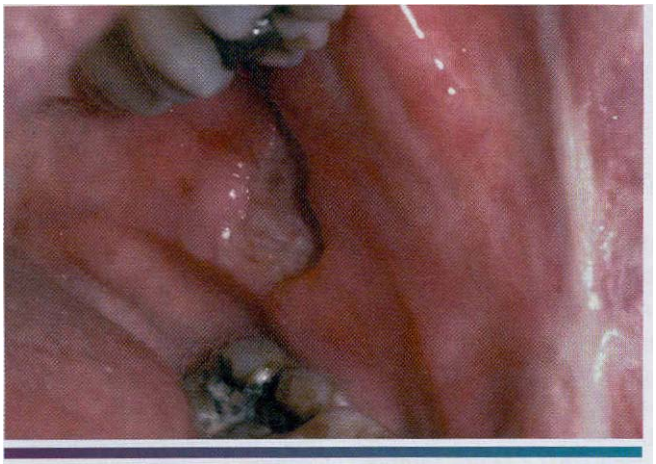

Figure 9-4 • **Major aphthous ulceration. Large, deep, and irregular ulceration of the posterior buccal mucosa. Note extensive scarring of the anterior buccal mucosa from previous ulcerations.**

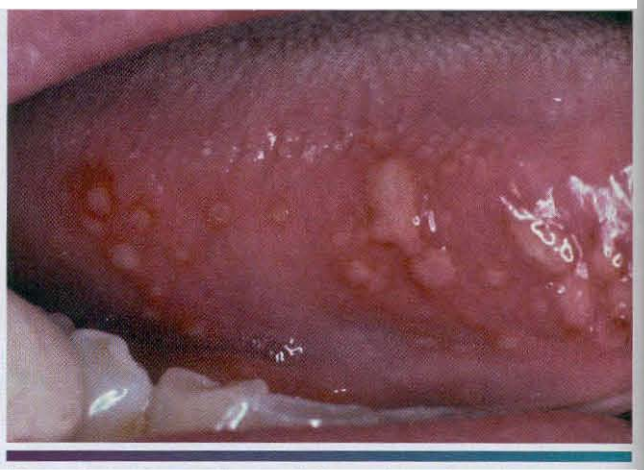

Figure 9-6 • **Herpetiform aphthous ulcerations. Numerous pinhead ulcerations of the ventral surface of the tongue. several of which have coalesced into larger more irregular areas of ulceration.**

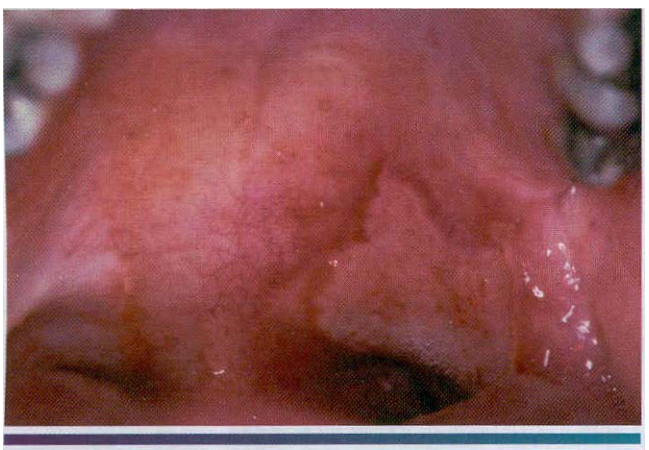

Figure 9-5 • **Major aphthous ulceration. Large. irregular ulceration of the soft palate.**

and herpetiform variants. The ulcerations are deeper **than the minor variant, measure from 1 to 3 em in diam**eter. take from 2 to 6 weeks to heal. and may cause scarring (Figure 9-4). The number of lesions varies from I to 10. Any oral surface area may be affected. but the labial mucosa, soft palate, and tonsillar fauces are the most commonly affected sites IFigure 9-5). The onset of major aphthae is after puberty. and recurrent episodes may continue to develop for up to 20 years or more.

***Herpetiform** aphthou« ulcerations.* Herpetiform aph**thous ulcerations demonstrate the greatest number of** lesions and the most frequent recurrences. The individual lesions are small. averaging i to 3 mm in diameter, and as many as 100may be present in a single recurrence. Because of their small size and large number, the lesions bear a superficial resemblance to a primary herpes simplex virus infection. Thus they are termed (rather confusingly) herpeliform. It is common for individual lesions **to coalesce into larger irregular ulcerations** (Figure 9-6), The ulcerations heal within 7 to 10 days. but the recurrences tend to be closely spaced. Many patients are affected almost constantly for periods as long as 3 years. 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 I to 2 weeks and recur infrequently. In **contrast. patients with complex aphthosis have numer**ous or large lesions. new lesions developing as older lesions resolve, severe pain, and (occasionally) associated genital or perianal lesions.

Histopathologic Features

The histopathologic picture of aphthous stomatitis is characteristic but not pathognomonic. The early ulcer**ative 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 vascularity and a mixed inflammatory cellular infiltrate that consists of lymphocytes. histiocytes. and polymorphonuclear leukocytes. The epithelium at the margin of the lesron demonstrates spongiosis and numerous mononuclear cells in the basilar one third. A band of lymphocytes intermixed with histiocytes is

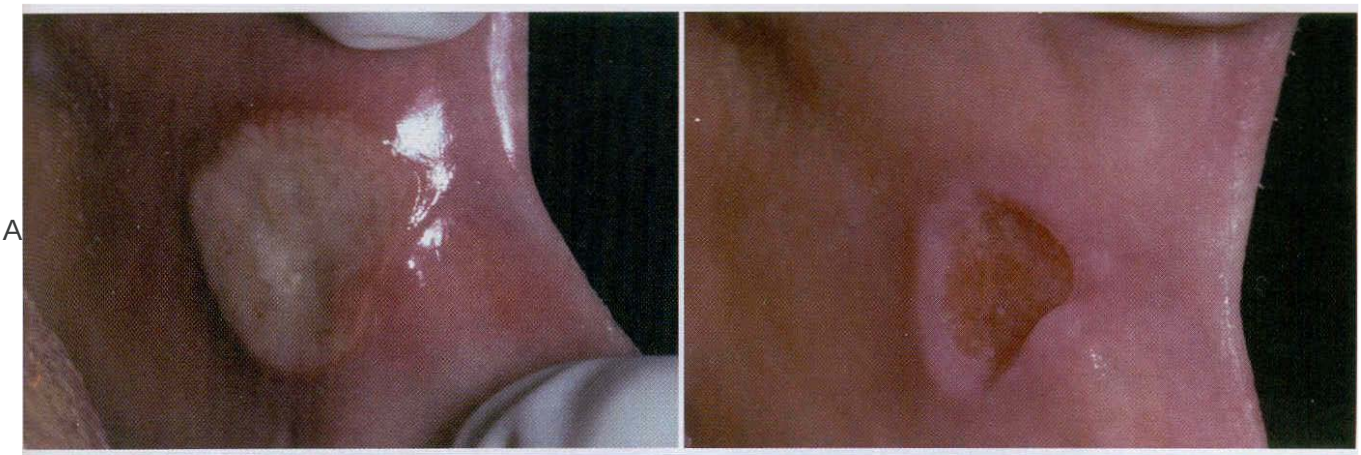

Figure 9-7 • **Major aphthous ulceration. A. Large ulceration of the left anterior buccal mucosa. B. Same lesion after 5 days of therapy with betamethasone syrup used in a swish-and-swallow method. The patient was free of pain by the second day of therapy. The ulceration healed completely during the following week.**

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). 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 aphthouslike ulcerations. Most patients with mild aphthosis receive either no treatment or periodic topical therapy that minimizes the frequency and severity of the attacks.

In patients with mild disease. the mainstay of therapy is topical corticosteroids. and the list of possible choices is long. Most patients with diffuse minor or herpetiform aphthae respond well to betamethasone syrup or 0.01% dexamethasone elixir used in a rinse-and-expectorate method. Patients with localized ulcerations can be treated successfully with 0.05% betarnethasone dipropionate 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 (Figure 9-7). 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. beclornethasone dipropicnate 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 or betarnethasene syrup in a swish-and-swallow method is preferable to prednisone tablets. In this way. the ulcerations will receive both topical and systemic therapy.

Many other medications have been used in an attempt to *resolve* the disease. Included within the list of therapies are acyclovir. amlexanox. topical 5-aminosalicylic acid. azelasnne hydrochloride. benzydamine hydrochloride. carbenoxolone sodium, chemical cauterizing agents. chlcrhextdlne, colchicine. cyclosporine. dapsone. deglycyrrhizinated liquorice. gamma globulin. hydrogen peroxide. hydroxypropyl cellulose films. interferon-a. irsogladine maleate. levarrusole, LongoVital. monoamine oxidase (MAO) inhibitors. pentoxifvlline, prostaglandin E-2 gel, sucralfate, sodium cromoglycate (cromolyn). tetracyclines. thalidomide. transfer factor (extract of irnrn unocytes). triclosan, and vitamins (especially zinc sulfate). The success of these therapies is highly variable. In addition. these treatments 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. Although laser ablation shortens the duration and decreases associated symptoms. its use is of *very* limited practical benefit because patients cannot return upon each recurrence.

Patients with complex aphthosis may 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.

As previously mentioned. the immune attacks arc usually a result of immunodysregulation, a decreased mucosal barrier, or an elevated antigenic stimulus. The evaluation for systemic disorders usually eliminates the first two causes. Typically. this is followed by patch tests for antigen stimuli or an elimination diet for possible offending foods. Therapeutic trials might be instituted against the viruses and bacteria that have been implicated in subsets of patients with aphthous stomatitis. The investigator should explain to the patient that the underlying causation is diverse; even with the most exhaustive search, the answer may be elusive. In many cases, stress appears involved. and all evaluations in these patients will be within normal limits. In spite of the high likelihood of an expensive and negative evaluation, discovery of an underlying abnormality that can be treated often leads to permanent resolution or dramatic improvement in the course of the recurrences.

BEHÇET'S SYNDROME (BEHÇET'S DISEASE)

The combination of chronic ocular inflammation and orogcnital ulcerations was reported as early as the era of the ancient Greeks, but it was not delineated until t937, when a Turkish dermatologist, Hulusi Behcet, described the disease that bears his name. Although the disease has been traditionally thought primarily to affect the oral, genital. and ocular regions, it now is recognized to be a muiti system disorder.

Although no clear causation has been established, Bchccts syndrome has an immunogenetic basis because of strong associations with certain HI A types. As in aphthous stomatitis. the disorder appears to be an immunodysreguiation that may be primary or secondary to one or more triggers. Investigators have correlated attacks to a number of environmental antigens, including bacteria (especially streptococci). viruses. pesticides. and *heavy* metals.

HI A-B51 has been linked closely to Behcet's syndrome, and the frequency of both the disease (approximateiy I in tODD) and haplotype is high in Turkey, Iapan, and the Eastern Mediterranean countries. This distribution appears correlated to the ancient "silk route" traveled by the Turks. Sexual reproduction between immigrants and locals along the route appears to have spread the genetic vulnerability.

Clinical Features

As mentioned previously, the highest prevalence occurs in the Middle East and Japan, with a much lower frequency noted in northern Europe, the United States, and the United Kingdom. At the time of discovery, most patients are young adults, with the disease diagnosed uncommonly in blacks. children, and the elderly.

Oral involvement is an important component of Bchcet's syndrome, and it is the first manifestation in 25% to 75% of the cases. Oral lesions occur at some point during the disease in 99% of the patients and typically precede other sites of involvement.

The lesions are similar to aphthous ulcerations occurring in otherwise healthy individuals and demonstrate the same duration and frequency. In spite of this, investigators have shown several statistically significant clinical variations that are different from typical aphthous ulcerations and may be used to increase the index of suspicion for Behcet's syndrome. When compared with patients with aphthae, a larger percentage of those with Behcet's syndrome demonstrate six or more ulcerations. The lesions commonly involve the soft palate and oropharynx, which are usually infrequent sites for the occurrence of routine aphthae. The individual lesions vary in size. have ragged borders. and are surrounded by a larger zone of diffuse erythema (Figure 9-8).

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 Behcet's syndrome. The herpetiform variant remains uncommon and is noted in approxtrnately 3%. Patients with major aphthae often demonstrate more frequent recurrences

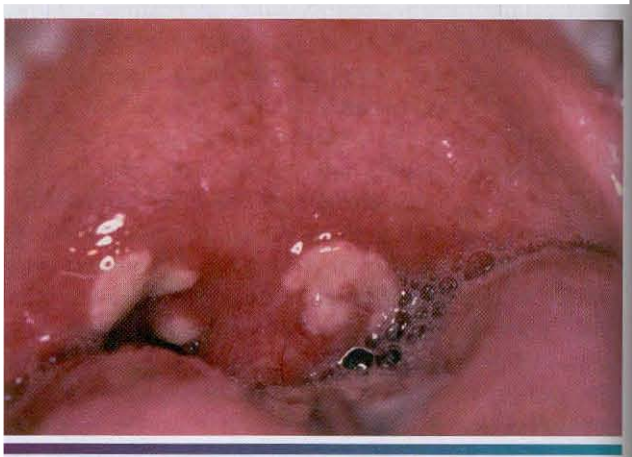

Figure 9-8 • Behcet's syndrome. Diffuse erythema surrounding numerous irregular ulcerations of the soft palate. (From Helm TN, Camisa C. Allen C. I owder C: Clinical features of Behcet's disease. *Oral Surg Oral Med Oral Pathol 72:30, 1991.)*

and more ulcerations per relapse. In spite of more severe oral disease, the presence of major aphthae in Behcet's syndrome does not correlate with an increased risk for more severe systemic expression.

The genital lesions are similar in appearance to the oral ulcerations. They occur in 75% of the patients and appear on the vulva, vagina, glans penis, scrotum, and perianal area (Figure 9-9). These lesions recur less frequentlythan do the oral ulcerations, are deeper, and tend to heal with scarring. The genital ulcerations cause more symptoms in men than in women and may be discovered only by a routine examination in women.

Common cutaneous lesions include erythematous papules, vesicles, pustules, pyoderma, folliculitis, acneiform eruptions, and erythema nodosum-like lesions. From a diagnostic standpoint, one of the most important skin manifestations is the presence of positive "pathergy." One or 2 days after the injection of an inert substance (e.g., sterile saline), a tuberculin-like skin reaction or sterile pustule develops (Figure 9-10). This skin hyperreactivity (pathcrgv) appears to be unique to Bchcet's syndrome and is present in 40% to 88% of patients with this disorder.

Ocular involvement is present in 70% to 85% of the cases and is more frequent and severe in males. The most common findings are posterior uveitis, conjunctivitis, corneal ulceration, papilledema, and arteritis. Although Behcet originally described hypopyon (pus in the anterior chamber) as a cause of blindness, this finding currently is rare. The most common secondary ocular complications are cataracts, glaucoma, and neovascularization of the iris and retina.

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.

Central nervous system (eNS) involvement is not common but. when present, is associated with a poor prognosis. From 10% to 25% of the patients demonstrate eNS involvement, and the alterations produced result in a number of changes that include paralysis and severe dementia.

Other alterations may be seen that involve the cardiovascular, gastrointestinal, hematologic, pulmonary, muscular, and renal systems. These most likely occur secondary to vasculitis and create a variety of clinical presentations.

Diagnosis

No laboratory finding is diagnostic of Behçet's syndrome. In an attempt to standardize diagnoses, definitive criteria have been developed. Table 9-1 delineates the requirements proposed by the Behcet's International Study Group. Although this system is used Widely, many authorities exclude acneiform skin lesions in young adults from the criteria because of the high prevalence of this finding in an otherwise normal population.

Histopathologic Features

The histopathologic features are not specific for Behcet's syndrome and can be seen in many disorders, including

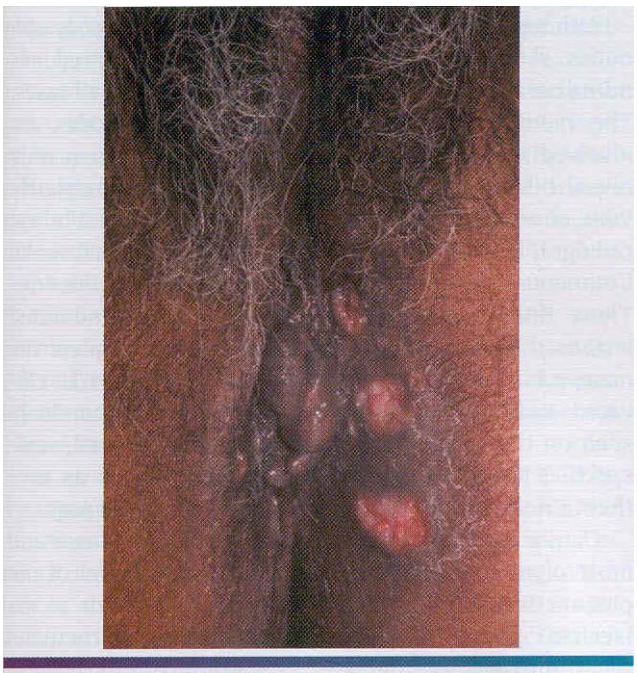

Figure 9-9. Behcet's syndrome. Numerous irregular ulcerations of the labia majora and perineum. (From Helm TN, Camisa C. Allen C, Lowder C: Clinical features of Behcet's disease, *Oral Surg Oral Med Oral Pathol* 72:30, 1991.)

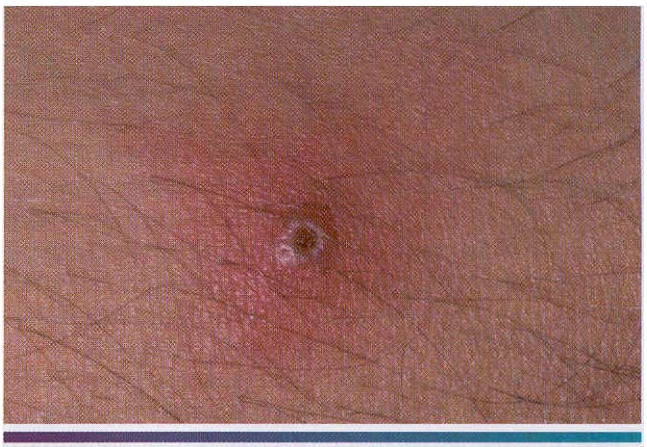

Figure 9-10. Behcet's syndrome. Sterile pustule of the skin that developed 1 day after injection of saline. This reaction is termed cutaneous pathergy.

Table 9-1 *tntemational SII/dy Group* ***Criteria*** *for* ***the*** *Diagnosis of Behcet's* ***Disease***

Recurrent oral ulceration	Minor. major. or herpetiform aphthae
Plus two of the following:	
Recurrent genital ulcerations	Aphthae-like 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 24-48 hours

aphthous stomatitis. The pattern most frequently seen is called Jeukocytoclastic 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

The oral and genital ulcerations typically respond well to potent topical or intralesional corticosteroids. In more *severe* cases. this therapy can be combined with oral colchicine or dapsone. Patients that fail this initiai conservative approach often require thalidomide, low-dose methotrexate. or systemic corticosteroids. Severe ocular or systemic disease often necessitates combined use of systemic immunosuppressive agents (e.g.• corticosteroids. cyclosporine. azathioprine, Interferon-nza).

Behcet's syndrome has a highly variable course. A relapsing and remitting pattern is typical, with attacks becoming more intermittent after 5 to 7 years. Mortality is typically low: when noted, it most frequently is secondary to pulmonary hemorrhage, CNS hemorrhage, or bowel perforation. In the absence of CNS disease or significant vascular complications. the prognosis is generally good.

SARCOIDOSIS

Sarcoidosis is a multisystem granulomatous disorder of unknown cause. 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. Sensitive polymerase chain reaction and DNA and RNA *in situ* hybridization techniques have detected abnormally high levels of mycobacterial DNA in bronchoalveolar lavage material from patients with sarcoidosis. The inappropriate defense response may result from prolonged or heavy antigenic exposure, an immunodysregulation (genetic or secondary to other factors) that prevents an adequate cell-mediated response, a defective regulation of the initial immune reaction, or a combination of all three of these factors. Future studies are needed to confirm a definitive relationship between sarcoidosis and any infectious agent.

Clinical Features

Sarcoidosis has a worldwide distribution but is recognized more commonly in the developed world. In North America, blacks are affected 10 to 17 times more lrequentiy than whites. There is a slight female predominance, and the disease typically arises between 20 and 40 years of age.

Sarcoidosis most commonly appears acutely over a period of days to weeks. and the symptoms are variable. Common clinical symptoms include dyspnea, dry cough. chest pain, fever, malaise, fatigue, arthralgia, and weight loss. Less frequently. sarcoidosis arises insidiously over months to years, without significant symptoms: when clinically evident, pulmonary symptoms are most common. 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 aimost 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 their 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, cars, lips, and face (Figure 9-11). Symmetric, elevated. indurated. purplish plaques arc also commonly seen on the limbs. back. and buttocks. Scattered. nonspecific, tender erythematous nodules. known as erythema nodosum, frequently occur on the lower legs.

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. Significant enlargement can occur in any major or minor salivary gland. Removal of intraoral rnucocelcs that occur in

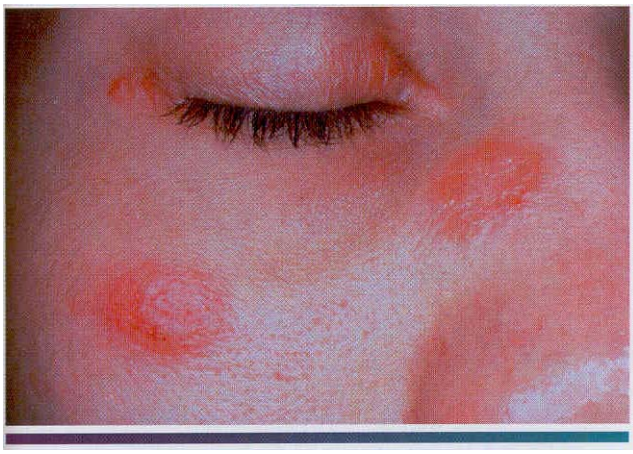

Figure 9-11 • Sarcoidosis. Violaceous indurated plaques of the right malar area and bridge of nose. (Courtesy of Dr. George Blozis.]

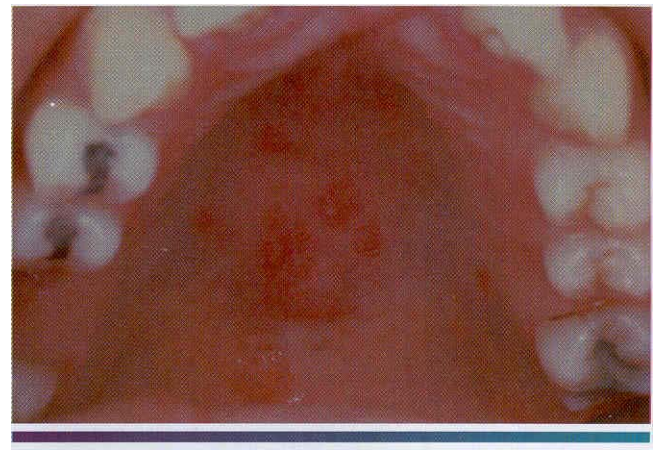

Figure 9-12 • Sarcoidosis. Multiple erythematous macules of the hard palate. (Courtesy of Dr. George Blozis.)

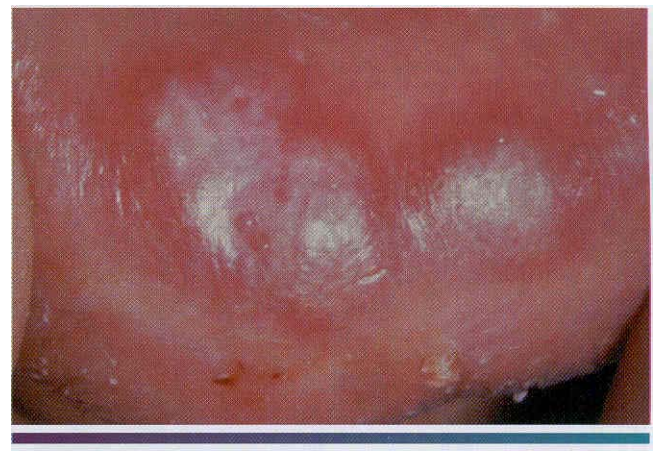

Figure 9-13 • Sarcoidosis. Erythematous macules with central hyperkeratosis of the lower labial mucosa.

the salivary glands affected by the granulomatous process has led to the initial diagnosis in some cases. The salivary gland enlargement, xerostomia. and keratoconjunctivitis sicca can combine to mimic Sjogren syndrome (see page 401).

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 arc affected.

Twodistinctive clinical syndromes are associated with acute sarcoidosis. Lofgren's syndrome consists of erythema nodosurn, bilateral hilar lymphadenopathy, and arthralgia. Patients with Heerfordt's 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, or an area of granularity. The mucosal lesions may be normal in color, brownish-red, violaceous, or hyperkeratotic (Figures 9-t2 and 9-i3). The most frequently affected intraoral soft tissue site is the buccal mucosa, followed by the gingiva. lips, floor of mouth. tongue. and palate. Most cases appearing in the floor of the mouth involve salivary glands and create mucus extravasation. Intraosseous lesions affect either [aw 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 a literature review of 4S reported cases of intraoral sarcoidosis, the oral lesion was the first documented clinical manifestation of the disease in the majority of 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 (Figure 9-14). The granulomas often contain laminated basophilic calcifications. known as Schaumann bodies, or stellate inclusions, known as asteroid bodies (Figure 9-15). Neither structure is specific for sarcoidosis. Special stains for fungal and bacterial organisms are negative. Nopolarlzable, dissolvable, or pigmented foreign material can be detected.

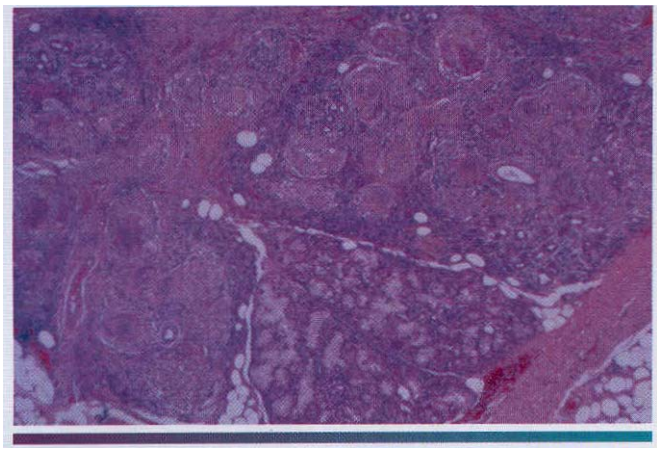

Figure 9-14 • Sarcoidosis. Photomicrograph of a labial minor salivary gland demonstrating granulomatous inflammation characterized by circumscribed collections of histiocytes, lymphocytes, and multinucleated giant cells.

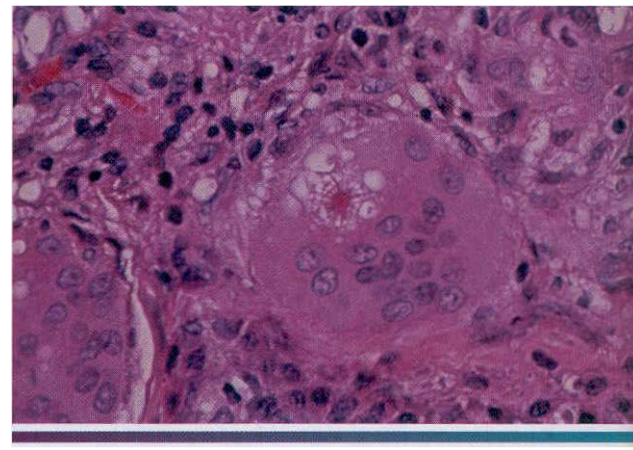

Figure 9-15 • Sarcoidosis. Photomicrograph illustrating multinucleated giant cell with intracytoplasmic asteroid body.

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. 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.

A skin test for sarcoidosis, the Kveim test, can be performed by intradermal injection of a sterilized suspension of human sarcoid tissue. Within 4 to 6 weeks, papulonodular lesions develop in affected patients. A biopsy is done to confirm granulomatous inflammation. The test is accurate in 50% to 85% of patients with sarcoidosis but is largely of historical interest because the clinical presentation and demonstration of granulomatous inflammation are adequate for the diagnosis in most cases. Although skin testing may be considered in atypical cases, when the biopsy is difficult, or the histopathologic findings are negative, the Kveim test is no longer widely available 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 Figure 9-14). Investigators have documented success rates between 38% and 58%. The misdiagnosis of Sjögren syndrome from minor salivary gland biopsy specimens has been reported in patients with sarcoidosis. 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. Of those affected, 20% can be treated successfully with corticosteroids. Those with significant involvement or disease that hinders normal function are candidates for corticosteroid treatment. Medications used in patients with refractory disease include methotrexate, azathioprine, chlorambucil, and cyclophosphamide. In 10% to 20% of those affected with sarcoidosis, resolution does not occur even with treatment. eNS and chronic extrathoracic involvement are associated with a poor response to therapy. Approximately 4% to 10% of patients die of pulmonary, cardiac, or eNS complications.

OROFACIAL GRANULOMATOSIS

Since its introduction in 1985 by Wiescnfeld, orofacial granulomatosis has become a well-accepted and unifying term encompassing a variety of clinical presentations that, upon biopsy, reveal the presence of nonspecific granulomatous inflammation. The conditions previously designated as Melkersson-Rosenthal syndrome and cheilitis granulomatosa of Miescher are subsets of orofacial granulomatosis, and neither represent a specific disease.

Table 9-2 Systemic Evaluation of Patients With Orofacial Granulomatosis

Systemic Cause	Preliminary Screening Procedures
Chronic granulomatous disease	Neutrophil nitroblue tetrazolium reduction test Perform if medical history of chronic infections is noted
Crohn's 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 $^{99}Tc^{m}$-HMPAO (hexamethylpropylene amine oxime); if initial screen is positive, recommend esophagogastroduodenoscopy, ileocolonoscopy, and small bowel radiographs
Sarcoidosis	Serum angiotensin-converting enzyme and chest radiograph (hilar lymphadenopathy)
Tuberculosis	Skin test and chest radiograph (negative AFB stains 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, response to local excision of a single focus should be evaluated.
Allergy	Cosmetics, foods, food additives, flavorings, oral hygiene products (e.g., toothpaste, 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.

The disorder is somewhat analogous to aphthous stomatitis, in that the cause is idiopathic but appears to represent an abnormal immune reaction. Sometimes oral lesions are seen that are identical to idiopathic orofacial granulomatosis but represent a secondary reaction to one or more of a variety of factors. Table 9-2 delineates systemic diseases *that* may mimic orotacial granulomatosis, and Table 9-3 lists possible local causes.

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. After initial diagnosis, the patient should be evaluated for several 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, the final diagnosis is altered appropriately.

Clinical Features

The clinical presentation of orofacial granulomatosis is highly variable. 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 (Figure 9-16). On rare occasions, superficial amber vesicles, resembling lymphangiomas, are found. When these signs are combined with facial paralysis and a fissured tongue, the clinical presentation is called

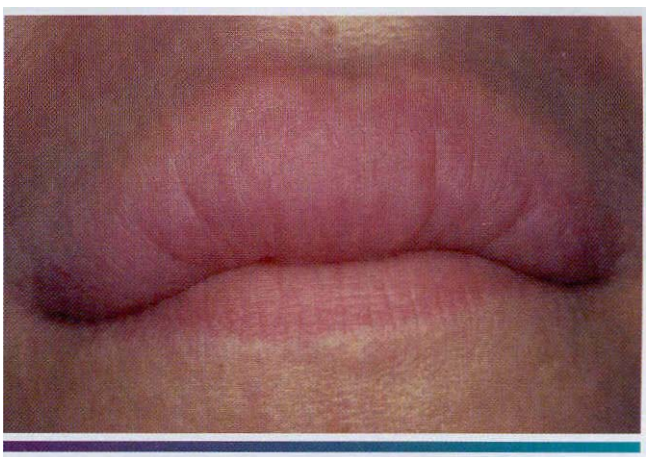

Figure 9-16 • Orofacial granulomatosis (cheilitis granulomatosa). Nontender, persistent enlargement of the upper lip. (From: Allen CM, Camisa C: Diseases of the mouth and lips, In Sams WM, Lynch P, editors: *Principles of dermatology*, New York, 1990, Churchill Livingstone, 1990.)

Melkersson-Rosenthal syndrome (Figures 9-17 and 9-18). Involvement of the lips alone is called cheilitis granulomatosa (of Miescher). Some consider cheilitis granulomatosa an oligosymptomatic form of Melkersson-Rosenthal syndrome, but it appears best to include all of these under the term orofacial granulomatosis. In addition to labial edema, swelling of other parts of the face may be seen.

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, ery-

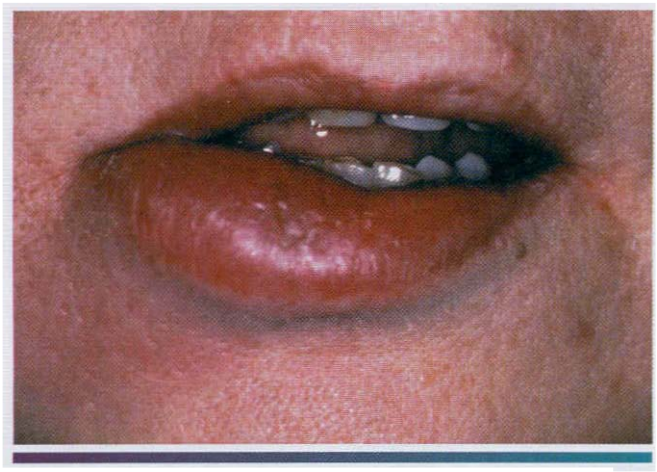

Figure 9-17 • Melkersson-Rosenthal syndrome. Persistent enlargement of the lower lip. (Courtesy of Dr. Richard Ziegler.)

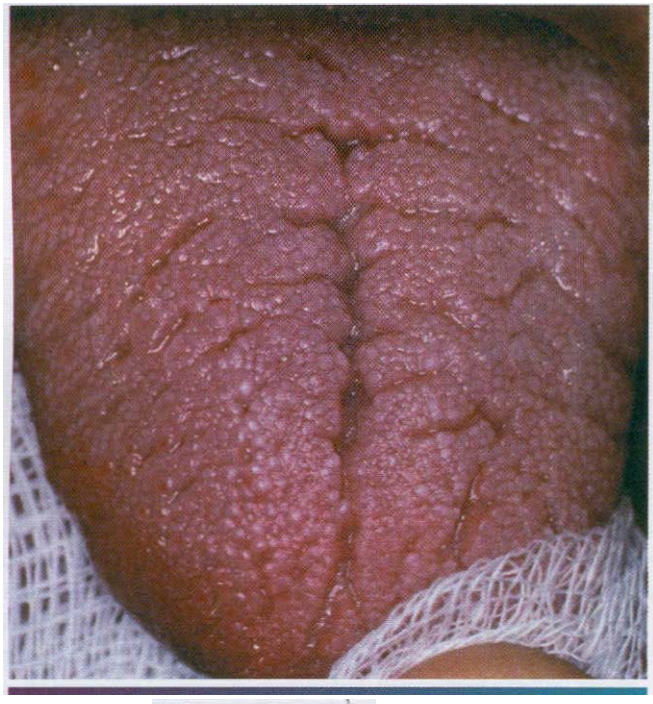

Figure 9-18 • Melkersson-Rosenthal syndrome. Same patient as depicted in Figure 9-1Z Note numerous furrows on the dorsal surface of the tongue. (Courtesy of Dr. Richard Ziegler.)

therna. **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 rnucobuccal fold. with linear ulcerations appear in the base of these folds (Figure 9-19). The palate may have papules or large **areas of hyperplastic tissue.** Hyposalivation **is rarely** reported.

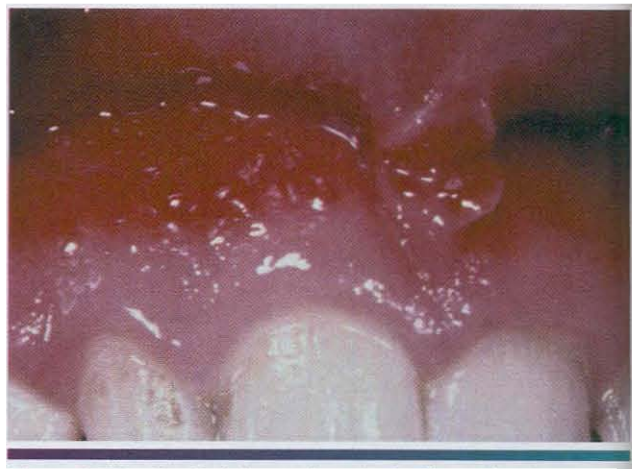

Figure 9-19 • Orofacial granulomatosis. Hyperplastic mucosa of the anterior maxillary mucobuccal fold. (Courtesy of Dr. Greg W. Dimmich.)

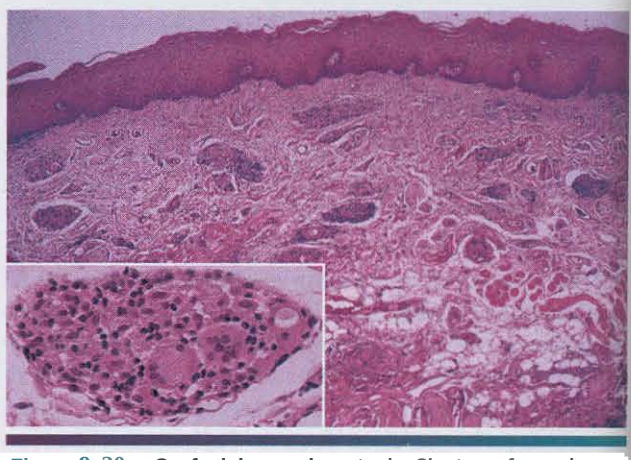

Figure 9-20 • Orofacial granulomatosis. Clusters of granulomatous inflammation around scattered vessels. The inset illustrates the histiocytes and multinucleated giant cells within the granulomas.

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 (Figure 9-20).

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

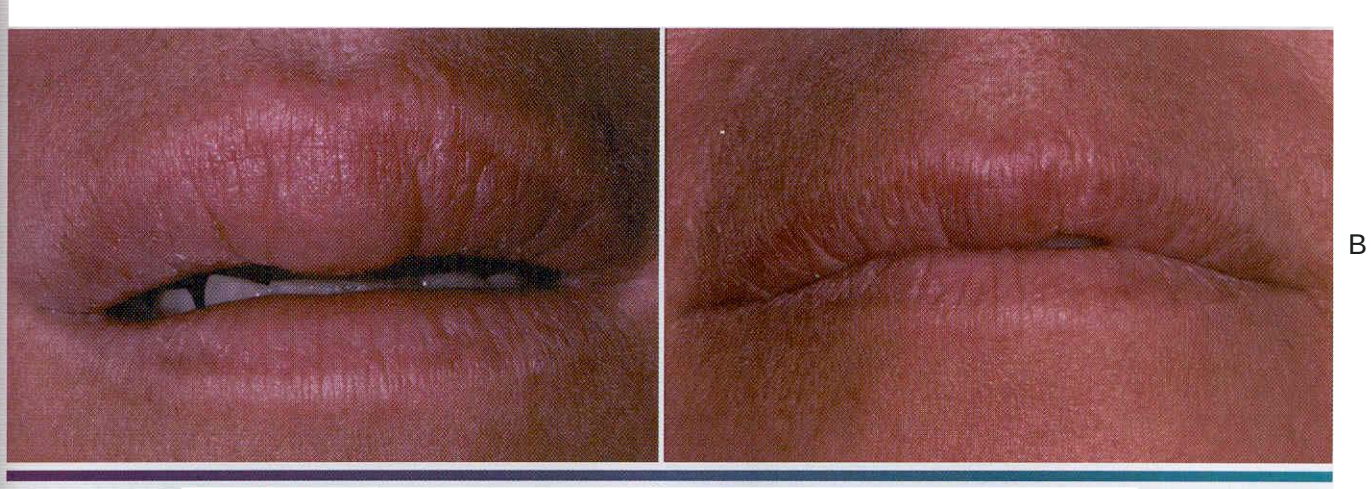

Figure 9-21 • Orofacial granulomatosis. A, Diffuse enlargement of the upper lip. B, Same patient after lntraleslonal **triamcinolone injections.**

gingivitis are due to subtle collections of foreign material (see page 142).

Diagnosis

The initial diagnosis of orofacial granulomatosis is made upon histopathologic demonstration of granulomatous **inflammation that is associated with negative special stains for organisms and no foreign material. Based on the clinical and historical findings, one or more conditions** may have to be considered in the differential diagnosis. It should be stressed that no one cause for the granulomas will be found when large groups of patients with orofacial granulomatosis are studied. (See Tables 9-2 and 9-3 for a list of conditions and suggested procedures **that may be appropriate to arrive at a more** definitive dlagnosis.)

Treatment and Prognosis

The first goal of management should be discovery of the initiating cause. although this may be most difficult. Often the trigger is elusive. Local measures to resolve the clinical manifestations can be attempted but. as would **be expected, recurrences are common. The individual lesions have been treated with a variety of interventions, with variable results. Intralesional corticosteroids, radio**therapy, salazosulfapyridine (sulfasalazine), hydroxychloroquine sulfate, azathioprine, cyclosporine A. **methotrexate, danazol, dapsone, c1ofazimine, metronidazole, and numerous other antibiotics have been** tried. Currently. most investigators administer intralesiena! **corticosteroids to control the progression of this** disease (Figures 9-21 and 9-22). Because of the natural variability of the disease's progression and the occurrence **of spontaneous remissions, therapies are difficult** to assess. In the absence of a response to other treatments, surgical recontouring has been used by 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. The "lucky" subset of patients **includes those who have found an initiating causation** and have resolved their problems by the exclusion of the offending agent.

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis is a well-recognized, although uncommon, disease process of unknown cause. The initial description of the syndrome by Wegener **included necrotizing granulomatous lesions of the respi**ratory tract. necrotizing glomerulonephritis. and sys**temic vasculitis of small arteries and *veins.* Hypotheses** about the cause of the disease include an abnormal **immune reaction secondary to a nonspecific infection or an aberrant hypersensitivity response to an inhaled** antigen. A possible hereditary predisposition has been **mentioned in some cases.**

Before the current treatment modalities were initiated, the disorder was uniformly fatal. The disease begins as a localized process, which may become more widely disseminated if left untreated. Most patients respond favorably to treatment: consequently, early diagnosis and **appropriate therapy are critical.**

Clinical Features

Wegener's granulomatosis demonstrates a wide age range from childhood to the elderly. with a mean of

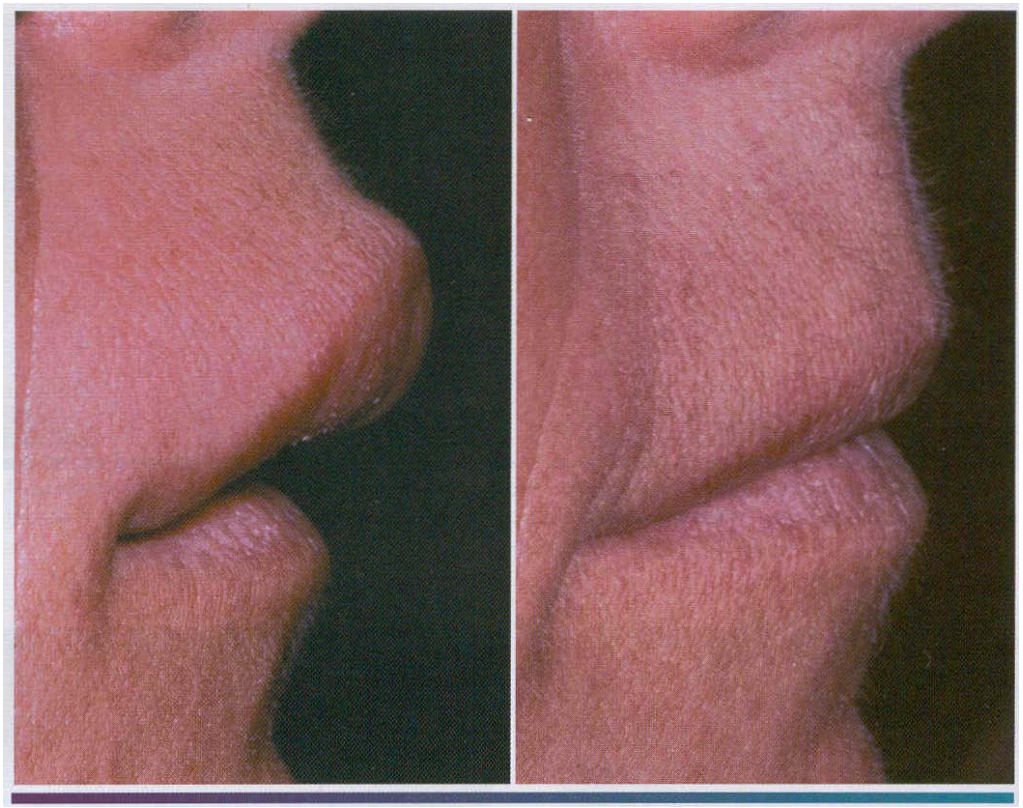

Figure 9-22 • Orofacial granulomatosis. Same patient depicted in Figure 9-21. A, Clinical appearance before local therapy. B, Significant resolution after intralesional corticosteroid.

approximately 40 years. No sex predilection is noted. and the prevalence has been reported to be 3.0 per 100.000. The disease can involve almost every organ system in the body. With classic Wegener's granulomatosis. patients initially show involvement of the upper and lower respiratory tract; if the condition remains untreated. renal involvement often rapidly develops.

Limited Wegener's 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's 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's granulomatosis.

Purulent nasal drainage, chronic sinus pain. nasal ulceration, congestion. and fever arc frequent findings from upper respiratory involvement. Persistent otitis media. sore throat. and epistaxis also arc reported. With progression. destruction of the nasal septum can result in a saddle nose deformity. Patients with lower respiratory 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.

Oral lesions are seen in the minority of those affected; occasionally, the oral changes may be the only clinically evident finding. The most characteristic oral rnanifestation is strawberry gingivitis. This distinctive but uncommon pattern of gingival alteration appears to be an early manifestation of Wegener's 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 (Figure 9-23). The buccal surfaces are affected more frequently, and the alterations are classically confined to the attached gingiva. The process appears to begin in the interdental region and demonstrates lateral spread to adjacent areas. At the time of diagnosis, the involvement may be localized or generalized to multiple quadrants. Destruction of underlying bone with the development of tooth mobility has been reported.

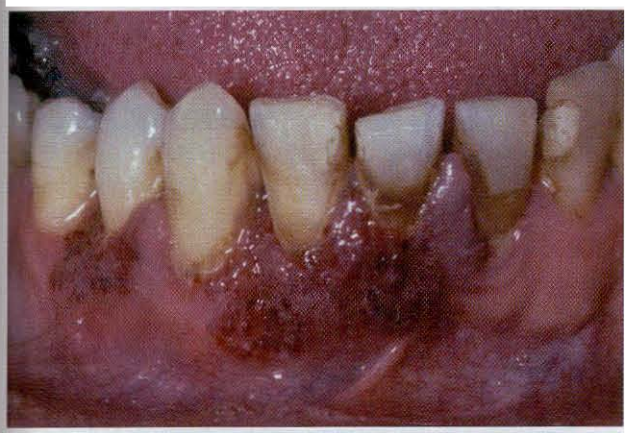

Figure 9-23 • **Wegener's granulomatosis. Hemorrhagic and friable gingiva (strawberry gingivitis) of the anterior mandibular facial gingiva.**

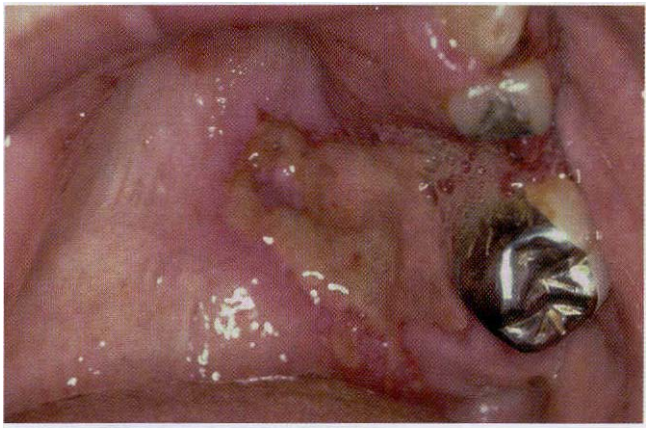

Figure 9-24 • **Wegener's granulomatosis. Deep, irregular ulceration of the hard palate on the left side. (From Allen CM, Camisa C, Salewski C, Weiland JE: Wegener's granulomatosis: report of three cases with oral lesions, *J Oral Maxillofac Surg* 49:294-298, 1991.)**

Oral ulceration also may be a manifestation of Wegener's granulomatosis. Unlike the strawberry gingiva, the ulcerations do not form a pattern that is unique. **These lesions are clinically nonspecific and may occur** on any mucosal surface (Figure 9-24). 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 in the course of the disease and may lead to early diagnosis and treatment.

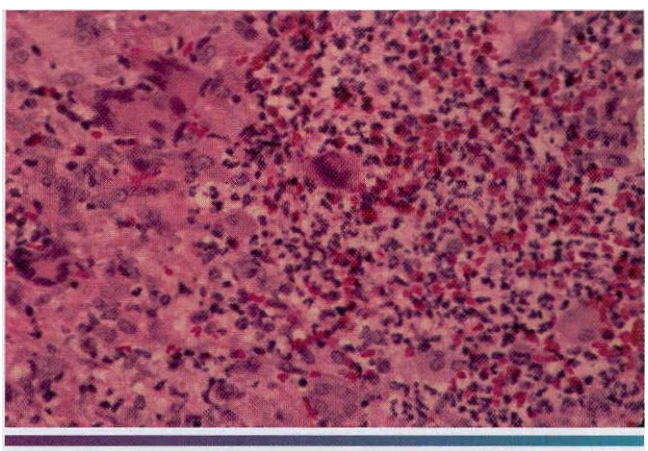

Figure 9-25 • **Wegener's granulomatosis. Connective tissue containing proliferation of numerous vascular channels and a heavy inflammatory infiltrate consisting of lymphocytes,** neutrophils, eosinophils, **and multinucleated giant cells.**

Histopathologic Features

Wegener's 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 (leukocytoclasnc 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 (Figure 9-25). 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 cosinophils, lymphocytes, and multinucleated giant cells. In addition, the lesions of strawberry gingivitis typically demonstrate prominent **vascularity with extensive red blood cell extravasation** (Figure 9-26).

Diagnosis

The diagnosis of Wegener's granulomatosis is made from the combination of the clinical presentation and the **microscopic finding of necrotizing and granulomatous** vasculitis. 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.**

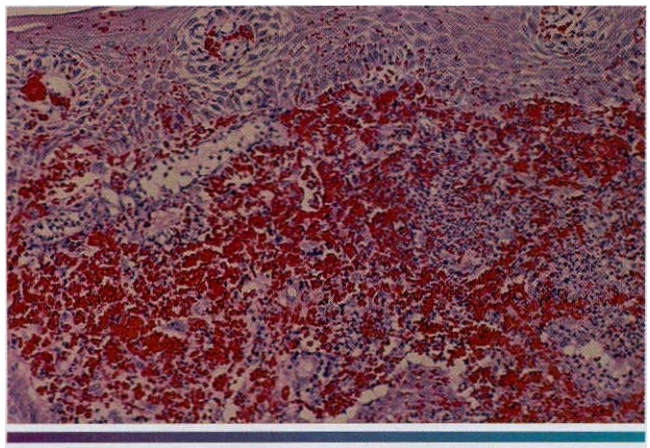

Figure 9-26 . Wegener's granulomatosis. Gingival biopsy specimen showing a mixed inflammatory cellular infiltrate obscured by extensive extravasation of red blood cells.

A laboratory marker for Wegener's granulomatosis has been identified, indirect immunofluorescence for serum antibodies directed against cytoplasmic components of neutrophils has been used to support a diagnosis of **Wegener's granulomatosis. There are two reaction pat**terns of these antineutrophil cytoplasm antibodies (ANCA):

r. Perinuclear (p-ANCA)

2, Cytoplasmic (c-ANCA)

Cytoplasmic localization (c-ANCA) is the most useful and is present in 90% to 95% of cases of acute generalized Wegener's granulomatosis. This positivity drops to 60% in early localized forms of the disease. When positive, a finding of c-ANCA confirms the diagnosis; however, when the immunologic studies are negative, the diagnosis of Wegener's granulomatosis is not ruled out.

Treatment and Prognosis

The mean survival of untreated patients with disseminated classic Wegener's granulomatosis is 5 months; 80% of the patients are dead at [year and 90% within 2 years. However, the prognosis is better for the limited and superficial forms of the disease.

The drugs of choice are cyclophosphamide and prednisone. but this approach is not without serious potential side effects. Trimethoprim-sulfamethoxazole has been used successfully in localized cases and when the immunosuppressive regimen has failed. 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. New treatment options under study include cyclosporine and intravenous pooled immunoglobulin.

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 and cure often is attainable when the disease is diagnosed and appropriately treated while the *involvement* is localized. The c-ANCA levels can be used to follow 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.**

ALLERGIC MUCOSAL REACTIONS TO SYSTEMIC DRUG ADMINISTRATION

The use of medications is not without potential intraoral complications. The list of offending medications and their resultant side effects appears almost endless. In a short and highly beneficial article, Matthews listed more than 150 frequently prescribed medications and related them to 46 oral and perioral side effects associated with **their use.**

An allergic reaction of the oral mucosa to the systemic **administration of a medication is called** stomatitis medicamentosa. **Besides erythema multiforme,** several different patterns of oral mucosal disease can be seen:

- Anaphylactic stomatitis
- intraoral fixed drug eruptions
- Lichenoid drug reactions
- Lupus erythematosus-like eruptions
- Pemphigus-like drug reactions
- **Nonspecific vesiculoulcerative lesions**

Anaphylactic stomatitis arises after the allergen enters the circulation and binds to 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.**

The *vast* number of medications capable of producing anaphylactic stomatitis precludes their listing, but common culprits are antibiotics (especially penicillin) and sulfa drugs. Medications reported to be associated with fixed drug eruptions are listed in Box 9-2 , lichenoid drug eruptions in Box 9-3, lupus erythematosus-like drug eruptions in Box 9-4 , pemphigus-like drug reactions in Box 9-5, and nonspecific vesiculoerosive eruptions in Box 9-6 .

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

Box 9-2 *Medications Implicated in Fixed Drug Eruptions*

- Analgin
- Barbiturates
- Co-tnmoxazole
- Dapsone
- Phenazone derivatives
- Phenolphthalein
- Sallcylates
- Sulfonamides
- Tetracycline

Box 9-3 *Medications Implicated in Lichenoid Eruptions*

- Allopurinol
- Amiphenazole
- Amphotericin B
- Arsenicals
- Bismuth
- Captopril
- Carbamazepine
- Chloroquine
- Chlorothiazide
- Chlorpropamide
- Cimetidine
- Cyanamide
- Dapsone
- Fenclofenac
- Furosemide
- Gold salts
- Hydroxychloroquine
- Ketoconazole
- Levamisole
- lithium
- lorazepam
- Mercury
- Methyldopa
- Metopromazine
- Oxyprenolol
- Palladium
- Para-aminosalicylic acid
- Penicillamine
- Phenothiazines
- Phenylbutazone
- Practolol
- Propranolol
- Pyrimethamine
- Pyritinol
- Quinacrine
- Quinidine
- Spironolactone
- Sulfonylureas
- Streptomycin
- Tetracycline
- Tolbutamide
- Triprolidine

Box 9-4 *Medications Implicated in Lupus Erythematosus-Like Eruptlons*

- Carbamazepine
- Chlorpromazine
- Ethosuximide
- Gold
- Griseofulvin
- Hydantoins
- Hydralazine
- Isoniazid
- lithium
- Methyldopa
- Penicillamine
- Primidone
- Procainamide
- Quinidine
- Reserpine
- Streptomycin
- Thiouracils
- Trimethadione

Box 9-5 *Medications Implicated in Pemphigus-Like Eruptions*

- Alpha-mercaptopropionyl glycine
- Ampicillin
- Captopril
- Cephalexin
- Ethambutol
- Glibenclamide
- Gold
- Heroin
- Ibuprofen
- Penicillamine
- Phenobarbital
- Phenylbutazone
- Piroxlcam
- Practolol
- Propranolol
- Pyritinol chlorhydrate
- Rifampin
- Thiopromine

Box 9-6 *Drugs Associated with Nonspecific Vesiculoerosive Lesions*

- Indomethacin
- Gold salts
- Meprobamate
- Methyldopa
- Naproxen
- Penicillamine
- Phenylbutazone
- Propranolol
- Spironolactone
- Thiazide diuretics
- Tolbutamide

or in conjunction with urticarial skin lesions or other signs and symptoms of anaphylaxis (e.g., hoarseness, respiratory distress, vomiting). The affected mucosa may exhibit multiple zones of erythema or numerous aphthouslike 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, and pemphigus-like drug reactions resemble their namesakes clinically, histopathologically, and Immunologically (Figure 9-27). These latter ehronic drug reactions may involve any mucosal surface, but the most **common sites are the posterior buccal mucosa and the** lateral borders of the tongue (Figures 9-28 and 9-29). Bilateral and symmetric lesions are fairly common.

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 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,

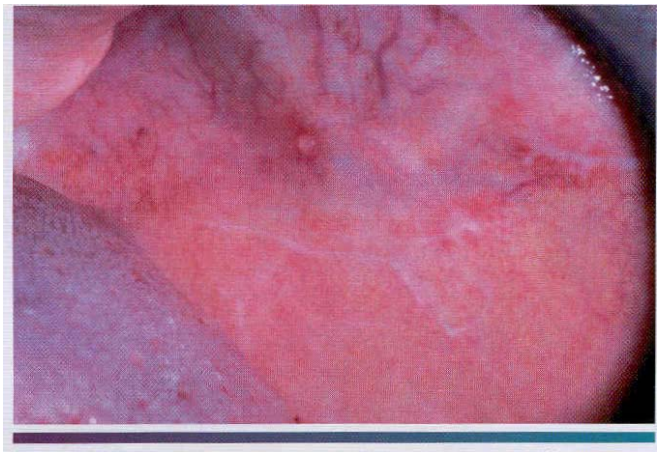

Figure 9-27 • Allergic mucosal reaction to systemic drug administration. Mucosal lesions associated with use of oxybutynin chloride (anticholinergic therapy for urinary incontinence). Note lichen planus-like striae. In addition, multiple superficial mucoceles occurred on the soft palate, floor of the mouth, and bilaterallyon the buccal mucosa.

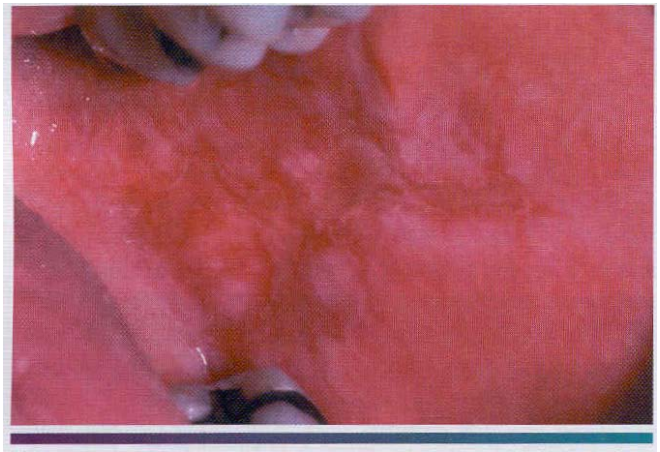

Figure 9-28 • lichenoid drug reaction to allopurinol. Irregular area of superficial erosion of the left buccal mucosa. Lesions were also present on the contralateral buccal mucosa and bilaterally on the lateral borders of the tongue.

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 vestculocroslve 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

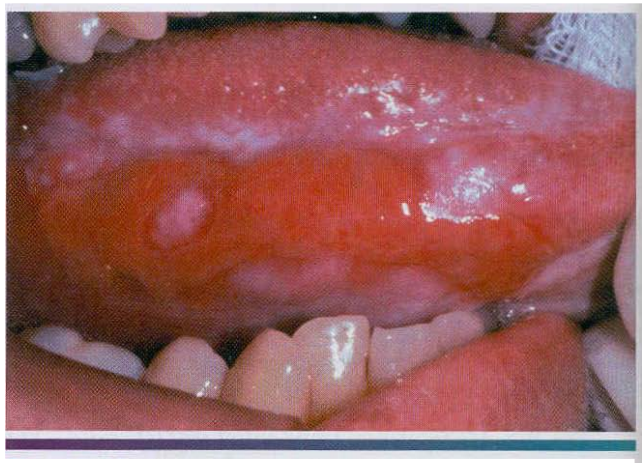

Figure 9-29 • Allergic mucosal reaction to systemic drug administration. Large irregular erosion of the right ventral surface of the tongue. The lesion arose secondary to use of oxeprozln. a nonsteroidal anti-inflammatory drug.

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 suspected 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, 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 resolution of the medication and recur upon reintroduction of the agent. Presumptive diagnosis is usually sufficient and justified when the mucosal alterations clear after cessation of the offending medication.

In suspected lupus-like drug reactions, serum evaluation for generic antinuclear antibodies (ANA) and antibodies against double-stranded DNA and histones often can be beneficial. Lupus-like drug reactions are typically associated with circulating generic ANA and antibodies against histoncs, whereas lupus erythematosus reveals antibodies to doubled-stranded DNA (a finding not typically noted in drug reactions).

Treatment and Prognosis

The responsible medication should be discontinued and. il necessary. replaced with another drug that provides a similar therapeutic result. Localized acute reactions can be resolved with topical corticosteroids. When systemic marufestations arc 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; corticosteroids. however. 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 compounds. cinnamon and amalgam. 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 anyone antigen from this contact appears to be rare. This was verified in a prospective study of 13.325 dental patients. in which only 7 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 probably because of the following;

- The period of contact is often brief.
- The saliva dilutes and removes many antigens.
- The anatomy of the mucosa allows rapid dispersal and absorption of antigens.
- 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 mayor may not demonstrate future clinical sensitlzation. In contrast. if the mucosa is sensitized initially. the skin usually demonstrates similar changes with future exposure.

In reviews of patients referred to allergy clinics with a preliminary diagnosis of hypersensitivity to dental materials. a small minority were definitively diagnosed as being allergic to a dental material. Positive skin test results to dental materials are insufficient for diagnosis because of the aforementioned lesser reactivity of the oral mucosa. Positive allergic history and skin tests become relevant only after a good state of oral health has been obtained. with no periodontal, endodontic. or occlusai problems. (Many symptoms thought to be caused by allergies to dental materiais are due to primary dental pathologic conditions.l

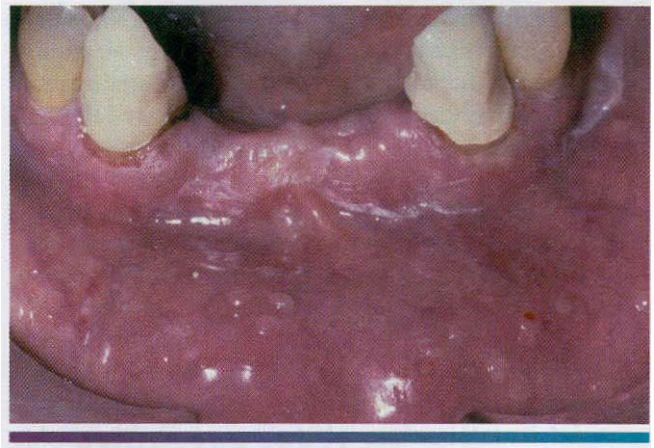

figure 9-30 • Allergic contact stomatitis to aluminum chloride. Mucosal erythema and vesicles of the lower labial mucosa caused by use of aluminum chloride on gingival retraction cord.

In addition to oral lesions. allergic contact reactions may produce exfoliative cheilitis (see page 266) 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 arc 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.

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 (Figure 9-30). 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 (Figure 9-31). 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 1411).

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. 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, 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.

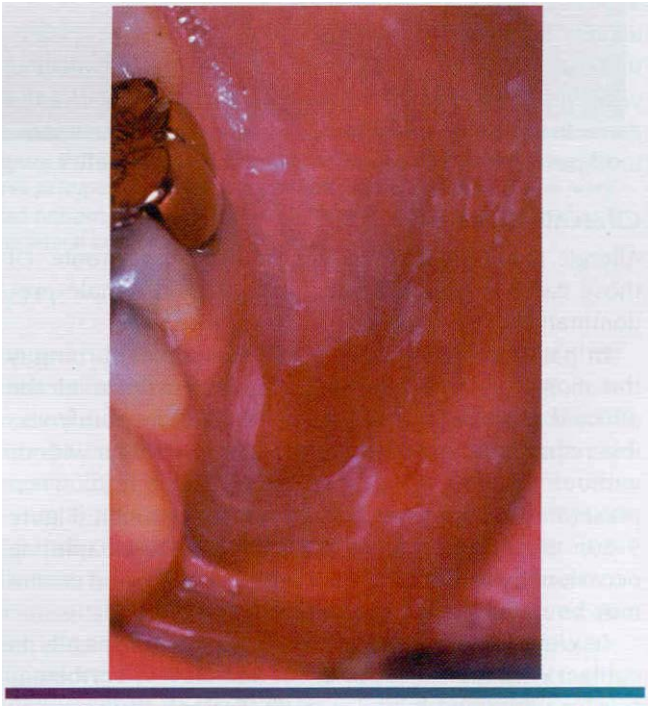

Figure 9-31 • Allergic contact stomatitis to toothpaste. Erythematous mucosa with superficial epithelial desquamation.

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 (e.g.. dyclonine HCn. is usually beneficial. **Chronic reactions respond *to* removal of the antigenic** source and application of a topical corticosteroid such as fluocinonide gel or dexamethasone elixir.

PERIORAL DERMATITIS

Perioral dermatitis refers to a unique inflammatory skin disease that involves the circumoral area. Although the **exact mechanism is uncertain, many investigators believe the process arises from an idiosyncratic response to a variety of exogenous substances: once this process is initiated, potent topical corticosteroid use worsens the** condition. Although the vast majority of affected patients **report topical corticosteroid use, only a minority initiate** this therapy before initial development of the dermatitis. Exogenous substances reported to initiate the rash include tartar-control toothpaste, bubble gum, moisturizers. night creams, and other cosmetic products (e.g.. foundation). 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 and papulopustulcs that involve the skin surrounding the vermilion border of the upper and lower lips (Figure 9-32). Ciassically. there is a zone of spared skin immediately adjacent to the vermilion border. Pruritus is variable. In adults. over 90% of affected patients are **women. lending further support to the association with cosmetic use. The prevalence of perioral dermatitis**

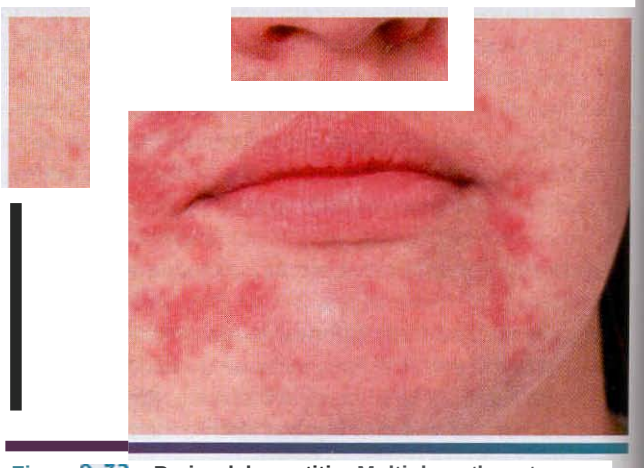

Figure 9-32 • Perioral dermatitis. Multiple erythematous papules of the skin surrounding the vermilion border of the lips. **(Courtesy of Dr. Charlie Camisa.)**

appears to be increasing and may be related to the greater percentage of cosmetic-wearing women in the workforce. In children. the female predominance is dramatically reduced or is nonexistent in some studies. In addition. an identical pattern of periorbital and perinasal dermatitis is often present in younger patients with classic perioral lesions.

Some investigators have reported perioral dermatitis that has arisen solely from use of tartar-control toothpaste (irritant contact dermatitis from pyrophosphate compounds), but ciose inspection reveals a different clinical presentation. In these reports. the dermatitis appears as a zone of erythema without papules or pustules; it involves only the skin immediately adjacent to the vermilion border. without the classic sparing of this area. This pathosis is classified most appropriately as circumorai dermatitis and does not fulfill the classic criteria for perioral dermatitis.

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

The first step in management is discontinuation of potent topical corticosteroid use. if present. Often this is followed by period of exacerbation. Topical metronidazole is typically prescribed with or without a course of peroral tetracycline, with erythromycin substituted in children. The topical metronidazole is continued until the dermatitis resolves. Other therapies used less frequently include topical erythromycin. sulfacetamide. and 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 widely recognized 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.

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 141); enlargement, edema, and erythema are common. Erythematous mucositis. occasionally combined with desquamation and 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 do not typically 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 (Figure 9-33). 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 may occasionally resemble the pattern seen in morsicatio (see page 253). Lingual involvement may become extensive and spread to the dorsal surface (Figure 9-34). Significant thickening of the surface epithelium can occur and may raise clinical concern for oral hairy leukoplakia (see page 241) or carcinoma (Figure 9-35).

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 are often present. The superficial lamina propria

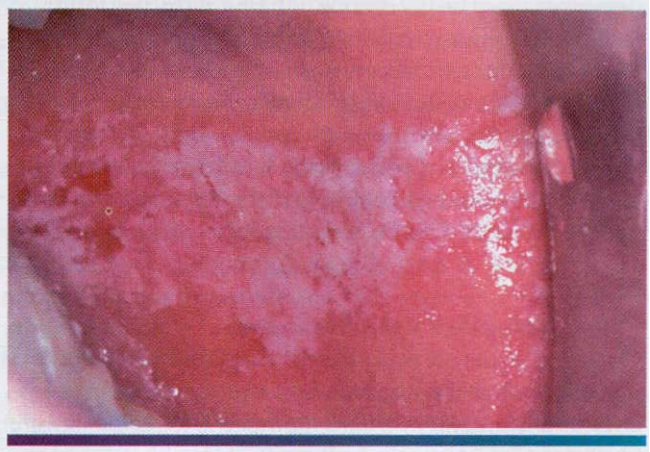

Figure 9-33 • Contact stomatitis from cinnamon flavoring. Oblong area of sensitive erythema with overlying shaggy hyperkeratosis.

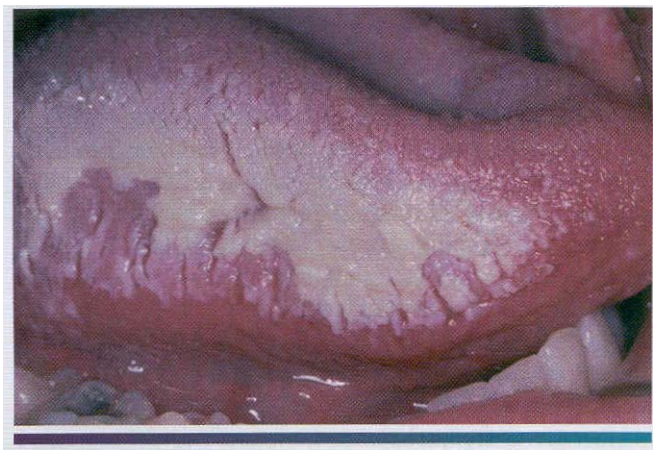

Figure 9-34. Contact stomatitis from cinnamon flavoring. Sensitive and thickened hyperkeratosis of the lateral and dorsal surface of the tongue on the right side.

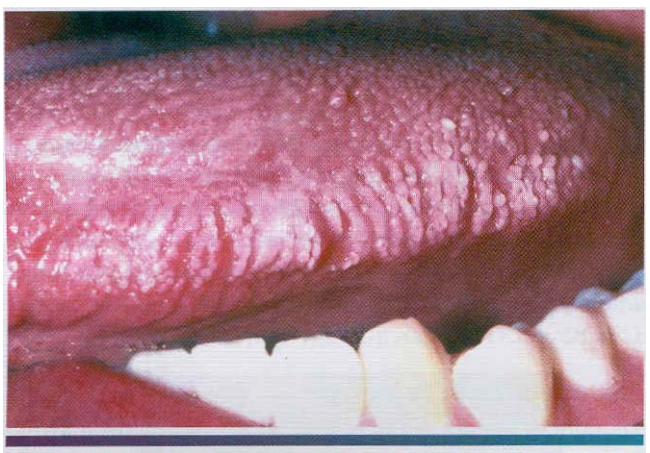

Figure 9-35. Contact stomatitis from cinnamon flavoring. left lateral border of the tongue demonstrating linear rows of hyperkeratosis that resemble oral hairy leukoplakia.

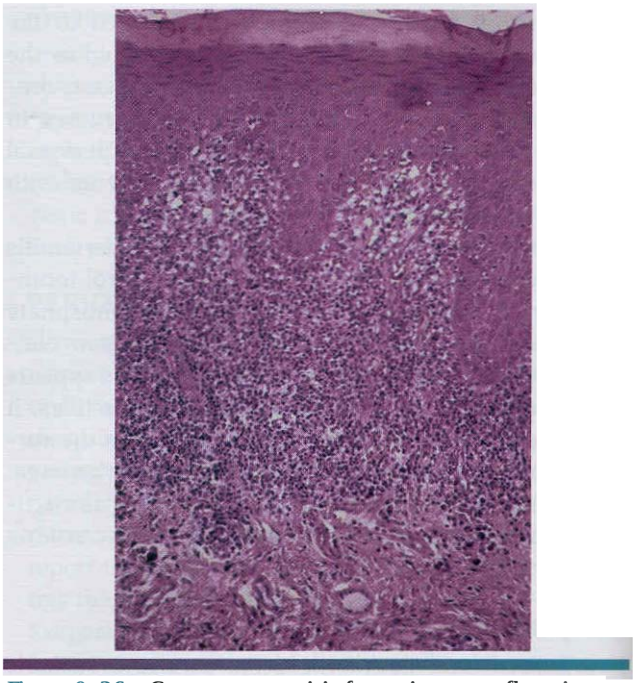

Figure 9-36 • Contact stomatitis from cinnamon flavoring. Oral mucosa demonstrating exocytosis and significant interface mucositis.

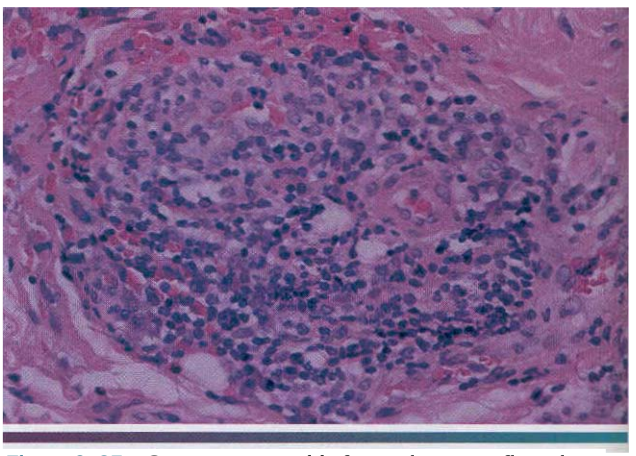

Figure 9-37 • Contact stomatitis from cinnamon flavoring. Perivascular inflammatory infiltrate consisting predominantly of lymphocytes and plasma cells.

demonstrates a heavy chronic inflammatory cell infiltrate that predominantly consists of lymphocytes. This infiltrate often obscures the epithelium and connective tissue interface (Figure 9-36). A characteristic feature is the presence of an obvious perivascular infiltrate of lymphocytes, with occasional plasma cells and rare eosinophils, which extends well below the superficial inflammatory infiltrate (Figure 9-37).

Diagnosis

With a high index of suspicion and a knowledge of the variations of the clinical pattern, the diagnosis of 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.

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, the lesions reappear, usually within 24 hours.

CHRONIC ORAL MUCOSAL CONTACT REACTIONS TO DENTAL AMALGAM

Since the nineteenth century when dental amalgam began to have widespread use, the material has been associated in the lay press with almost every medical ailment known to man. Such accusations tend to occur in cycles. Mercury within amalgam has been accused of producing neurotoxicity. kidney dysfunction. reduced immunocompetence, alterations of oral and intestinal bacteria. birth defects, and adverse effects on general health. In spite of intense scrutiny. there appears to be no relationship between any of these physical disorders and the use of amalgam restorations. An Investigation of patients with concerns associated with their amalgam restorations reveals that most of their complaints *can* be associated with oral. dental. or medical problems unrelated to the restorations.

A review of the ill effects of mercury in dental amalgam demonstrates that the occurrence of toxicity is negligible. but a small percentage (1% to 2%) of those who are allergic to mercury can react to the mercury released from dental amalgams. The frequency of adverse effects to dental amalgam is estimated to be one case per million. Acute hypersensitivity reactions typically appear 2 to 24 hours after the removal and replacement of dental amalgam. and the symptoms disappear after to to 14 days.

Rarely. chronic reactions also can occur and may be from hypersensitivity or a chronic toxic reaction. when the reaction is related to hypersensitivity. the most frequent antigen is mercury or a mercury compound: rarely, copper. palladium. silver. tin. or zinc is responsible. Some investigators have called these alterations "galvanic lesions" and have suggested that the changes develop from electrical currents *developed* between *restorative* metals. *However,* neither clinical nor experimental studies support the electrogalvanic hypothesis of origin.

The lesions appear clinically and histopathologically similar to lichen planus (see page 680) but demonstrate a difference in evolution. When patients with true oral lichen planus are examined. no evidence of a significantly increased hypersensitivity to dental restorative materials can be found, and these patients exhibit minimal to no clinical improvement upon removal of their amalgams.

However. within the population of patients with conditions previously diagnosed as lichenoid lesions, there is a subgroup whose lesions do not migrate and usually *involve* only the mucosa directly in contact with dental amalgams. These lesions resolve rapidly after removal of adjacent amalgams and should be diagnosed as a contact lichenoid reaction to amalgam. not as true lichen planus.

When patch tested for mercury. approximately SO% of patients with contact lichenoid reactions reveal positivity: this compares with less than 5% noted in normal controls and patients with conventional idiopathic lichen planus. Although the percentage of patients having skin test reactivity dramatically exceeds that noted in control populations. the number initially demonstrating no response is surprising. This discrepancy may be the result of contact reactions that arise from direct toxicity or from an allergic contact reaction to another substance within amalgam other than mercury.

Clinical Features

The most commonly affected sites in contact reactions to amalgam are the posterior buccal mucosa and the *ventral* surface of the lateral borders of the tongue. Gingival cuffs adjacent to subgingival amalgams also may be affected. The lesions are usually confined to the area of contact and may be white or erythematous with or without peripheral striae (Figure 9-38). Most patients have no symptoms. but periodic erosion may be noted.

Diagnosis

The diagnosis is made from the clinical appearance of the lesions. the lack of migration, and the correlation to adjacent amalgams (Figure 9-39). Although the histopathologic features may be indistinguishable from lichen planus. biopsy is occasionally performed to confirm the clinical impression and to rule out other pathoses (e.g.. epithelial dysplasia). In the past, skin testing to mercury has been stressed as an important diagnostic procedure. but numerous subsequent investigators have failed to demonstrate positive reactivity in the majority of affected patients. Therefore. the diagnosis is made best by correlating the clinical presentation with the histopathologic features, irrespective of results of patch testing for mercury sensitivity.

Histopathologic Features

Biopsy material from contact reactions to amalgam exhibits numerous features of lichen planus. The surface epithelium may be hyperkeratotic. atrophic, or ulcerated. Areas of hydropic degeneration of the basal cell layer are often 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.

Treatment and Prognosis

Local measures. such as improved oral hygiene. smoothing, polishing. and recontouring, should be attempted before more aggressive measures, because clinically similar lesions have been noted as a result of surface plaque accu-

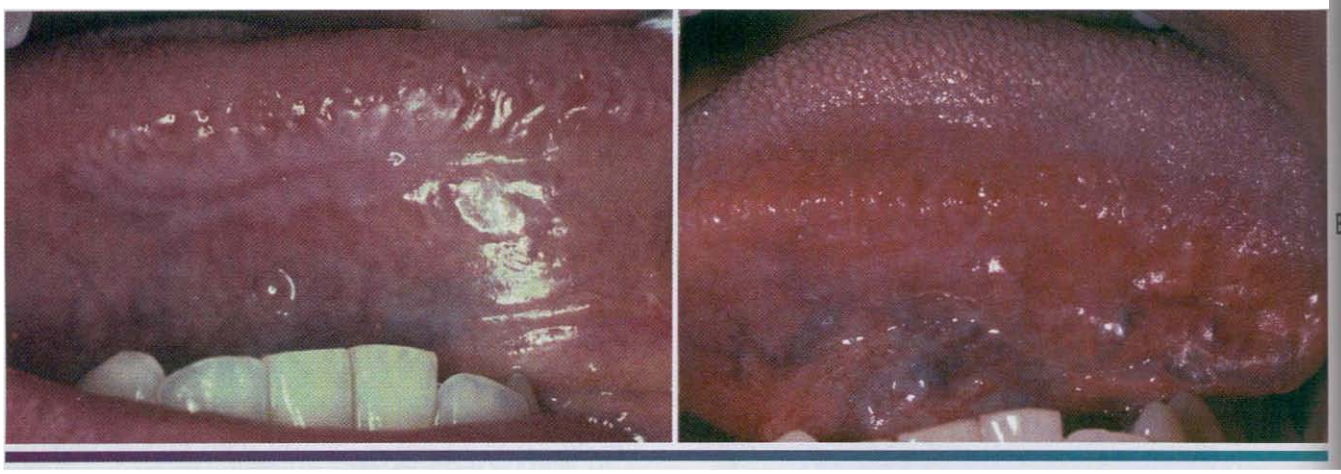

Figure 9-38 • Oral mucosal contact reaction to dental amalgam. A. Hyperkeratotic lesion with a peripheral radiating pattern on the lateral border of the tongue on the right side; the altered mucosa contacted the amalgams of the adjacent mandibular molar teeth. The lesion remained in the same location 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.

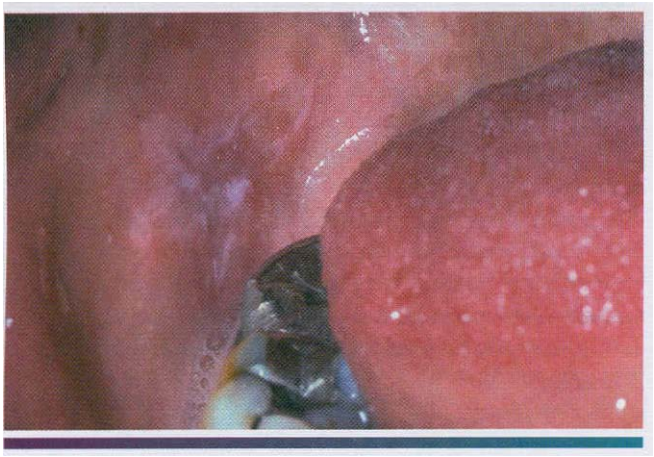

Figure 9-39 • Oral mucosal contact reaction to dental amalgam. Radiating pattern of hyperkeratotic striae on the posterior buccal mucosa that contacts a large distobuccal amalgam of the permanent mandibular second molar

mulation. If this is unsuccessful, the amalgam in question should be replaced with a nonmetallic restoration, if possible. Other material choices include yellow gold, white gold, and porcelain-fused-to-metal (PFM) crowns.

In one study of 142 patients with lichenoid contact reactions, the offending amalgams were replaced with either yellow gold or PFM crowns. In this group, all mucosal lesions dramatically improved or resolved in patients who received gold crowns, whereas 95% of the lesions responded positively to the placement of PFM crowns. However, in other studies, uncommon failures were reported when yellow gold crowns were used.

Even if the lichenoid contact reaction was not present, replacement of the offending amalgam is typically beneficial in most patients, because many of these teeth have large buccal extensions and would benefit from restoration replacement. The reported prevalence of mucosal healing after replacement of the adjacent amalgam in patients with lichenoid contact reactions *varies* from 87% to 100%. Although the number of lesions that fail to respond is low, many of the nonresponders are most likely due to inappropriate selections of the replacement material. A small number of investigators have reported recurrence after replacement with composite resin, but others *believe* that this phenomenon is due to subsequent plaque accumulation and not true recurrence. A biopsy is recommended if the clinical diagnosis is in question or if the mucosal changes do not respond to the recommended therapy.

ANGIOEDEMA (ANGIONEUROTIC EDEMA; QUINCKE'S 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's 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.

Knowledge of the mechanisms of angioedema has increased significantly. These advances have allowed us

to appreciate the fact that the disorder is much more complicated than originally thought. but such insights have directly influenced therapeutic approaches. 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 tgE isthetype associated with use of drugs called angioten sinconverting enzyme (ACE) inhibitors. These medications are a popular treatment of essential hypertension and chronic heart failure; commonly prescribed ACE inhibitors include captoprtl, enalaprIl. and lisinopri!. The drugs apparently cause angioedema because of increased levels of bradykinin. and the swelling does not respond well to antihistamines. 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 7 years. Attacks precipitated by dental procedures have been reported in long-term users of ACE inhibitors.

In addition. angioedema can result from activation of the complement pathway. This may be hereditary or acquired. Two rare autosomal dominant hereditary forms areseen. Type I. comprising 85% of the hereditary cases. iscaused by a quantitative reduction in the inhibitor that **prevents the transformation of CI to CI esterase.** Without adequate levels of this inhibitor (CI-INH). CI esterase cleaves C4 and C2 and results in angioedema. Type II exhibits normal levels of CI-INH. but the inhibitor is dysfunctiona!.

The acquired type of CI-INH deficiency is seen in association with certain types of lymphoproliferative diseases or in patients who develop specific autoantibodies. Thelymphoid proliferation increases the consumption of CI-INH. and the autoantibodies prevent binding of CI-iNH to CI. In both the acquired and hereditary forms **of abnormal CI-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. viral or bacterial infections) and in patients with grossly elevated peripheral blood eosinophil **counts.**

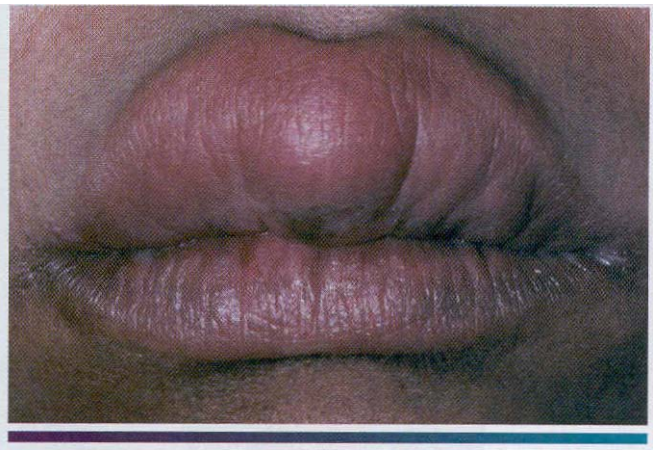

Figure 9-40 • Angioedema. Diffuse upper lip swelling that arose rapidly.

Clinical Features

Angioedema is characterized by the relatively rapid onset of soft. nontender tissue swelling. which may be solitary or multiple and most commonly involves the face. lips. tongue. pharynx. and larynx (Figure 9-40). Involvement **of the skin and mucous membranes can cause enlargements that may measure up to several** centimeters **in** diameter (Figure 9-41). In addition to the face, other sites of dermatologic involvement include the hands. arms. legs. genitals. and buttocks. Although pain is unusual. itching is common and erythema may be present. The enlargement typically resolves over 24 to 72 hours.

Involvement of the respiratory and gastrointestinal systems occurs mainly in the hereditary forms. In these forms. most affected patients become symptomatic during the second decade of life and then follow a highly **variable frequency of recurrences. Most attacks occur** without apparent reason. Gastrointestinal symptoms **may mimic surgical emergencies and include continuous** pain, vomiting. and (rarely) watery diarrhea. Respiratory involvement centers on the upper airway (pharynx and larynx) and can be life threatening if the patient's airway becomes closed; hoarseness and difficulty in swallowing or breathing are important signs. Laryngeal involvement also is not unusual in cases related to ACE inhibitors.

Perioral and periorbital involvement is typical of allergic angioedema. In addition. allergic angioedema and the type that is related to ACE inhibitors frequently demonstrate intraoral involvement, which can affect the lips. tongue. uvula, floor of the mouth. or facial cheek areas.

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

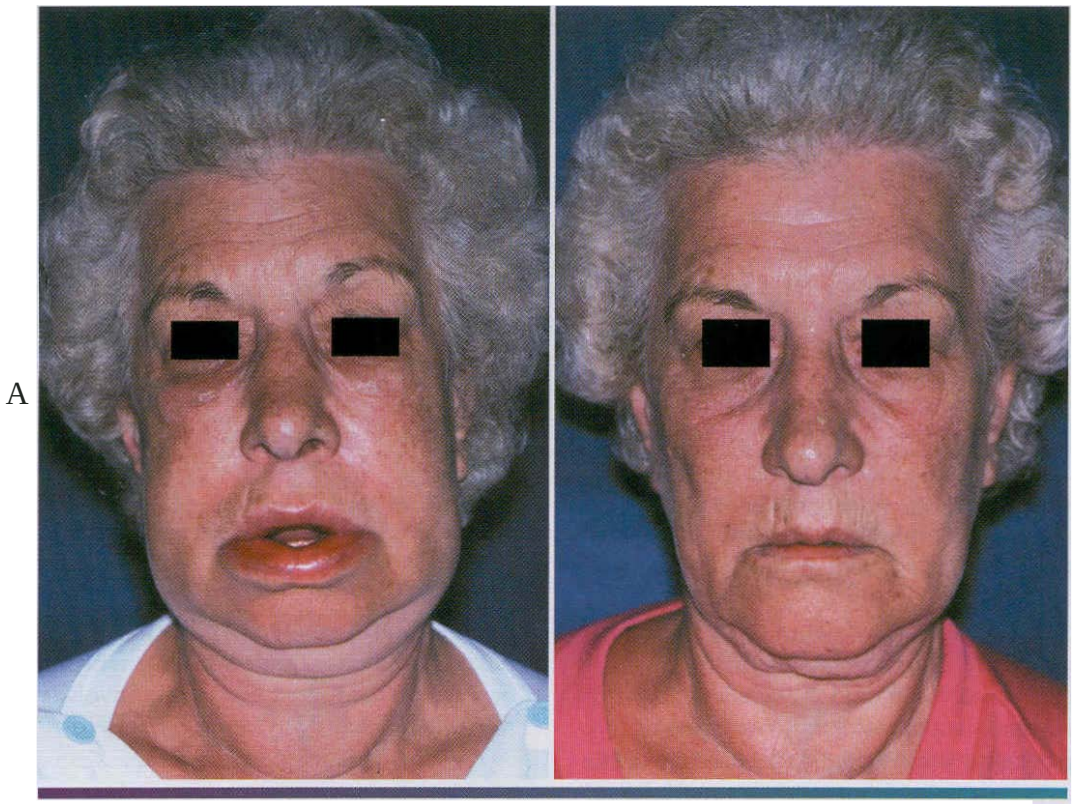

Figure 9-41 • **Angioedema. A, Soft. nontender tissue swelling of the face arose relatively rapidly after dental treatment. B, Facial appearance after resolution of edematous facial enlargement.**

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 CI-INH. In the hereditary types. both forms exhibit normal levels of CI and decreased levels of *functional* CI-INH. Type I demonstrates a decreased quantity of CI-INH; type II exhibits normal levels of the inhibitor (but it is not functional). Both acquired forms demonstrate low levels of both CI-INH and Ci.

Treatment and Prognosis

The treatment of angioedema usually consists of oral antihistamines. **If** the attack is not controlled or if **laryngeal involvement is present. intramuscular epinephrine** should be administered. If the epinephrine does not stop **the attack. intravenous corticosteroids and antihistamines** should be given. Cases of angioedema related to ACE inhibitors arc not IgE-mediated and may not respond **to antihistamines and corticosteroids. Because the** airway may have to be opened. affected patients are kept under close observation until the swelling begins to subside. If angioedema has been associated with use of a particular ACE inhibitor. all types of ACE inhibitors should be avoided in the future.

Those cases related to CI-INH deficiency do not **respond to antihistamines, corticosteroids, or adrenergic drugs.** 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 CI-INH but also potentially harmful CI esterase. CI. C2, and C4. **CI-INH concentrate and esterase-inhibiting drugs** (aprotinin or tranexamic acid) arc the treatments of **choice for acute attacks. Because acute attacks of** hereditary angioedema arc not only unpleasant but also potentially life threatening, prevention is paramount. Patients should avoid violent physical activity and trauma. Medical prophylaxis is recommended before any dental or surgical procedure. **All** patients should carry medical warning cards that state the diagnosis and list elementary precautions. Prophylaxis for CI-INH deficiency is recommended in patients who have more than three attacks per year. Androgens induce hepatic synthesis of CI-INH, and either of the attenuated androgens (danazol or stanozolol) is used for both the hereditary forms and the acquired type that is related to lymphoproliferative disorders. The autoimmune acquired type is best prevented through the use **of corticosteroids.**

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CHAPTER 10

Epithelial Pathology

CHAPTER OUTLINE

SQUAMOUS PAPILLOMA

The squamous papilloma is a benign proliferation of stratified squamous epithelium, resulting in a papillary or verruciform mass. Presumably, this lesion is induced by the human papillomavirus (HPV). HPV comprises a large family (more than 100 types) of double-stranded DNA viruses of the papovavirus subgroup A. Recent research has shown that 81% of normal adults have buccal epithelial cells that contain at least one type of HPV, although case control studies using more rigorous criteria have usually shown distinct differences, with high levels of HPV in oral lesions and low levels in normal controls.

The virus is capable of becoming totally integrated with the DNA of the host cell, and at least 24 types are associated with lesions of the head and neck. HPV can be identified by *in situ* hybridization, immunohistochemical analysis, and polymerase chain reaction (PCR) techniques, but it is not visible with routine histopathologic staining. Viral subtypes 6 and 11 have been identified in up to 50% of oral papillomas, as compared with less than 5% in normal mucosal cells.

The exact mode of transmission is unknown. In contrast to other HPV-induced lesions, the viruses in this lesion appear to have an extremely low virulence and infectivity rate. A latency or incubation period of 3 to 11 months has been suggested. The squamous papilloma occurs in one of every 250 adults and makes up approximately 3% of all oral lesions submitted for biopsy.

Clinical Features

The squamous papilloma occurs with equal frequency in both men and women. Some authors have asserted that it develops predominantly in children, but epidemiologic studies indicate that it can arise at any age and, in fact, is diagnosed most often in persons 30 to 50 years of age. Sites of predilection include the tongue, lips, and soft palate, but any oral surface may be affected. This lesion is the most common of the soft tissue masses arising from the soft palate.

The squamous papilloma is a soft, painless, usually pedunculated, exophytic nodule with numerous finger-like surface projections that impart a "cauliflower" or wartlike appearance (Figure 10-1). Projections may be pointed or blunted (Figures 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 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 317), condyloma

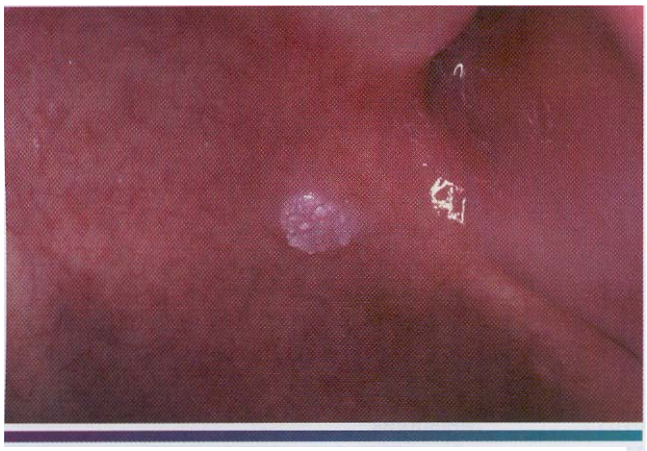

Figure 10-1 • **Squamous papilloma.** An exophytic lesion of the soft palate with multiple short, white surface projections.

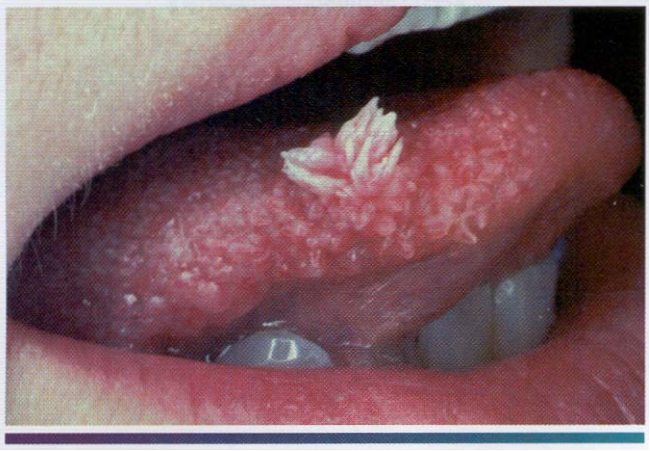

Figure 10-2 • **Squamous papilloma.** A pedunculated lingual mass with numerous long, pointed, and white surface projections. Note the smaller projections around the base of the lesion.

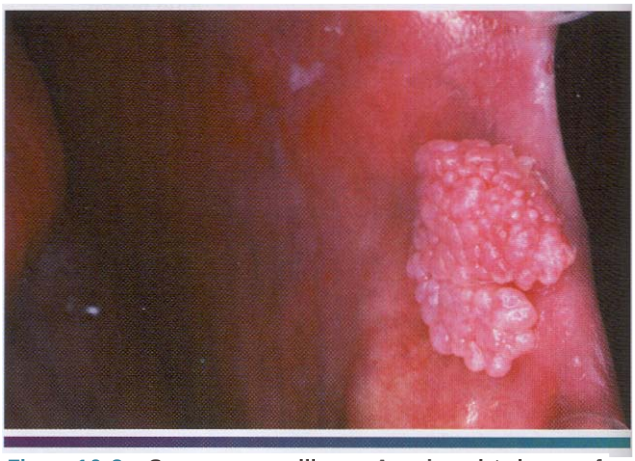

Figure 10-3 • **Squamous papilloma.** A pedunculated mass of the buccal commissure, exhibiting short or blunted surface projections and minimal white coloration.

acuminatum (see page 318), verruciform xanthoma (see page 324), or focal epithelial hyperplasia (see page 320), In addition. extensive coalescing papillary lesions (papillomatosis) of the oral mucosa may be seen in several skin disorders. including nevus unius lateris, acanthosis nlgrtcans, and focal dermal hypoplasia (Goltz-Gorll nl syndrome. Laryngeal papillomatosis. a rare and potentially devastating disease of the larynx and hypopharynx. has 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.

Histopathologic Features

The papilloma is characterized by a proliferation of keratinized stratified squamous epithelium arrayed in finger-like **projections with fibrovascular connective tissue cores** (Figure 10-4). The connective tissue cores may show inflammatory changes. depending on the amount of trauma sustained by the lesion. The keratin layer is thickened in lesions with a whiter clinical appearance. and the epithelium typically shows a normal maturation pattern (Figure 10-5). Occasional papillomas demonstrate basilar hyperplasia and mitotic activity. which can be mistaken lor mild epithelial dysplasia. Koilocytes. virus-altered epithelial clear cells with small dark (pyknotic) nuclei. are sometimes seen high in the prickle 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 transformation into malignancy, continuous enlargement. or dissemination to other parts of the oral cavity.

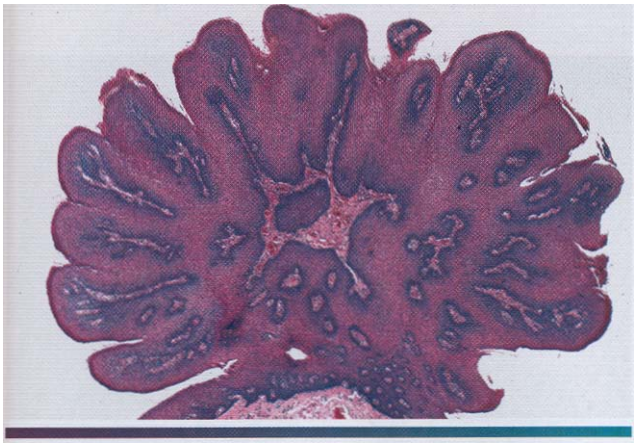

Figure 10-4 • Squamous papilloma. Low-power view showing a pedunculated squamous epithelial proliferation. There are multiple papillary projections with fibrovascular connective tissue cores.

Iuvenile-onset laryngeal papillomatosis tends to be continuously proliferative. sometimes leading to death by asphyxiation. The papillomatosis is treated by repeated surgical debulking procedures to relieve airway obstruction. Adult-onset lesions are typically less aggressive and tend to be single. Conservative surgical ***removal*** **may be necessary to eliminate hoarseness from vocal cord involvement. In rare instances, squamous cell** carcinoma will develop in long-standing laryngeal papil-**lomatosis, sometimes in a smoker or a patient with a his-**tory of irradiation to the larynx.

VERRUCA VULGARIS (COMMON WART)

Verruca vulgaris is a benign. virus-induced. focal hyperplasia of stratified squamous epithelium. One or more of the associated human papillomavirus (HPV) types 2. 4. 6. and 40 are found in virtually all examples. Verruca vulgaris is contagious and can spread to other parts of a **person's skin or mucous membranes by way of auto-**inoculation. It infrequently develops on oral mucosa but **is extremely common on the skin.**

Clinical Features

Verruca vulgaris is frequently discovered in children. but occasional lesions may arise even into middle age. The skin of the hands is usually the site of infection (Figure 10-6). When the oral mucosa is involved. the lesions arc usually found on the vermilion border. labial mucosa. or **anterior tongue,**

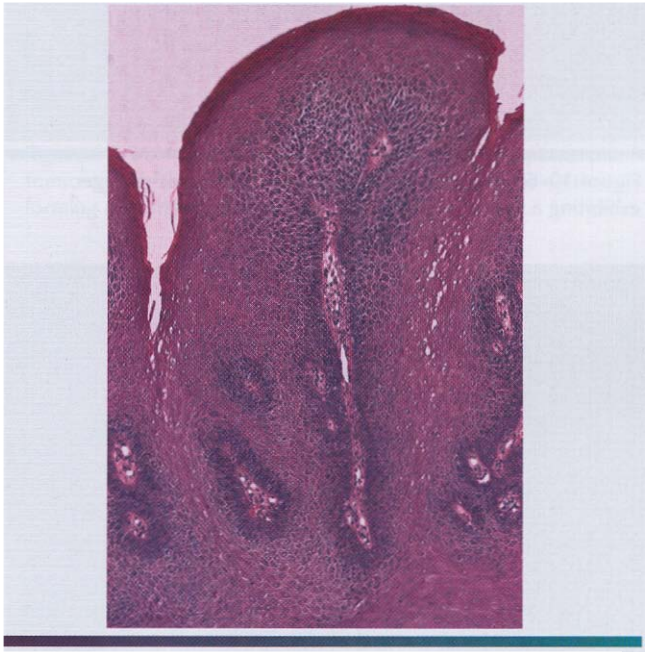

Figure 10-S • Squamous papilloma. The tip of a papillary projection shows mature stratified squamous epithelium with a slightly thickened parakeratin surface layer.

Typically, the verruca appears as a painless papule or nodule with papillary projections or a rough pebbly surface (Figure 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 less than 5 mrnl, 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 several millimeters in height. termed a cutaneous horn or keratin horn. Other cutaneous lesions. including seborrheic keratosis (see page 325). actinic keratosis (see page 351), and squamous cell carcinoma. may also create a cutaneous horn.

Histopathologic Features

The verruca vulgaris is characterized by a proliferation of hyperkeratotic stratified squamous epithelium arranged into fingerlike or pointed projections with connective tissue cores (Figure 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 are often seen in the superficial spinous layer. Koilocytes are HPV-altered epithelial cells with perinuclear clear spaces and small. dark nuclei (pyknosis). Eosinophilic intranuclear viral inclusions are often noted within the cells *at* the granular layer.

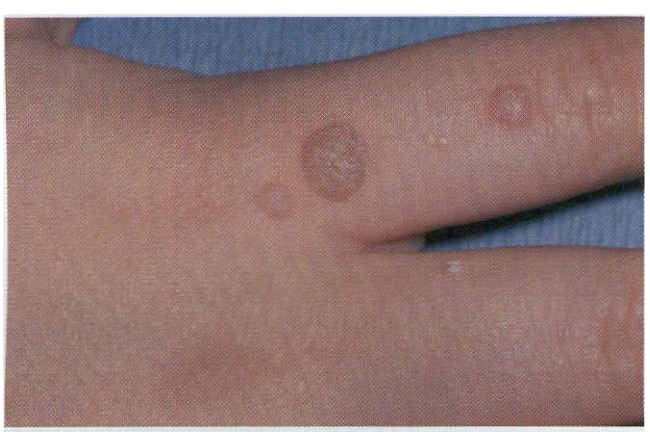

Figure 10-6 • Verruca vulgaris. Several warts on the finger, exhibiting a rough, papillary surface.

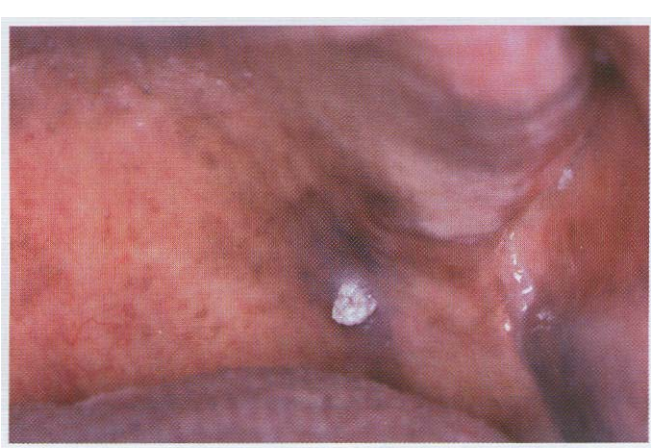

Figure 10-7 • Verruca vulgaris. Exophytic. white. papillary lesion of the lateral soft palate.

Treatment and Prognosis

Skin verrucae are treated effectively by liquid nitrogen cryotherapy. conservative surgical excision or curettage. or topical application *at* keratinolytic agents (usually containing salicylic acid and lactic acid), Oral lesions are usually surgically excised, 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 it to slough away. All destructive or surgical treatments should extend to include 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 virus-induced proliferation of stratified squamous epithelium of the genitalia, perianal region, mouth, and larynx. One or more of the HPV types 2, 6. 11,53, and 54 are usually detected in the lesion. However, the high-risk types 16 and 18 also are found with frequency. especially in anogenital lesions.

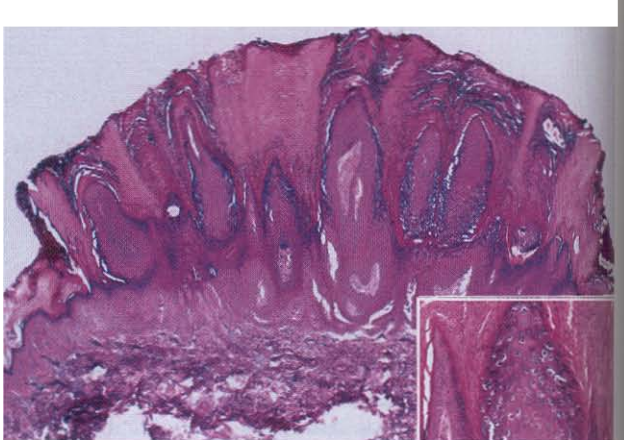

Figure 10-8 • Verruca vulgaris. Numerous papillary projections are covered by hyperkeratotic stratified squamous epithelium. Elongated rete ridges at the edge of the lesion converge toward the center. The inset shows clear koilocytes in the upper epithelial layers.

Condyloma is considered to be a sexually transmitted disease (STD), with lesions developing at a site of sexual contact or trauma. This lesion represents 20% of all STDs diagnosed in STD clinics and may be an indicator of sexual abuse when diagnosed in young children. It is not unusual for oral and anogenital condylomata to be present concurrently.

The incubation period for a condyloma is 1 to 3 months from the time of sexual contact. Once present, autoinoculation to other mucosal sites is possible.

Clinical Features

Condylomata are usually diagnosed in teenagers and young adults, but people of all ages are susceptible. Oral lesions most frequently occur on the labial mucosa, soft palate, and lingual frenum. The typical condyloma appears as a sessile, pink, well-demarcated, nontender exophytic mass with short, blunted surface projections (Figure 10-9). The condyloma tends to be larger than the papilloma and is characteristically clustered with other condylomata. The average lesional size is 1.0 to 1.5 ern, but oral lesions as large as 3 em have been reported.

Histopathologic Features

Condyloma acuminatum appears as a benign proliferation of acanthotic stratified squamous epithelium with mildly keratotic papillary surface projections (Figure 10-10). Thin connective tissue cores support the papillary epithelial projections, which are more blunted and broader than those of squamous papilloma and verruca vulgaris, imparting an appearance of keratin-filled crypts between prominences.

The covering epithelium is mature and differentiated, but the prickle cells often demonstrate pyknotic nuclei surrounded by clear zones (kollocytes), a microscopic feature of HPV infection (Figure 10-11). Ultrastructural examination reveals vmons within the cytoplasm or nuclei of kollocytes, and the virus also can be demonstrated by immunohistochemical analysis, *in situ* hybridization, and PCR techniques.

Treatment and Prognosis

The oral condyloma is usually treated by conservative surgical excision. Laser ablation also has been used, but this treatment has raised some question as to the airborne spread of HPV through the aerosolized microdroplets created by the vaporization of lesional tissue. Regardless of the method used, a condyloma should be removed because it is contagious and can spread to other oral surfaces and to other persons through direct (usually sexual) contact. In the anogenital area, condylomata infected with HPV-16 or HPV-18 are associated with an increased risk of malignant transformation to squamous cell carcinoma, but this has not been demonstrated in oral lesions.

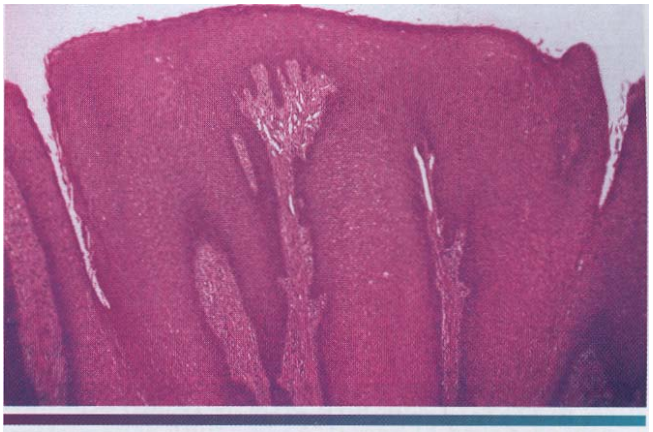

figure 10-10 . Condyloma acuminatum. Medium-power photomicrograph showing acanthotic stratified squamous epithelium forming a blunted projection.

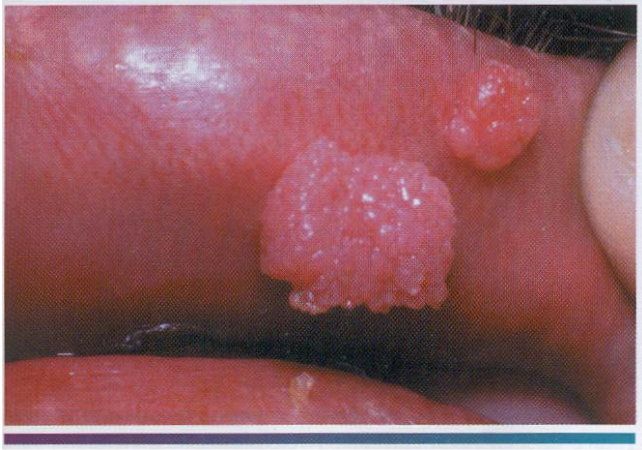

Figure 10·9 • Condyloma acuminatum. Two lesions of the upper lip mucosa exhibit short, blunted projections. (Courtesy of Dr. Brian Blochen)

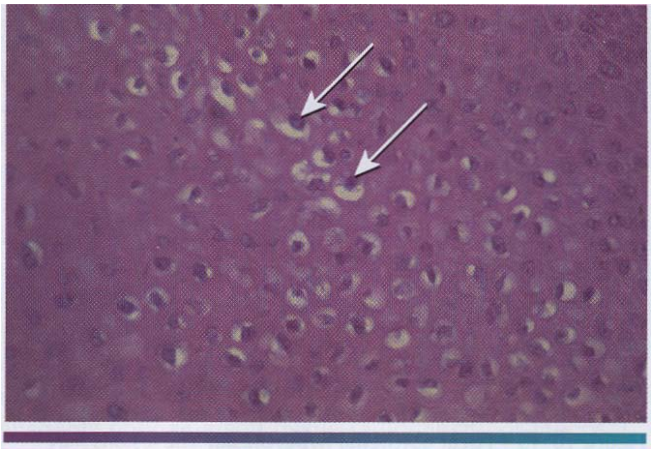

figure 10-11 • Condyloma acuminatum. High-power photomicrograph demonstrating koilocytes *(arrows)* in the spinous layer.

FOCAL EPITHELIAL HYPERPLASIA (HECK'S DISEASE; MULTIFOCAL PAPILLOMA VIRUS EPITHELIAL HYPERPLASIA)

Focal epithelial hyperplasia is a virus-induced, localized proliferation of oral squamous epithelium that was first described in native Americans and Inuits (Eskimos). Currently, it is known to exist in many populations and ethnic groups and is apparently produced by the human papillomavirus type 13 and possibly 32. In some populations, as many as 39% of children are affected. Multiple papillary lesions similar to focal epithelial hyperplasia arise with increased frequency in AIDS patients (see page 244).

Clinical Features

Usually a childhood condition, focal epithelial hyperplasia occasionally affects young and middle-aged adults. There is no gender bias. Sites of greatest involvement include the labial, buccal, and lingual mucosa, but gingival and tonsillar lesions also have been reported.

This disease typically appears as multiple soft, nontender, flattened or rounded papules, which are usually clustered and the color of normal mucosa, although they may be scattered, pale, or rarely white (Figure 10-12). Occasional lesions show a slight papillary surface change (Figure 10-13). Individual lesions are small (0.3 to 1.0 cm), discrete, and well demarcated, but they frequently cluster so closely together that the entire area takes on a cobblestone or fissured appearance.

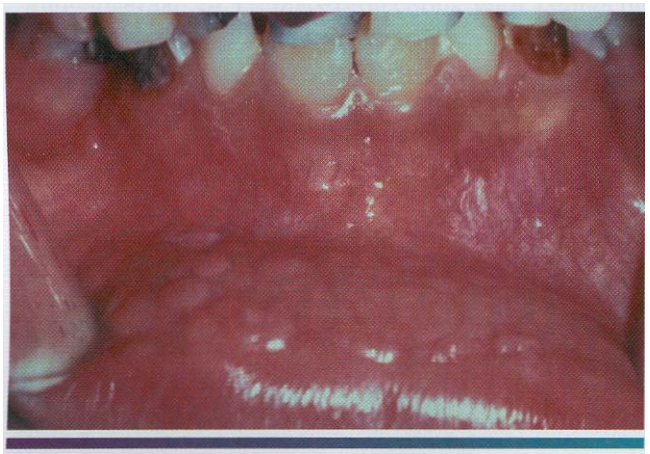

Figure 10-12 • Focal epithelial hyperplasia. Multiple, flat-topped papules and nodules of normal coloration are seen on the lower lip of a child.

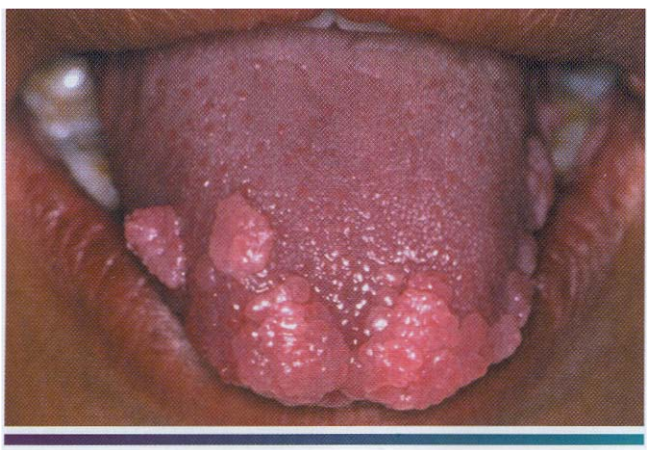

Figure 10-13 • Focal epithelial hyperplasia. The lesions may demonstrate a papillary surface change and paleness, as demonstrated on this child's tongue. (Courtesy of Dr. Román Carlos.)

Histopathologic Features

The hallmark of focal epithelial hyperplasia is an abrupt and sometimes considerable acanthosis of the oral epithelium (Figure 10-14). Because the thickened mucosa extends upward, not down into underlying connective tissues, the lesional rete ridges are at the same depth as the adjacent normal rete ridges. The ridges themselves are widened, often confluent, and sometimes club shaped. Some superficial keratinocytes show a koilocytic change similar to that seen in other HPV infections. Others occasionally demonstrate an altered nucleus that resembles a mitotic figure (mitosoid cell) (Figure 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 with both DNA *in situ* hybridization and immunohistochemical analysis.

Treatment and Prognosis

Spontaneous regression of focal epithelial hyperplasia has been reported after months or years and is inferred from the rarity of the disease in adults. Conservative surgical excision of lesions may be performed for diagnostic or aesthetic purposes. The risk of recurrence after this

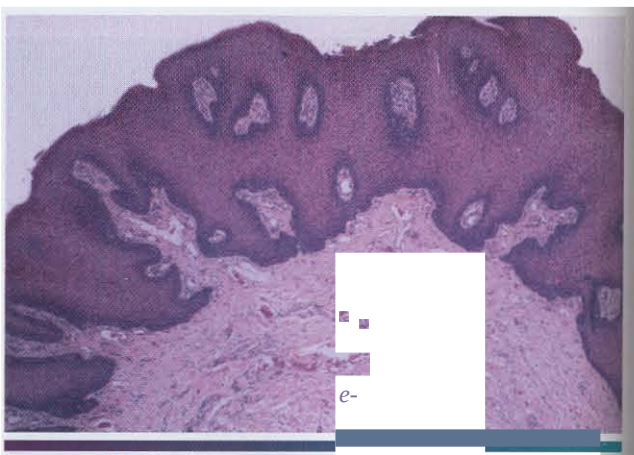

Figure 10-14. Focal epithelial hyperplasia. Prominent acanthosis of the epithelium with broad and elongated rete ridges. The slightly papillary surface alteration noted here may or may not be present.

therapy is minimal. and there seems to be no malignant transformation potential.

SINONASAL PAPILLOMAS

Papillomas of the sinonasal tract are benign. localized proliferations of the respiratory mucosa of this region. This mucosa gives rise to three histomorphologically distinct papillomas:

1. Fungiform
2. Inverted
3. Cylindrical cell

In addition. a keratinizing squamous papilloma, similar to the oral squamous papilloma (see page 316), may rarely occur in the nasal vestibule.

Collectively, sinonasal papillomas represent 10% to 25% of all tumors of the nasal and paranasal region. Half of the sinonasal papillomas arise from the mucosa of the lateral nasal wall: the remainder predominantly involves the maxillary and ethmoid sinuses and the nasal septum. Multiple lesions may be present.

The cause of sinonasal papillomas remains controversial and unclear. Some authorities say that these lesions represent neoplasms: others consider them to be a reactive hyperplasia secondary to a variety of environmental stimulants. such as allergy, chronic bacterial or viral (human papillomavirus [HPV] type 11) infection. and tobacco smoking.

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. Almost all examples** are positive for HPV type 6 or 11.

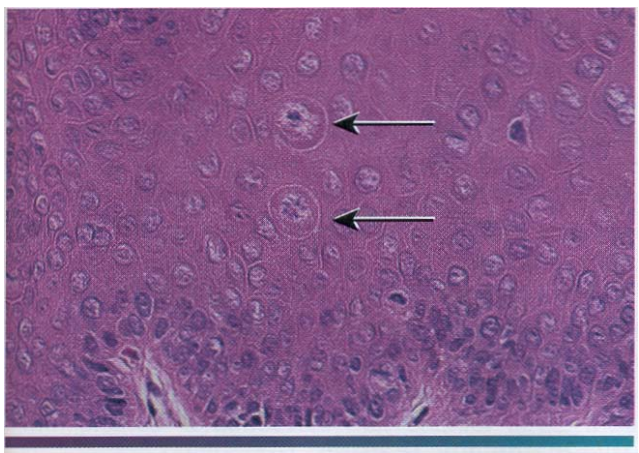

Figure 10-15 • **Focal epithelial hyperplasia. Mitosoid cells** *(arrows)* **contain altered nuclei in this otherwise mature and well-differentiated stratified squamous epithelium.**

Clinical Features

The fungiform papilloma arises almost exclusively on the **nasal septum and is twice** as common **in men as in women.** It occurs primarily in people 20 to 50 years of age. Typically, it exhibits unilateral nasal obstruction or epistaxis and appears as a pink or tan. broad-based nodule with papillary or warty surface projections.

Histopathologic Features

The fungiform papilloma has a microscopic appearance similar to that of the oral squamous papilloma, although the stratified squamous epithelium covering the finger-like 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 underlying **connective tissue 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 is common, developing in approximately one third of all cases: however, this may be caused by incomplete excision. Most **authorities consider this lesion to have minimal or no potential for malignant transformation.**

INVERTED PAPILLOMA (INVERTED SCHNEIDERIAN PAPILLOMA)

The most common (50% to 76%) sinonasal papilloma. the inverted papilloma, is also the variant with the greatest potential for local destruction and malignant transformation. HPV types 6, 11. and 16 have been identified in less than 7% of cases.

Clinical and Radiographic Features

The inverted papilloma seldom occurs in patients younger than 20 years of age; the median age is 55 years. A strong male predilection is noted (2:1 male-to-female ratio). This lesion arises predominantly from the lateral nasal cavity wall or a paranasal sinus, usually the antrum. Typically. the inverted papilloma results in unilateral nasal obstruction, but it may cause pain, epistaxis, purulent discharge, or local deformity. The papilloma appears as a soft, pink or tan. polypoid or nodular growth. Multiple lesions may be present.

Pressure erosion of the underlying bone is usually present and may be visible radiographically as an irregular **radiolucency. Primary sinus lesions may be distinguishable** only as a soft tissue radiodensity or mucosal thickening on radiographs; sinus involvement generally **represents extension from the nasal cavity. Magnetic** res-

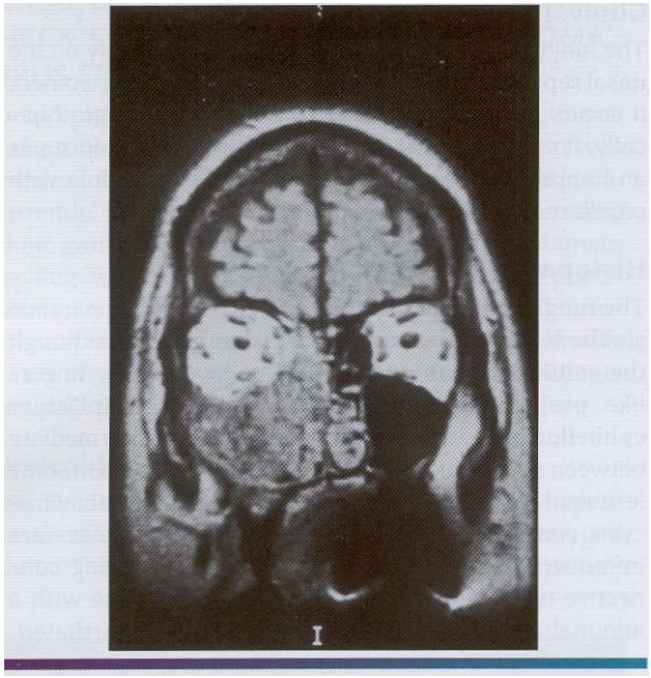

Figure 10-16. Inverted papilloma. T1-weighted coronal MRI showing a tumor of the right lateral nasal fossa. The tumor fills the right maxilla and ethmoid sinuses and involves the floor of the orbit. (Courtesy of Dr. Pamela VanTassel.)

onance imaging (MRI) can help to identify the extent of the lesion (Figure 10-16).

Histopathologic Features

Microscopically, the inverted papilloma is characterized by squamous epithelial proliferation into the submucosal stroma (Figure 10-17). The basement membrane remains intact, and the epithelium appears to be "pushing" into 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 dysplasia may be seen. Papillary surface projections are present and deep clefts may be seen between projections. The stroma consists of dense fibrous or loose myxomatous connective tissue with or without inflammatory cells. Destruction of underlying bone frequently is noted. Immunohistochemical expression of CD44, a cell adhesion molecule, is increased in this papilloma, which may help to distinguish it from invasive papillary squamous cell carcinoma, which lacks this feature.

Treatment and Prognosis

The inverted papilloma has a significant growth potential and, if neglected, may extend into the nasopharynx, middle ear, orbit, or cranial base. In some studies, recurrence after conservative surgical excision has occurred in nearly 75% of all cases. The recommended treatment, therefore, is a lateral rhinotomy and en bloc excision of the involved lateral nasal wall. The mucosa of the adjacent paranasal sinus also is removed and adjunctive radiotherapy may be considered for those lesions not able to be resected completely. With surgery, the recurrence rate is less than 14% of cases. Recurrences are usually 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 of multiple recurrences.

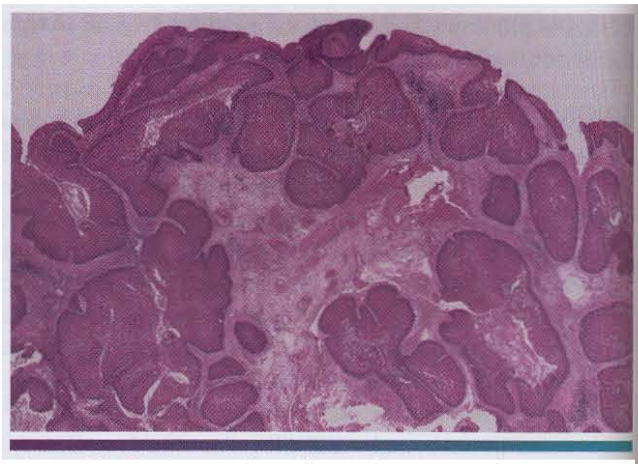

Figure 10-17 • Inverted papilloma. low-power photomicrograph showing a squamous epithelial proliferation, with multiple "inverting" islands of epithelium extending into the underlying connective tissue.

The inverted papilloma also is associated with malignancy, usually squamous cell carcinoma, in 3% to 24% of cases. In such an eventuality, of course, the lesion is treated as a malignancy, typically by performing more 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. This lesion is considered by some authorities to be a variant of the inverted papilloma because of the similarity in clinical and histopathologic features and a similarly low frequency of HPV.

Clinical Features

Cylindrical cell papilloma typically occurs in adults 20 to 80 years of age. There is a strong male predominance, with a predilection for the maxillary antrum, lateral nasal cavity wall, and ethmoid sinus. The presenting symptom is usually unilateral nasal obstruction, and it 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 intracpithclial microcysts filled with mucin, neutrophils, or both.

Treatment and Prognosis

Cylindrical cell papilloma is treated in the same manner as inverted papilloma (see previous topic). The potential for recurrence and malignant transformation seems to be lower than that of the inverted papilloma.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a virus-induced epithelial hyperplasia produced by the molluscum contagiosum **virus, 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. After an incubation period of 14 to 50 days, infection produces multiple papules of the skin or, rarely, mucous **membranes. These remain small for months or years and** then spontaneously involute.

During its active phase, the molluscum contagiosum virus is sloughed from a central core in each papule. Routes of transmission **include sexual contact (in adults) and such** nonsexual contacts (in children and teenagers) as sharing **clothing, wrestling. communal bathing, and swimming. lesions have a predilection for warm portions of the skin and sites of recent injury; florid cases have been reported** in immunocompromised patients (see page 245).

Clinical Features

Molluscum contagiosum is usually seen in children and young adults. The papules almost always are multiple and occur predominantly on the skin of the neck, face (particularly eyelids), trunk, and genitalia. Infrequently, oral involvement occurs, usually on the lips, buccal **mucosa, or palate.**

lesions are pink, smooth-surfaced, sessile, nontender, and nonhemorrhagic papules that arc 2 to 4 mm in diameter (Figure 10-18). Many show a small central Indentation **or keratin-like plug from which a curdlike substance can be expressed. Some are surrounded by a mild** inflammatory erythema and may be slightly tender.

Histopathologic Features

Molluscum contagiosum appears as a localized lobular proliferation of surface stratified squamous epithelium (Figure 10-19). The central portion of each lobule is filled with bloated keratinocytes that contain large, intra-**nuclear, basophilic viral inclusions called molluscum** bodies (Figure 10-20). These bodies begin as small eosinophilic structures in cells just above the basal layer. As they approach the surface, these bodies increase so much In size that they frequently become larger than the **original size of the invaded cells. A central crater is formed at the surface as stratum corneum cells disintegrate** to release their molluscum bodies. These unique **features make the diagnosis readily apparent.**

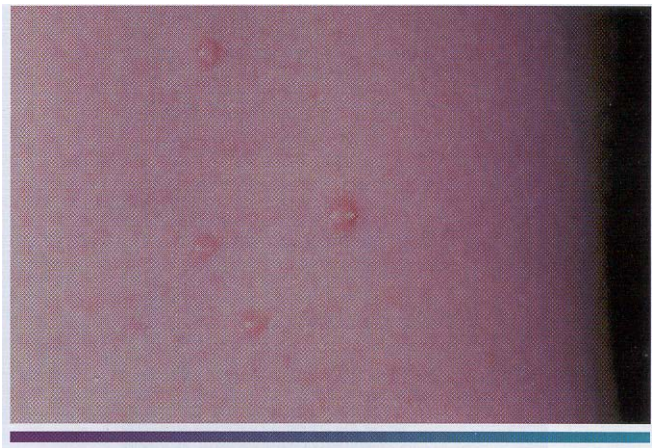

Figure 10-18 . Molluscum contagiosum. Multiple, smooth-**surfaced papules, with several demonstrating small keratin-like plugs, are seen on the neck of a child.**

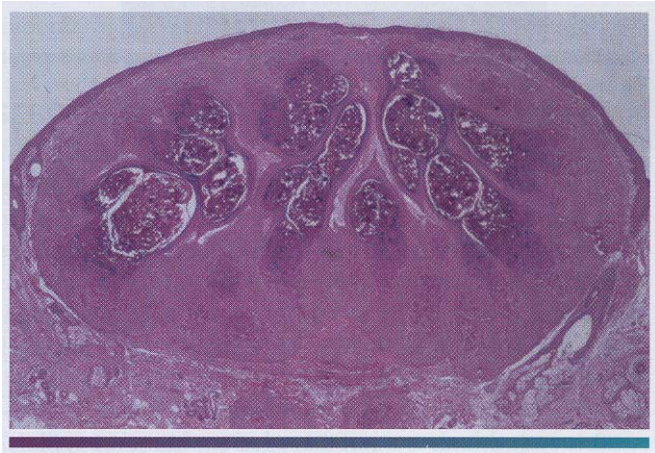

Figure 10-19 • Molluscum contagiosum. Well-defined epidermal proliferation demonstrating a central craterlike depression filled with virally altered keratinocytes.

Treatment and Prognosis

In most cases of molluscum contagiosum, spontaneous remission occurs within 6 to 9 months; however, curettage and cryotherapy are effective treatments for papules removed electively. Podophyllotoxin and tretinoin therapies arc popular but less effective, and **topical imiquimod, an immune-response modifier, recently has been shown to be effective in reducing or** eliminating the lesions. There is no apparent potential **to transform into carcinoma, and the lesions tend not to recur after treatment.**

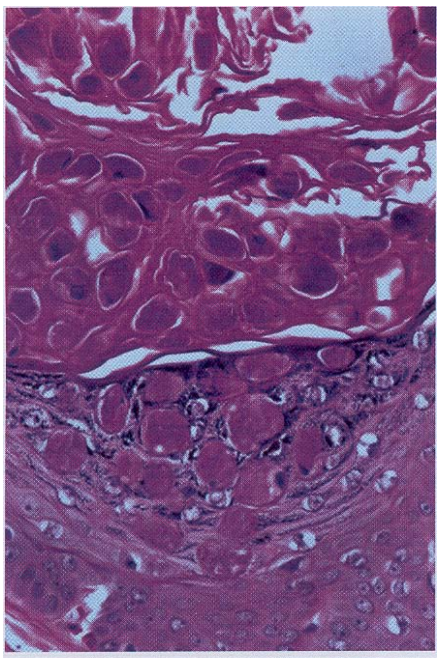

Figure 10-20 • Molluscum contagiosum. Higher-power photomicrograph showing keratinocytes with large, basophilic viral inclusions (molluscum bodies) being sloughed into the central crater (top).

VERRUCIFORM XANTHOMA

Verruciform xanthoma is a hyperplastic condition of the epithelium of the mouth, skin, and genitalia, with a characteristic accumulation of lipid-laden histiocytes beneath the epithelium. First reported in 1971, it remains largely an oral disease; its cause is still unknown. Although verruciform xanthoma is a papillary lesion, human papillomavirus does not appear to play a role in its pathogenesis. 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, pemphigus vulgaris, warty dyskeratoma, graft-versus-host disease). The lesion is histopathologically similar to other dermal xanthomas, but it is not associated with diabetes, hyperlipidemia, or any other metabolic disorder.

Clinical Features

Verruciform xanthoma is typically Seen in whites, 40 to 70 years of age. There is a strong female predilection (a 1:2 male-to-female ratio). Approximately half of the 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 (Figures 10-21 and 10-22). Rarely,

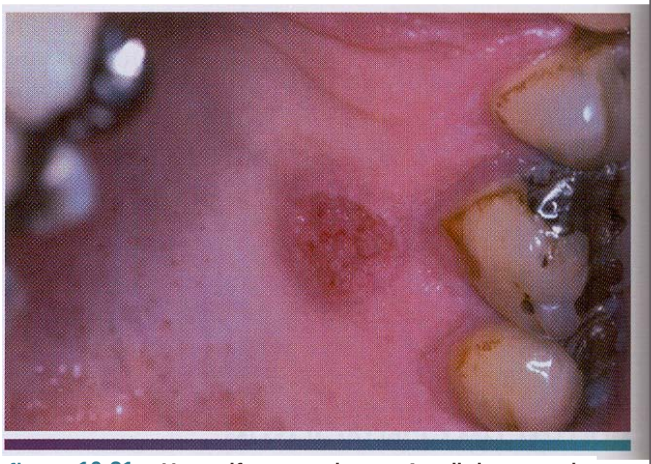

figure 10-21 • Verruciform xanthoma. A well-demarcated, slightly elevated lesion of the hard palate that demonstrates a roughened or papillary surface.

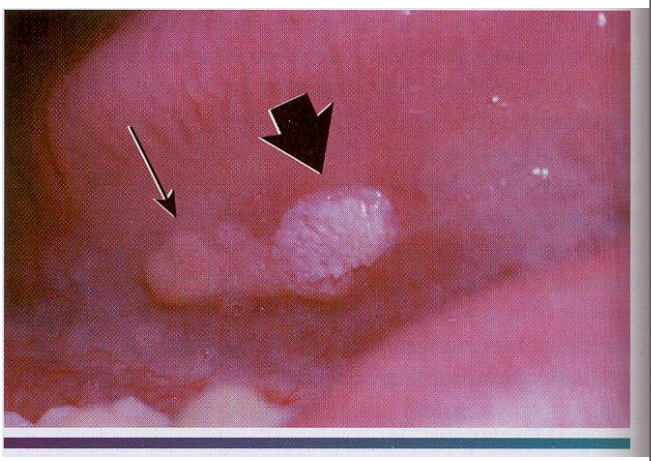

Figure 10-22 • Verruciform xanthoma. A lesion of the ventral tongue exhibits a biphasic appearance. The anterior aspect demonstrates elongated white (well-keratinized) projections *(large arrow)*. The posterior aspect demonstrates a surface of yellow, blunted projections *(small arrow)*.

flat-topped nodules are seen without surface projections. Most lesions are smaller than 2 em in greatest diameter; no oral lesion larger than 4 em has been reported. Multiple lesions occasionally have been described. Clinically, verruciform xanthoma may be similar to squamous papilloma, condyloma acuminatum, or early carcinoma.

Histopathologic Features

Verruciform xanthoma demonstrates papillary, acanthotic surface epithelium covered by a thickened layer of parakeratin. On routine hematoxylin and eosin staining, the keratin layer often exhibits a distinctive orange coloration (Figure 10-23). Clefts or crypts between the epithelial projections are filled with parakeratin, and rete ridges are elongated to a uniform depth. The most impor-

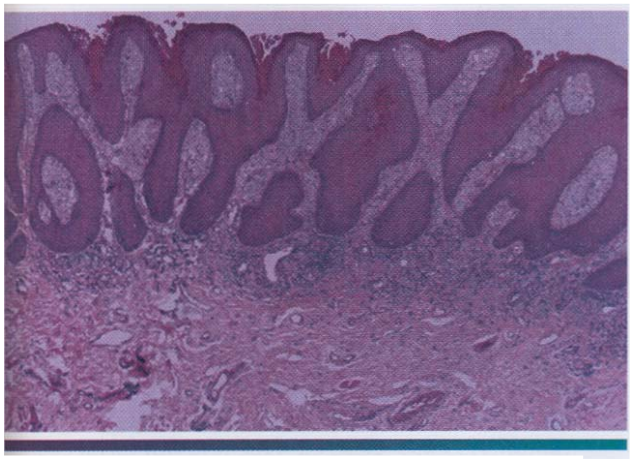

Figure 10-23 • Verruciform xanthoma. A slight papillary appearance is produced by hyperparakeratosis, and the rete ridges are elongated to a uniform depth. Note the paraleratin pluggingbetween the papillary projections.

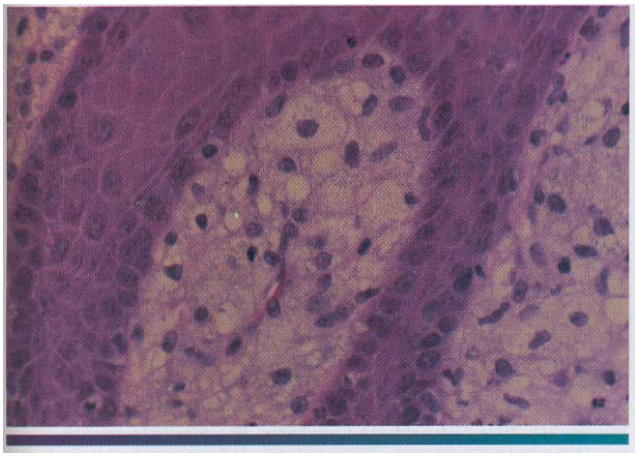

Figure 10·24. Verruciform xanthoma. Connective tissue papillae are composed almost exclusively of xanthoma cells – large macrophages with foamy cytoplasm.

tant diagnostic feature is the accumulation of numerous large macrophages with foamy cytoplasm. which typically are confined to the connective tissue papillae (Figure 10-24). These foam cells. also known as xanthoma cells. contain lipid and periodic acid-Schiff (PAS)-positive, diastase-resistant granules.

Treatment and Prognosis

The verruciform xanthoma is treated with conservative surgical excision. Recurrence after removal of the lesion is rare, and no malignant transformation has been reported. However. two cases have been reported in which averruciform xanthoma occurred in association with carcinoma *in situ* or squamous cell carcinoma. This 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.

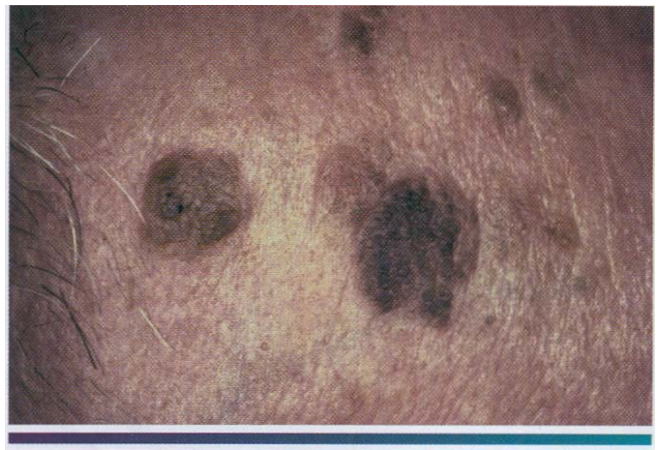

Figure 10-25 • Seborrheic keratosis. Multiple brown plaques of the face of an elderly man exhibit a fissured surface. They had been slowly enlarging for several years.

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. Seborrheic keratosis docs 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 indistinguishable clinically from actinic lentigines (see page 328), and which gradually enlarge and elevate {Figures 10-25 and 10-26). Individual lesions are sharply demarcated plaques and have surfaces that are finely fissured. pitted. or verrucous, but may be smooth. They tend to 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% of blacks and frequently has an autosomal dominant inheritance pattern. This condition typically appears as multiple, small (I to 2 mm), dark-brown to black papules scattered about the zygomatic and periorbital region (Figure 10-27).

Histopathologic Features

Seborrheic keratosis consists of an exophytic proliferation of basilar epithelial cells that exhibit varying degrees of surface keratinization. acanthosis, and papillomatosis (Figure 10-28). Characteristically, the entire epithelial

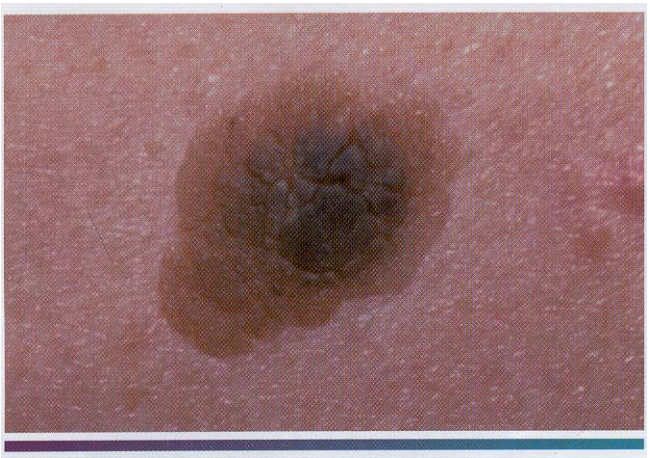

Figure 10-26 • Seborrheic keratosis. Crusted and pigmented epidermal plaque.

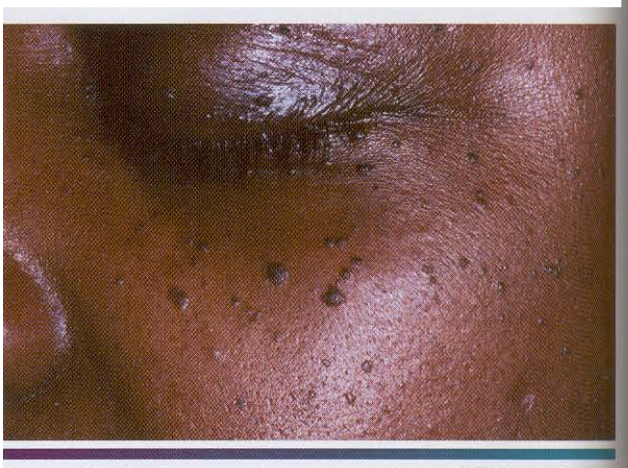

Figure 10-27 • Dermatosis papulosa nigra. Multiple small pigmented papules of the malar area.

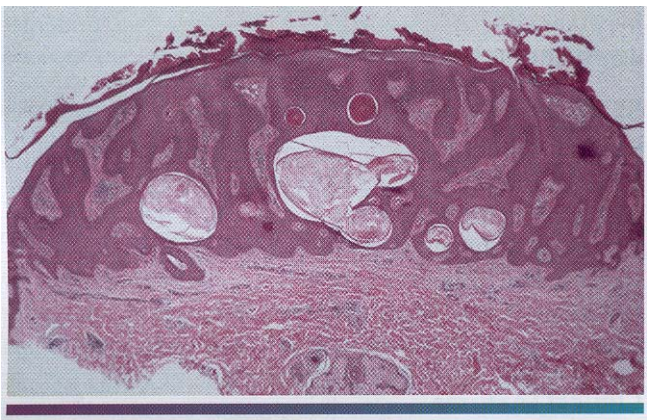

Figure 10-28 • Seborrheic keratosis. The acanthotic form demonstrates considerable acanthosis, surface hyperkeratosis, and numerous pseudocysts. The epidermal proliferation extends upward, above the normal epidermal surface.

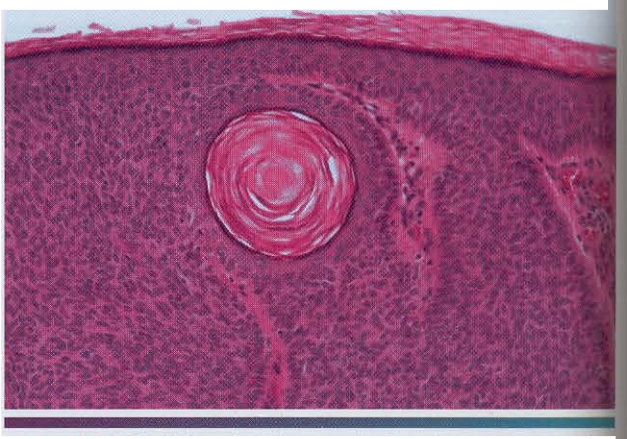

Figure 10-29 • Seborrheic keratosis. Pseudocysts are actually keratin-filled invaginations, as seen toward the left in this high-power photomicrograph. The surrounding epithelial cells are basaloid in appearance.

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 (Figure 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 dermatosis papulosa nigra are predominantly of the adenoid and acanthotic types.

Chronic trauma may alter these histopathologic features, and the lesion known as inverted follicular **keratosis of Helwig is thought to represent an irritated** seborrheic keratosis. This lesion shows a mild degree of **proliferation into the connective tissue and a** chronic inflammatory cell infiltrate adjacent to the lesion. Squamous metaplasia of the lesional cells results in whorled epithelial patterns called squamous eddies. Inflamed seborrheic keratosis **may show 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 for aesthetic purposes, a seborrheic keratosis **seldom is removed. Cryotherapy with liquid nitrogen** or

simple curettage is the treatment of choice for lesions that are removed. Although the keratosis has no malignant potential, other more significant skin lesions may develop in areas contiguous to it. Moreover. the sudden appearance of numerous seborrheic keratoses with pruritus has been associated with internal malignancy. a rare event called the Leser-Trelat sign.

SEBACEOUS HYPERPLASIA

Sebaceous hyperplasia is characterized by a localized proliferation of sebaceous glands of the skin. tt has no known cause and is common on the facial skin. The major significance of this entity 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 of age. It occurs most commonly on the skin of the face. especially the cheeks and forehead. and is characterized by one or more soft. nontender papules with white. yellow. or normal coloration (Figure to-30). Lesions are usually umbilicated. with a small central depression. representing the area where the ducts of the involved sebaceous lobules terminate. Most lesions are smaller than 5 mm in greatest diameter and take considerable time to reach even this small size.

Compression of the lesion usually causes sebum. the thick yellow-white product of the sebaceous gland. to be expressed in the central depressed area. This feature helps clinically to distinguish 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 of the buccal mucosa.

Histopathologic Features

Histopathologically. sebaceous hyperpiasia is characterized by a collection of enlarged but otherwise normal sebaceous gland lobules grouped around one or more centrally located sebaceous ducts (Figure iO-31).

Treatment and Prognosis

No treatment is necessary for sebaceous hyperplasia except for aesthetic reasons or unless basal cell carcinoma cannot be eliminated from the clinical differential diagnosis of cutaneous lesions. Excisional biopsy is curative,

EPHELIS (FRECKLE)

An ephelis is a common small hyperpigmented macule of the skin that represents a region of increased melanin production. Ephelides are seen most often on the face. arms. and back of fair-skinned. blue-eyed persons; they may be associated with a strong genetic predilection (autosomal dominant). The skin discoloration is produced by a relative excess of melanin deposition in the epidermis. not by a local increase in the number of melanocytes.

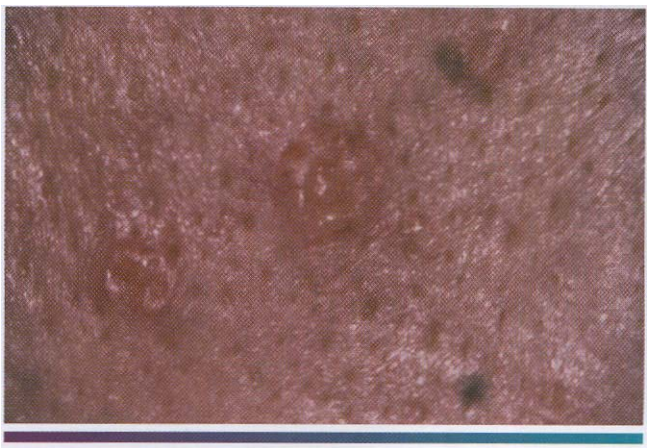

figure 10-30 . Sebaceous hyperplasia. Multiple soft papules of the midface are umbilicated and small. Sebum can often be expressed from the central depressed area.

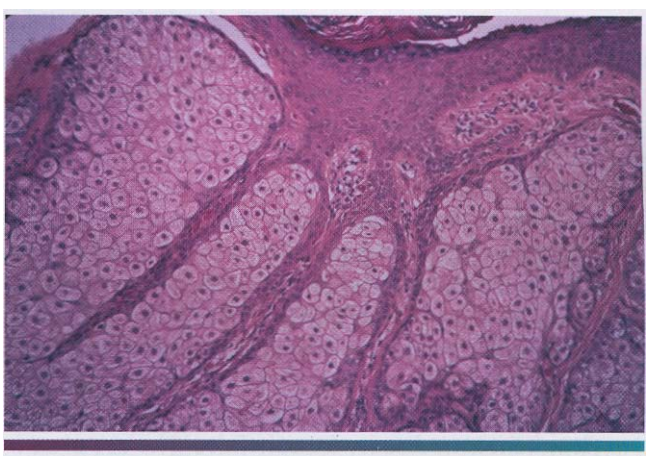

Figure 10-31 • Sebaceous hyperplasia. Sebaceous glands are enlarged and more numerous than normal, but they demonstrate no other pathologic changes.

Clinical Features

Ephelides become noticeable during the first decade of life. and new macules seldom arise after the teenage years. During adult life the macules typically become less prominent. There is no sex predilection; however, persons with blonde or red hair are more likely to have ephelides. The lesions become more pronounced after sun exposure.

Each individual macule is round or *oval,* and typically remains less than 3 mm in diameter (Figure 10-32). It has a uniform light-brown coloration and is sharply demarcated from the surrounding skin. There is great variability in the numbers of ephelides present. Many individuals have less than 10. whereas some have hundreds of mac-

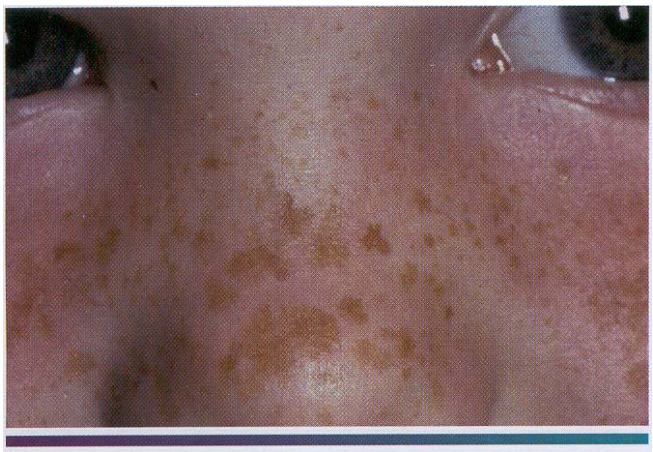

Figure 10-32 • Ephelides. Multiple brown macules over the bridge of the nose.

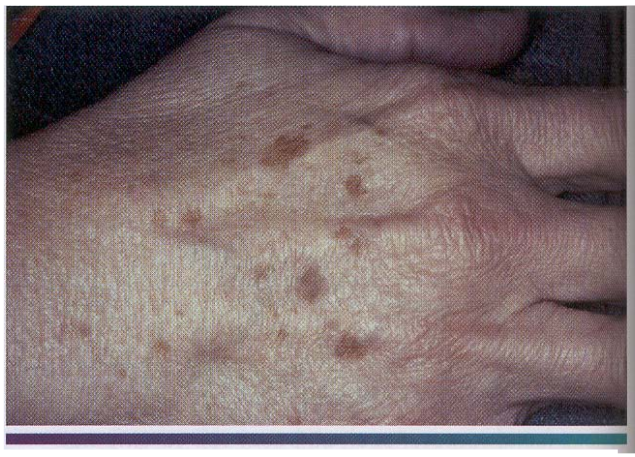

Figure 10-33 • Actinic lentigines. Multiple lesions on the sun-exposed skin of the hand of an elderly person. Lesions are brown maculas with irregular borders.

ules. The brown color is not as dark as the lentigo simplex (see page 329), and there is never elevation above the surface of the skin, as may occur in a melanocytic nevus (see page 332).

Histopathologic Features

The ephelis is comprised of stratified squamous epithelium with abundant melanin deposition in the basal cell layer. Despite the increased melanin, the number of melanocytes is normal or may be somewhat reduced. In contrast to lentigo simplex, there is no elongation of rete ridges.

Treatment and Prognosis

No treatment is necessary for ephelides. The use of 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 results from chronic ultraviolet light damage to the skin. It is found in more than 90% of whites older than 70 years of age and rarely is seen before age 40. It does not occur within the mouth but is seen frequently on the facial skin. Persons who have facial ephelides (freckles) in childhood are more likely to develop actinic lentigines later in life.

Clinical Features

Actinic lentigo is common on the dorsa of the hands, on the face, and on the arms of elderly whites (Figures 10-33 and 10-34). It is typically multiple, but individual lesions appear as uniformly pigmented brown to tan macules with well-demarcated but irregular borders. Although the lesion may reach more than 1 cm in diameter, most examples are smaller than 5 mm. Adjacent lesions may coalesce, and new ones continuously arise with age. Unlike ephelides, no change in color intensity is seen after exposure to ultraviolet light.

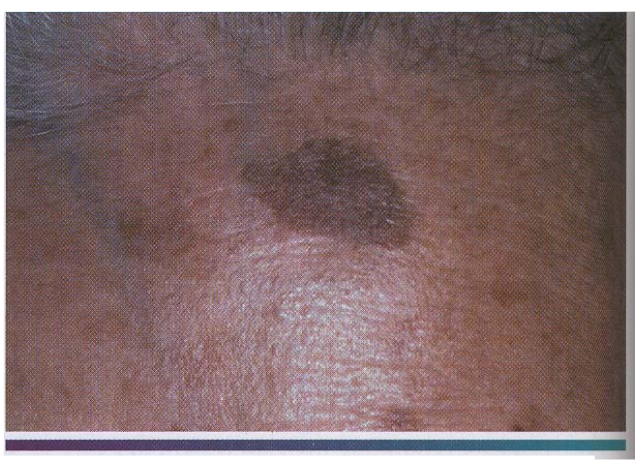

Figure 10-34 • Actinic lentigo. Large, flat, evenly pigmented lesion on the forehead of an elderly man.

Histopathologic Features

Rete ridges are elongated and club shaped in actinic lentigines, with thinning of the epithelium above the connective tissue papillae (Figure 10-35). The ridges sometimes seem to coalesce with one another. Within each rete ridge, melanin-laden basilar cells are intermingled with excessive numbers of heavily pigmented melanocytes.

Treatment and Prognosis

No treatment is required for actinic lentigo, except for aesthetic reasons. Topical retinoic acid can reduce the color intensity in some cases, and the lesion can be completely destroyed using a Q-switched ruby laser. Actinic

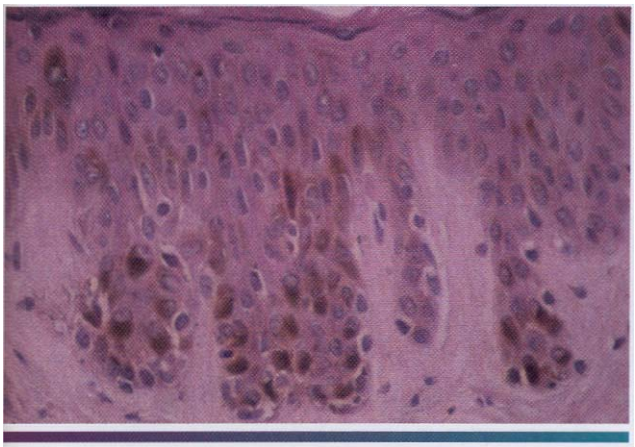

Figure 10-35 • Actinic lentigo. Reteridges are elongated and occasionally intertwining. Pigmented melanocytes (with clear cytoplasm) areexcessiveand commingled with melanin-laden basilar cells.

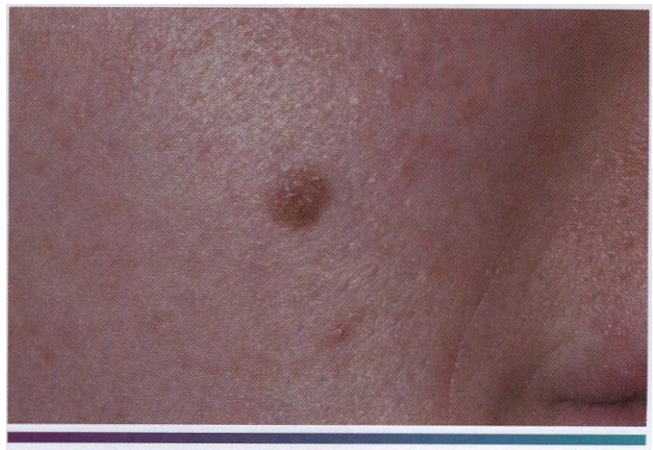

Figure 10-36 • Lentigo simplex. A sharply demarcated lesion of uniform brown coloration is seen on the midface.

lentigo does not undergo malignant transformation; if removed, it rarely recurs. New lesions, however, can arise in adjacent or distant skin at any time.

LENTIGO SIMPLEX

Lentigo simplex is one of several forms of benign cutaneous rnelanocvnc hyperplasia of unknown cause. It usually occurs on skin that is not exposed to sunlight, but it may occur on any skin surface and at any age. Its color intensity does not change with variations in sun exposure. lentigo simplex is darker in color than the common ephelis (see page 3271. Ephelides, moreover, are found predominantly on sun-exposed skin, become more pronounced with increased sun exposure, and represent merely an increase in local melanin production rather than an increase in the number of productive melanocytes.

Some investigators believe that lentigo simplex represents the earliest stage of another common skin lesion, the melanocytic nevus (see page 332). Oral lesions have been reported, but they are rare and may be examples of the oral melanotic macule (see page 330).

Clinical Features

lentigo simplex usually occurs in children but may occur at any age. The typical lesion is a sharply demarcated macule smaller than S mm in diameter, with a uniformly tan to dark-brown color (Figure 10-36). It is usually solitary, although some patients may have several lesions scattered on the skin of the trunk and extremities. l entigo simplex reaches its maximum size in a matter of months and may remain unchanged indefinitely thereafter.

Clinically, individual lesions of lentigo simplex arc indistinguishable from the nonelevated melanocytic nevus. With multiple lesions, conditions such as lenttginosis profusa, Peutz-leghers syndrome (see page 653), andthe multiple lentigines or LEOPARD' syndrome must be considered as diagnostic posstbtllties.

Histopathologic Features

Lentigo simplex shows an increased number of benign mclanocytes within the basal layer of the epidermis, and these often are clustered at the tips of the rete ridges.

Abundant melanin is distributed among the melanocytes and basal keratlnocytes. 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 aesthetic reasons. Conservative surgical excision is curative, and no malignant transformation potential has been documented for lesions not removed.

MELASMA (MASK OF PREGNANCY)

Melasma is an acquired. symmetric hyperpigmentation of the sun-exposed skin of the face and neck. The cause is unknown, but it is strongly associated with pregnancy and the use of oral contraceptives that contain both estrogen and progesterone. Dark-complexioned persons are more likely to develop melasma.

Clinical Features

Melasma appears in adult women as bilateral light to dark-brown cutaneous maculcs that vary in size from a few millimeters to more than 2 em in diameter (Figure 10-37). Lesions develop slowly with sun exposure and occur primarily on the midface, forehead, upper lip, chin, and (rarely) the arms. It is not unusual for the entire face to be involved. The pigmentation may remain faint or darken over time. Rarely, melasma is seen in men.

•Lentigines (multiple); Electrocardiographic abncrma hncs: Ocular hypertelor-Ism; pulmonary stenosis; Abnormalities of gcnnane : Retc rdatlon 01growth; and Deafness (sensorineural).

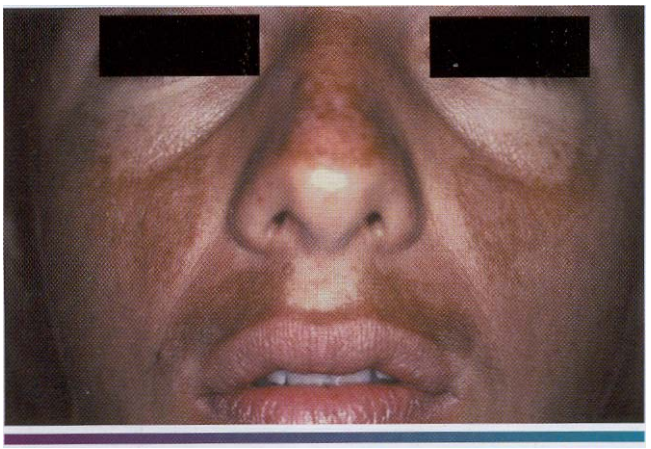

Figure 10-37 • Melasma. Diffuse hyperpigmentation of the facial skin in a pregnant woman.

Histopathologic Features

Melasma is characterized by increased melanin deposition within an otherwise unremarkable epidermis. Pigment also may be seen within numerous melanophages in the dermis.

Treatment and Prognosis

Topical treatment with 3% hydroquinone and tretinoin is generally effective for melasma, but the pigmentation can be prevented or diminished by minimizing sun exposure. 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).

Clinical Features

The oral melanotic macule occurs at any age in both men and women; however, biopsy samples demonstrate a 2:1 female predilection. The average age of patients is 43 years at the time of diagnosis. The vermilion zone of the lower lip is the most common site of occurrence (33%), followed by the buccal mucosa, gingiva, and palate.

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 smaller (Figures 10-38 and 10-39). Occasional lesions may be blue or black. Lesions are not reported to enlarge after diagnosis, which suggests that the maximum dimension is achieved rather rapidly and remains constant thereafter.

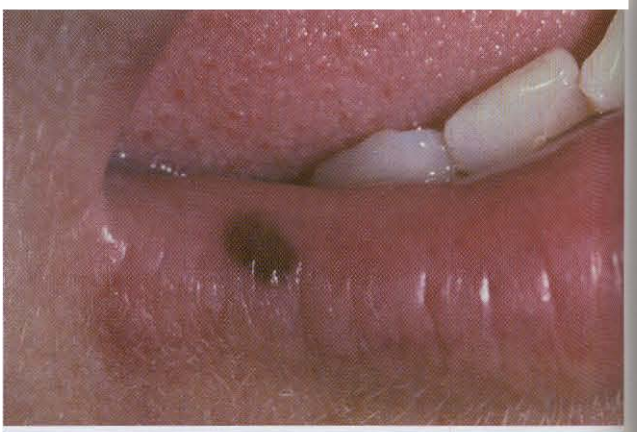

Figure 10-38 • Oral melanotic macule. A single small, uniformly pigmented brown macule on the lower lip vermilion.

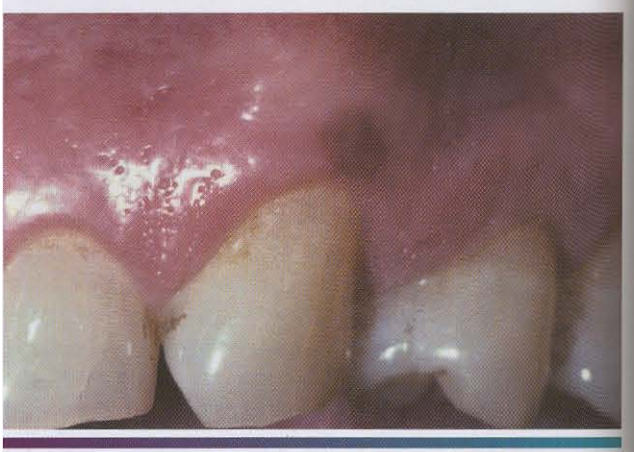

Figure 10-39 • Oral melanotic macule. A well-demarcated brown macule of the gingival mucosa.

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 (Figure 10-40). Melanin also may be seen free or within melanophages in the subepithelial connective tissue (melanin incontinence). The lesion typically does not show elongated rete ridges like actinic lentigo (see page 328).

Treatment and Prognosis

Treatment is usually not required for the melanotic macule, except for aesthetic considerations. When necessary, exci-

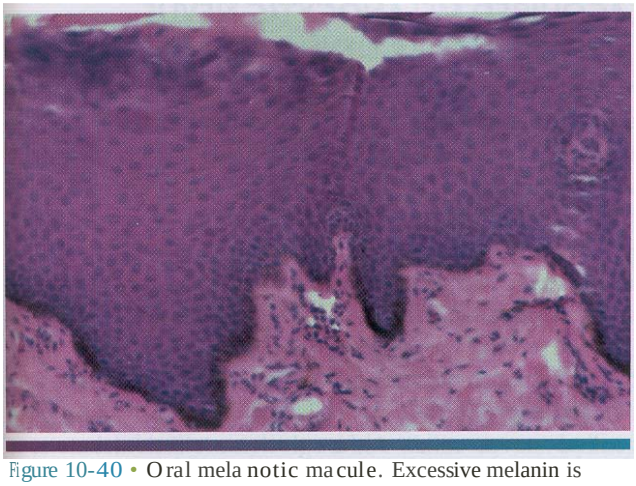

Figure 10-40 • Oral melanotic macule. Excessive melanin is confined to the basal and parabasallayers of an otherwise unremarkable stratified squamous epithelium. Occasional melanin may be seen within underlying connective tissues (pigment incontinence). The pictured lesion demonstrates elongated rete ridges and a keratin layer because it was removed from the attached gingiva; these are not lesional changes.

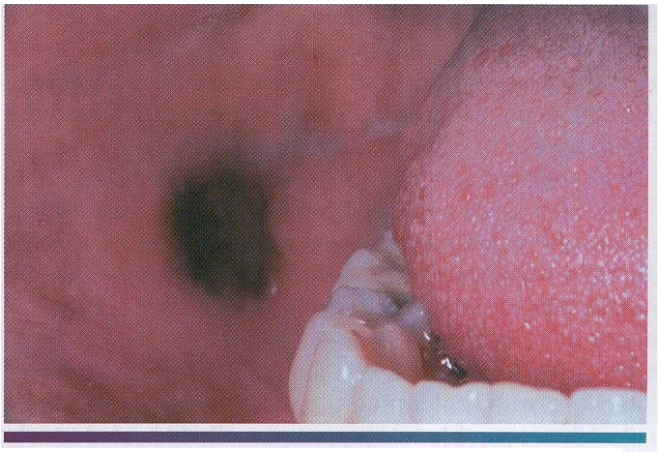

Figure 10-41 • Oral melanoacanthoma. A smooth, darkly pigmented macule of the buccal mucosa is seen in a young adult.

sional biopsy is the preferred treatment. Electrocautery, laser ablation, or cryosurgery is *effective,* but no tissue remains for histopathologic examination after these procedures. The intraoral melanotic macule has no malignant transformation potential. but an early melanoma can have a similar clinical appearance. For this rcason, all oral pigmented macules of recent onset, large size, irregular pigmentation, unknown duration, or recent enlargement should be submitted for microscopic examination.

On occasion, flat pigmented lesions are encountered that arc clinically and microscopically similar to the melanotic macule; however, these lesions represent a sign of systemic or genetic disease or may be a consequence of the use of certain medications. A list of these conditions is shown in Box 10- 1.

ORAL MELANOACANTHOMA (MELANOACANTHOSIS)

Oral melanoacanthoma is a benign and uncommon acquired pigmentation of the oral mucosa characterized by dendrltic melanoeytes dispersed throughout the epithelium. The lesion appears to be a reactive process and is unrelated to the melanoacanthoma of skin.

Clinical Features

Oral melanoacanthoma is seen almost exclusively in blacks, shows a female predilection, and is most common during the third and fourth decades of life. The buccal mucosa is the most common site of occurrence. The lesion is smooth, flat or slightly raised, and dark-brown to black in color Il-igure 10-41). Lesions often demonstrate a rapid increase in size, and they occasionally reach a diameter of several centimeters within a period of a few weeks.

Box 10-1 *Associations With Melanin Pigmentation of Drat Mucosa*

PHYSIOLOGIC OR SYNDROMIC ASSOCIATIONS

- Racial or physiologic pigmentation
- Peutz-leghers syndrome
- McCune-Albright syndrome
- LEOPARD syndrome (Ientiginosis profusa, no intraoral melanosis)
- Cronkhite-Canada syndrome
- Bloom syndrome
- Dunnigan syndrome
- Dyskeratosis congenita
- Endocrine candidosis
- Incontinentia pigmenti
- Oculo-cerebro-cutaneous syndrome
- Roth mund-Thomson syndrome
- Trisomy 14 mosaicism
- Unusual facies, vitiligo. spastic paraplegia syndrome
- Xeroderma pigmentosum
- Addison disease
- Neurofibromatosis

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 PCB)

SYSTEMIC MEDICATIONS

- Chloroquine and other quinine derivatives
- Phenolphthalein
- Estrogen
- AIDS-related medications

From Bouquot IE. Nlkal H: Lesions of the oral cavity, In Gnepp DR: *Diagnostic surgical pathology of the head and neck*. pp 141-238. Philadelphia, 2001, WB Saunders.

Histopathologic Features

The oral melanoacanthoma is characterized by numerous benign dendritic melanocytes (cells that are normally confined to the basal cell layer) scattered throughout the lcsional epithelium (Figures 10-42 and 10-43). Basal layer rnelanocytes are also present in increased numbers. Spongiosis and mild acanthosis are typically noted. In addition, eosinophils and a mild to moderate chronic inflammatory cell infiltrate are usually seen within the underlying connective tissue.

Treatment and Prognosis

Because of the alarming growth rate of oral rnelanoacanthoma, incisional biopsy is usually indicated to rule out the possibility of melanoma. Once the diagnosis has been established, no further treatment is necessary. In several instances, lesions have undergone spontaneous resolution after Inclslonal biopsy.

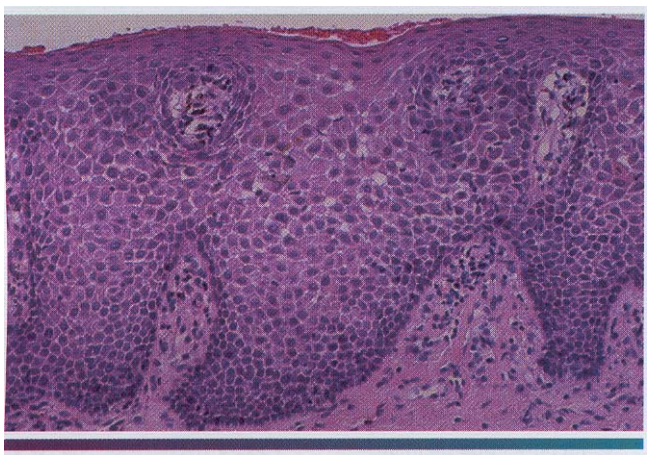

Figure 10-42 • Oral melanoacanthoma. Medium-power photomicrograph showing acanthosis of the epithelium. Spongiosis is demonstrated by intercellular spaces between the keratinocytes.

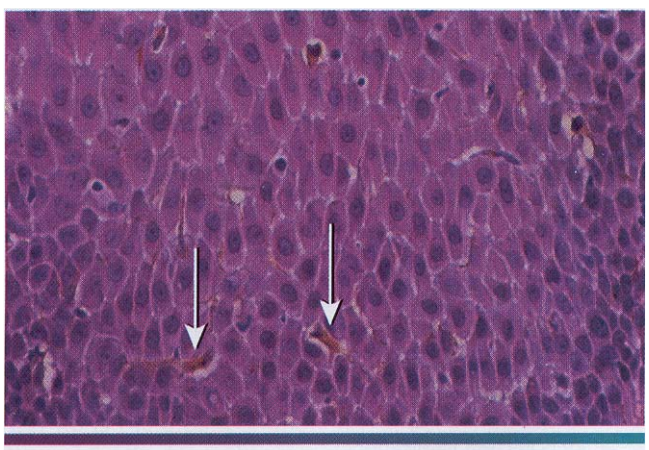

Figure 10-43 • Oral melanoacanthoma. High-power view showing numerous dendritic melanocytes *(arrows)* extending between the spinous epithelial cells.

ACQUIRED MELANOCYTIC NEVUS (NEVOCELLULAR NEVUS; MOLE)

The generic term *nevus* refers to malformations of the skin (and mucosa) that are congenital or developmental in nature. *Nevi* may arise from the surface epithelium or any of a *variety* of underlying *connective* tissues. The most commonly recognized *nevus* is the acquired melanocytic *nevus,* or common mole—so much so, that the simple term *nevus* is often used synonymously for these pigmented lesions. *However,* many developmental nevi also are recognized (Box 10-2).

The acquired melanocytic nevus represents a benign, localized proliferation of cells from the neural crest, often called "nevus cells." Although there is little debate as to their neural crest origin and their ability to produce melanin, *various* authorities are divided on the issue of whether these cells represent melanocytes or are merely "first cousins" of melanocytes. These melanocytic cells migrate to the epidermis during development, and lesions may first appear shortly after birth. The acquired melanocytic *nevus* is probably the most common of all human "tumors," and white adults *have* an *average* of 10 to 40 cutaneous *nevi* per person. Intraoral lesions occur but are not common.

Clinical Features

Acquired melanocytic *nevi* begin to develop on the skin during childhood, and most cutaneous lesions are present before 35 years of age. They occur in both men and women, although women usually *have* a few more than men. Racial differences are seen. Whites have more *nevi* than Asians or blacks. Most lesions are distributed *above* the waist, and the head and neck region is a common site of involvement.

Acquired melanocytic *nevi evolve* through several clinical stages, which tend to correlate with specific histopathologic features. The earliest presentation (known microscopically as a junctional *nevus)* is that of a sharply demarcated, brown or black macule, typically less than 6 mm in diameter. Although this lcsional appearance 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

Box 10-2 *Types of Developmental Nevi*

- Epidermal nevus
- Nevus sebaceus
- Nevus flammeus (see page 471)
- Basal cell nevus (nevoid basal cell carcinoma) (see page 598)
- White sponge nevus (see page 645)

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) (Figures to-44 and 10-45). How*ever,* the nevus usually remains less than 6 mm in diameter. Ulceration is not a feature unless, for example. the nevus is situated in an area where a belt or bra strap traumatizes it easily. Throughout the adult years, many acquired melanocytic nevi will involute and disappear; therefore, fewer of these lesions can be detected in elderly persons.

Intraoral melanocytic nevi arc distinctly uncommon. Most arise on the palate or gingiva, although any oral mucosal site may be affected (Figure 10-46). Intraoral melanocytic nevi have an evolution and appea rance similar to skin nevi, although mature lesions typically do not demonstrate a papillary surface change. More than one in five intraoral nevi lack clinical pigmentation (Figure 10-47). Approxima tely two thirds of intraoral examples are found in females; the average age at diagnosis is 35 years.

Histopathologic Features

The acquired rnelanocytl c nevus is characterized by a benign, unencapsulated proliferation of small, ovoid cells (nevus cells). The lesional cells have small, uniform nuclei and a moderate amount of eosinophilic cytoplasm, with indistinct cell boundaries. These cells demonstrate a variable capacity to produce melanin, with the pigment primarily evident in the superficial aspects of the lesion. Nevus cells typically lack the dendritic processes that rnelanocytes possess. A characteristic microscopic feature is that the superficial nevus cells tend to be organized into small. round aggregates *ttheques).*

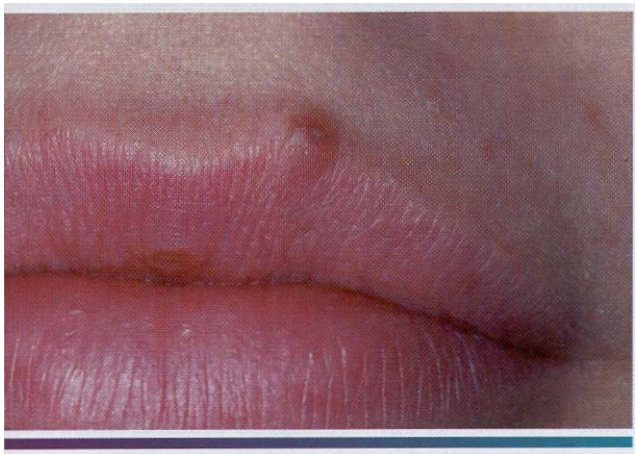

figure 10-44 . **Melanocytic (intradermal) nevus.** A pigmented, well-demarcated. dome-shaped papule is seen at the edge of the vermilion border of the upper lip.

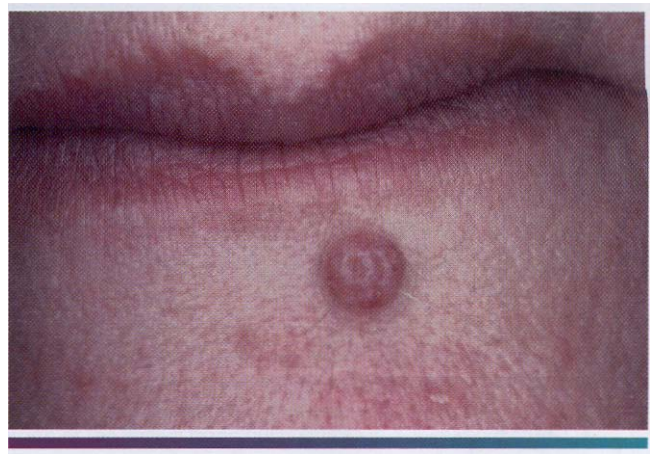

Figure 10-45 • **Melanocytic (intradermal) nevus.** Several coarse hairs are seen to project from this pigmented papule of the skin of the lower lip.

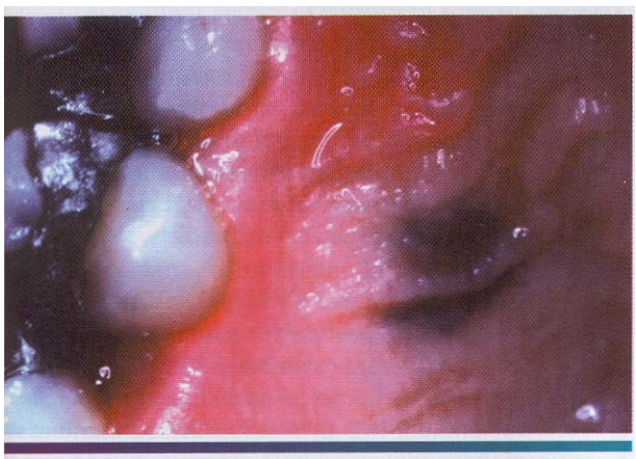

Figure 10-46 . **Intramucosal melanocytic nevus.** Pigmented lesion of the anterior hard palate. (Courtesy of Dr. lewis Claman.)

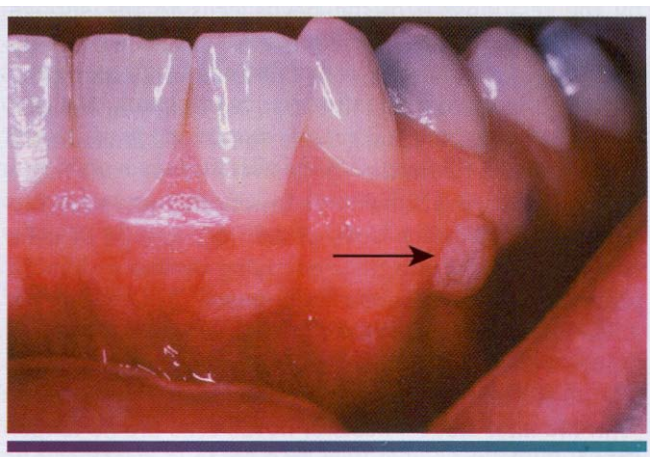

Figure 10-47 . **Intramucosal melanocytic nevus.** This intramucasal nevus *(arrow)* of the mandibular gingiva is nonpigmented. (Courtesy of Dr. John Lenox.]

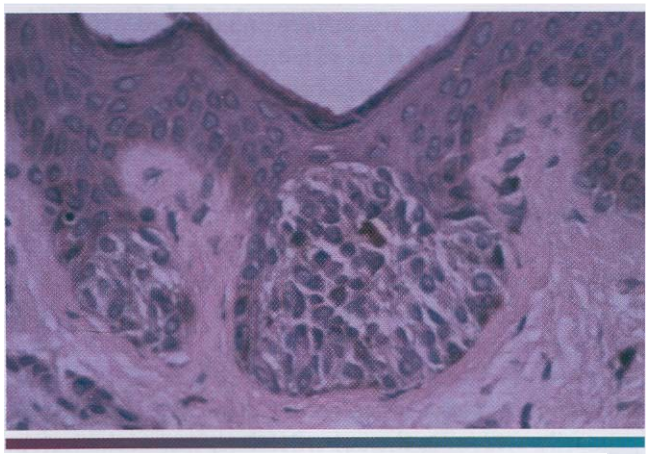

Figure 10-48 • Junctional nevus. Nests of melanocytic nevus cells along the basal layer of the epithelium.

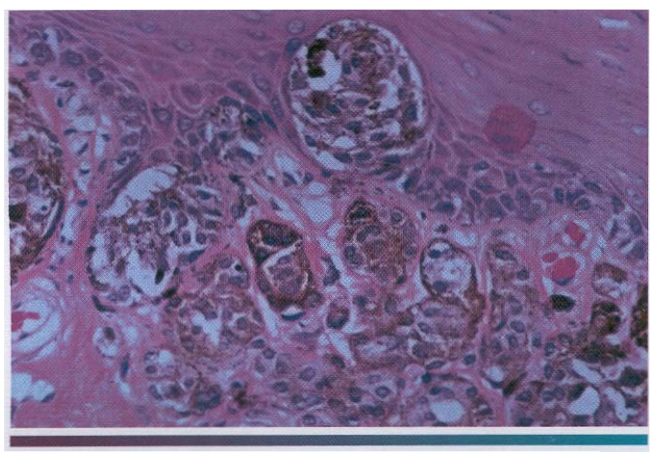

Figure 10-49 • Compound nevus. High-power view showing nests of pigmented nevus cells within the epithelium and the superlicial lamina propria.

Melanocytic nevi are classified histopathologically according to their stage of development. which is reflected by the relationship of the nevus cells to the surface epithelium and underlying connective tissue. In the eariy stages. *theques* of nevus cells are found only along the basal cell layer of the cpithellurn. especially at the tips of the rete ridges. Because the leslonal cells are found at the junction between the epithelium and the connective **tissue. this stage is known as a junctional nevus (Figure** 10-48). As the nevus cells proliferate. groups of cells begin to drop off into the underlying dermis or lamina propria. Because cells are now present both along the **junctional area and within the underlying connective tissue, the lesion then is called a compound nevus** (Figure 10-49).

In the later stages. nests of nevus cells are no longer found within the epithelium but are found only within **the underlying connective tissue. Because of the con-**nective tissue iocation of the iesional cells. on the skin

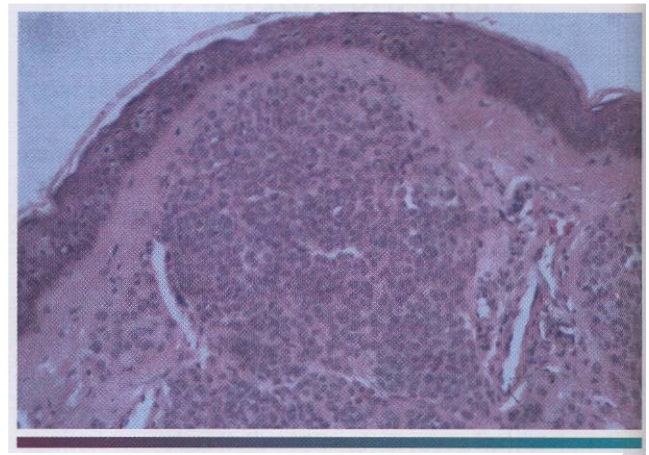

Figure 10-50 • Intradermal nevus. Collections of melanocytic nevus cells only within the dermis.

this stage is called an intradermal nevus (Figure 10-50l. **The intraoral counterpart is called an intramucosal** nevus. Zones of differentiation often are seen throughout the lesion. The superficial cells typically appear larger and epithelioid. with abundant cytoplasm. frequent **intracellular melanin, and a tendency to cluster into** *theques*. Nevus cells of the middie portion of the lesion have less cytoplasm. are seldom pigmented. and appear much like iymphocytes. Deeper nevus cells appear elongated and spindle shaped. much like Schwann cells or **fibroblasts. Some authorities classify these variations** as type A (epithelioid), type B (lymphocyte-like). and type C (spindle-shaped) nevus cells.

Most intraoral melanocytic nevi are classified micro-scopically as inJramucosal nevi. However. this probably simply reflects the age (average. 35 years) at which most oral nevi undergo biopsy and diagnosis. because these lesions would have earlier evolved through junctionai and compound stages.

Treatment and Prognosis

No treatment is indicated for a cutaneous mclanocytic nevus unless it is cosmetically unacceptable. is chronically irritated by clothing. or shows ciinical evidence oi **a change in size or color. By** midhfe, **cutaneous** rnclanocytic nevi tend to regress; by age 90. very few remain. if **removal is elected, conservative surgical excision is the treatment of choice; recurrence is unlikely.**

At least some skin melanomas arise from long-standing or irritated nevi of the skin. Overall. the risk of **transformation of a particular acquired melanocytic nevus to melanoma is approximately I in I million.** How-**ever, because oral mclanocytic nevi clinically can** mimic an early melanoma. it is generally advised that biopsy be performed for all unexplained pigmented oral lesions. especially because of the extremely poor prognosis for **oral melanoma discovered in its later stages.**

VARIANTS OF MELANOCYTIC NEVUS

CONGENITAL MELANOCYTIC NEVUS

Congenital melanoeytie nevus affects approximately I% of newborns in the United States. This entity is usually divided into two types: (I) small « 20 em in diameter) and (2) large (> 20 em in diameter). Approximately 15% of congenital nevi are found in the head and neck area. although intraoral involvement is quite rare.

Clinical Features

The small congenital melanocytic nevus may be similar in appearance to an acquired melanocytic nevus. but it is frequently larger in diameter (Figures 10-51 and 10-52). The large congenital lesion classically appears as a brown to black plaque. usually with a rough surface or multiple nodular areas. However, the clinical appearance often changes with time. Early lesions are flat and light tan, becoming elevated, rougher. and darker with age. A common feature is the presence of hypertrichosis (excess hair) within the lesion, which may become more prominent with age (giant hairy nevus). A very large congenital nevus sometimes may be referred to as bathing trunk nevus or garment nevus, because it gives the appearance of the patient wearing an article of clothing.

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 the acquired nevus. Both congenital and acquired types are comprised of nevus cells. which may have either a [uncuonal, compound, or intradermal pattern. The congenitalnevusis usually of the compound or intradermal type. In contrast to the acquired melanocytic nevus. the congenital nevus often shows extension of nevus cells into the deeper levels of the dermis, with "infiltration" of cells between collagen bundles. In addition. congenital nevus cells often are seen intermingled with neurovascular bundles in the reticular dermis and surrounding normal adnexal skin structures (e.g.. hair follicles, sebaceous glands). Large congenital melanoeytic nevi may show extension of nevus cells into the subcutaneous fat.

Treatment and Prognosis

Many congenital melanocytic nevi are excised for aesthetic purposes. in addition. 5% to 10% of large congenital nevi may undergo malignant transformation into melanoma. Whenever feasible, therefore. these lesions should be removed completely by conservative surgical excision. Close follow-up is required for lesions not removed.

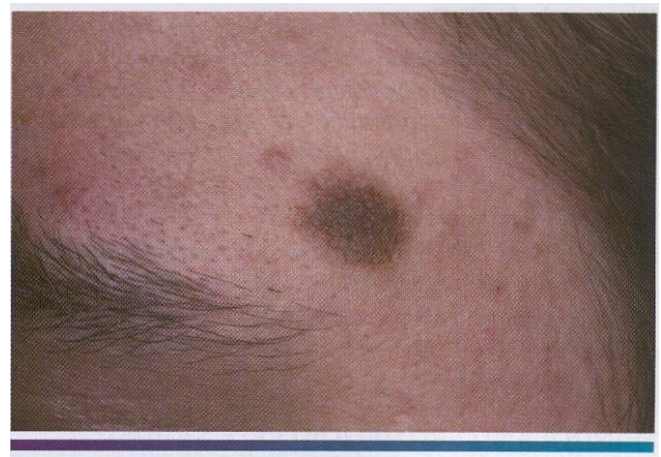

Figure 10-51 • Congenital melanocytic nevus. Pigmented lesion of the left temporal area.

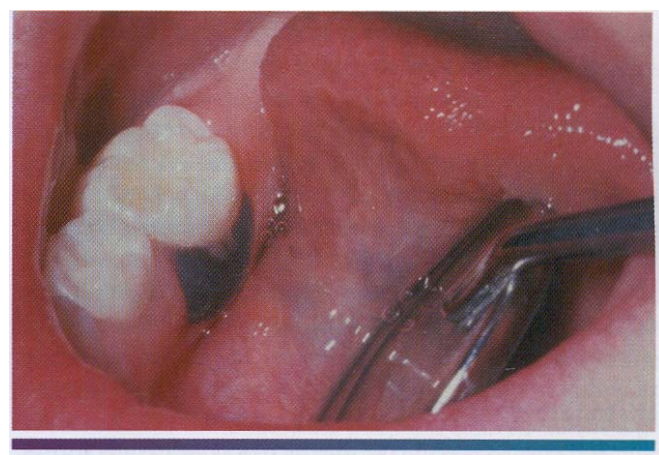

Figure 10-52 • Congenital melanocytic nevus. Deeply pigmented lesion of the lingual mandibular gingiva in a 3-year-old child.

HALO NEVUS

Halo nevus is a melanocytic nevus with a pale hypopigmented border or "halo" of the surrounding epithelium, apparently as a result of nevus cell destruction by the immune system. The halo develops because the immune cells also attack the melanocytes adjacent to the nevus. The cause of the immune attack is unknown. but regression of the nevus usually results. interestingly. the development of multiple halo nevi has been seen in patients who have had a recent excision of a melanoma.

Clinical Features

The halo nevus is typically an isolated phenomenon associated with 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 central pigmented papule or macule, surrounded by a uniform, 2-to 3-mm zone of hypopigmentation. Sometimes this peripheral zone is much wider.

Histopathologic Features

Histopathologically, the halo nevus differs from the routine acquired melanocytic nevus only in the presence of an intense chronic inflammatory cell infiltrate. which surrounds and infiltrates the nevus cell population,

Treatment and Prognosis

usually. treatment is not required for halo nevus because it eventually will regress entirely, If treatment is elected, conservative surgical removal is curative and recurrence is unlikely,

SPITZ NEVUS (BENIGN JUVENILE MELANOMA; SPINDLE AND EPITHELIOID CELL NEVUS)

Spitz nevus is an uncommon type of meJanocytic nevus that shares many histopathologic features with melanoma. It was, in fact. first described as a "juvenile melanoma," The distinctly benign biologic behavior of the lesion was first emphasized by Spitz in 1948. The first oral example was not reported until 1990.

Clinical Features

The Spitz nevus typically develops on the skin of the extremities or the face during childhood. it appears as a solitary, dome-shaped, pink to reddish-brown papule, usually smaller than 6 mm in greatest diameter. The young age at presentation and the relatively small size of the Spitz nevus are useful features to help distinguish it from melanoma.

Histopathologic Features

The Spitz nevus has the overall microscopic architecture of a compound nevus, showing a zonal differentiation from the superficial to deep aspects of the lesion, and showing 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 cell cohesiveness. Mitotic figures, all normal in appearance, may be seen in the superficial aspects of the lesion. Ectatic superficial blood vessels, which probably impart much of the reddish color of some lesions, are seen frequently. The nevocellular nature of the lesional cells is demonstrated by immunohistochemical reactivity for S-IOO protein and neuron-specific enolase.

Treatment and Prognosis

Conservative surgical excision is the treatment of choice for a Spitz nevus. There is little chance of recurrence after the nevus is removed.

BLUE NEVUS (DERMAL MELANOCYTOMA; JADASSOHN-TIEcHE NEVUS)

Blue nevus is an uncommon, benign proliferation of dermal rnclanocytcs, usually deep within subepithelial connective tissue. Two types of blue nevus are recognized: (I) 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.

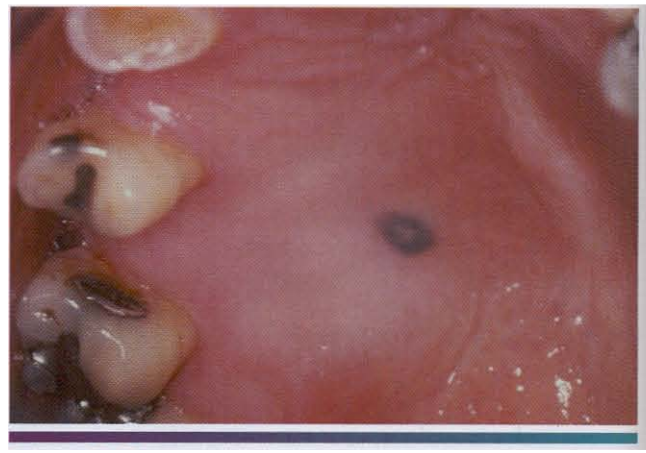

Figure 10-53 • Blue nevus. A well-circumscribed, deep-blue macular lesion is seen on palatal mucosa.

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 biue nevus, the melanin particles are deep to the surface, so that the light reflected back has to pass through the overlying tissue. Colors with long wavelengths (reds and yellows) tend to be more readily absorbed by the tissues; the shorter-wavelength blue light is more likely to be reflected back to the observer's eyes.

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. Oral lesions are found almost always on the palate. The lesion usually occurs in children and young adults, and a female predilection is seen. It appears as a macular or dome-shaped, blue or blue-black lesion smaller than I cm in diameter (Figure 10-53).

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

Histopathologicaily, the common blue nevus consists of a collection of elongated, slender rnelanocytes with branching dendritic extensions and numerous melanin

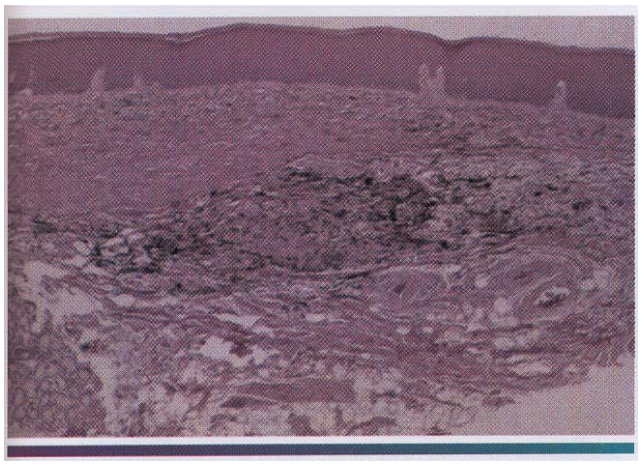

Figure 10-54 • Blue nevus. Abundant melanin is seen within spindle-shaped melanocytes located relatively deep within the lamina propria and parallel to the surface epithelium.

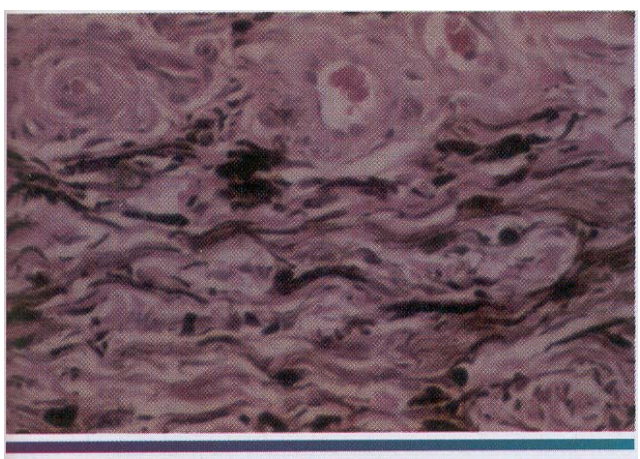

Figure 10-55 • Blue nevus. High-power view showing heavily pigmented spindle-shaped cells.

globules. These cells are located deep within the dermis or lamina propria (Figures 10-54 and 10-55) and usually align themselves parallel to the surface epithelium. The cellular blue nevus appears as a well-circumscribed, highly cellular aggregation of plump, melanin-producing spindle cells within the dermis or submucosa. More typical pigmented dendritic spindle cells are seen at the periphery of the lesional tissue. Occasionally, a blue nevus **is found in conjunction with an overlying meJanocytic nevus, in which case the term combined nevus is used.**

Treatment and Prognosis

If clinically indicated, conservative surgical excision is the treatment of choice for the blue nevus of the skin. **Recurrence is minimal with this treatment. Malignant transformation to melanoma is rare but has been reported. However, because an oral blue nevus clinically can mimic an early melanoma, it is usually advisable to** perform a biopsy of Intraoral pigmented lesions, especially because of the extremely poor prognosis for oral melanoma (see page 376).

LEUKOPLAKIA (LEUKOKERATOSIS; ERYTHROLEUKOPLAKIA)

Oral leukoplakia *([leuko* = white; *plnkia* = patch) is defined by the World Health Organization (WHO) as "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 (chronic cheek nibbiing), frictional **keratosis, 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 is not associated with a specific histopathologic diagnosis, it is typically considered to be **a precancerous or premalignant lesion. When the outcome of a large number of leukoplakic lesions is reviewed, the frequency of transformation into malignancy is greater than the risk associated with normal or unaltered mucosa. Because there is considerable misunderstanding** of this concept, Box 10-3 provides definitions that are used throughout the chapter.

Incidence and Prevalence

Although leukoplakia is considered a premalignant lesion, the use of the clinical term in no way suggests that histopathologic features of epithelial dysplasia are present in all lesions. Dysplastic epithelium or frankly **invasive carcinoma is, in fact, found in only 5% to 25%** of biopsy samples of leukoplakia. The precancerous nature of leukoplakia has been established, not so much on the basis of this association or on the fact that more than one third of orai carcinomas have leukoplakia in close proximity, as on the results derived from clinical investigations that followed numerous leukoplakic lesions for long periods. The latter studies suggest a **malignant transformation potential of 4% (estimated** lifetime risk). Specific clinical subtypes or phases, mentioned later, are associated with potential rates as high as 47%. These figures may be artificially low because many lesions are surgically removed at the beginning of follow-up.

Box 10-3 *Precancer Terminology Used ill this Book*

- **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.
- **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.

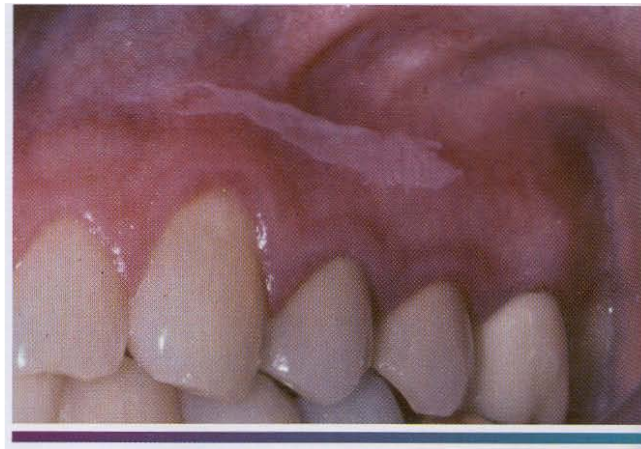

Figure 10-56 • **Sanguinaria-associated keratosis. Thin white plaque on the maxillary alveolar mucosa.**

Leukoplakia is by far the most common oral precancer, **representing 85% of such lesions. It also is relatively** common, with some studies suggesting that it affects as many as 3% of white adults. There is a strong male predilection (70%), except in regional populations in which **women usc 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 on the part of health professionals (rather than because of a real **increase in frequency).**

Etiology

The cause of leukoplakia remains unknown, although hypotheses abound:

Tobacco. The habit of tobacco smoking appears most closely associated with leukoplakia development. More than 80% of patients with leukoplakia arc smokers. When large groups of adults are examined, 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. Also, a large proportion of leukoplakias in persons who stop smoking either disappear or become **smaller within the first year of habit cessation.**

The smokeless tobacco habit produces a somewhat different result. It often leads to a clinically distinctive white oral plaque called tobacco pouch keratosis (see page 346). This lesion probably is not a true leukoplakia.

Alcohol. Alcohol, which seems to have a strong synergistic effect with tobacco relative to oral cancer production, has not been associated with leukoplakia. People **who excessively use mouth rinses with an alcohol con-**tent greater than 25% may have grayish buccal mucosal plaques, but these are not considered true leukoplakia.

Sanguinaria. **Persons who use toothpaste or mouth rinses containing the herbal** extract, **sanguinaria, may** develop a true leukoplakia. This type of leukoplakia **(sanguinaria-as sociated keratosis) is usually located** in the maxillary vestibule or on the alveolar mucosa of the maxilla (Figure 10-56), More than 80% of individuals with vestibular or maxillary 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 lcukoplakias, although the potential *tor* the development of cancer is uncertain. The leukoplakic plaque may not disappear even after the patient stops using the product: some lesions have persisted for years afterwards.

Ultraviolet radiation. **Ultraviolet radiation is** accepted as a causative factor for leukoplakia of the lower lip vermilion. This is usually associated with actinic cheilosis (see page 353). Immunocompromised persons, especially transplant patients, arc especially prone to the development of leukoplakia and squamous cell caret**noma of the lower lip vermilion.**

Mtcroorganisms. **Several microorganisms have** been implicated in the cause of leukoplakia. *Treponemapallidum,* for example. produces glossitis in the late stage of syphilis. **with or without the arsenic therapy in popular use** before the advent *at* modern antibiotics. The tongue is stiff and frequently has extensive dorsal leukoplakia.

Tertiary syphilis is rare today. but oral infections by another microorganism, *Candida albicans.* arc not. *Candida* can colonize the superficial epithelial layers of the oral mucosa, often producing a thick, granular plaque with a

mixed white and red coloration. The terms candidal leukoplakia and candidal hyperplasia have been used to describe such a lesion, and biopsy may show dysplastic or hyperplastic histopathologic changes. it is not known whether this yeast produces dysplasia or secondarily infects previously altered epithelium, but some ofthese **lesions disappear or become less extensive, even** less severely dysplastic, after antifungal therapy. Tobacco smoking may cause the leukoplakia and also predispose thepatient to develop candidiasis.

Human papillomavirus (HPV), in particular subtypes 16 and 18, has been identified in some oral leukoplakias. These are the same HPV subtypes associated with uterine **cervical carcinoma and a subset of oral squamous cell carcinomas. Such viruses, unfortunately, also can be found in** normal oral epithelial cells, and so their presence is perhaps no more than coincidental. It may be significant, however, that HPV-16has been shown to induce dysplasia-like changes in normally differentiating squamous epithelium **in an otherwise sterile *in vitro* environment.**

***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 rather than a response to the carcinogens within** the smoke (see page 350). 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 awhite lesion with a roughened keratotic surface, termed frictional keratosis, Although the resulting lesion is clinically similar to true leukoplakia, such a lesion is now thought to be no more than a normal hyperplastic response (similar to a callus on the skin). Keratoses ofthis typeare readily reversible after elimination of the trauma, and such obviously traumatic lesions as linea alba (see page 253), morsicatio (seepage 2531.and toothbrush gingival "abrasion" **have never been documented to have** transformed into malignancy, nor does the presence of **dentures or broken and missing teeth increase the cancer** risk. Frictional keratosis (Figure 10-57) should be differentiated from the group of oral precancers.

Clinical Features

Leukoplakia usually affects persons older than 40 years of age. Prevalence increases rapidly with age, especially for males, and as many as 8% of men older than 70years of age reportedly are affected (Figure 10-581. The average age of affected persons (60 years) is similar to **the average age 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.**

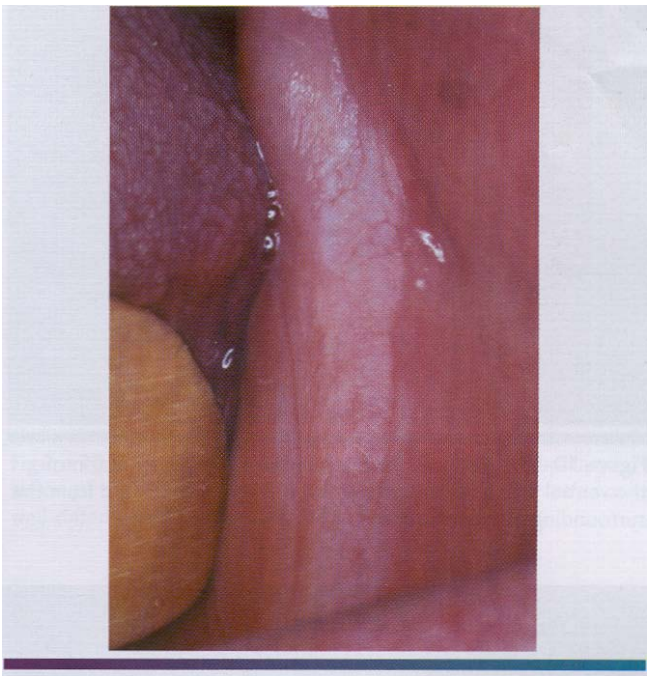

Figure 10-57 • Frictional keratosis. There is a rough. hyperkeratotic change to the posterior mandibular alveolar ridge ("ridge keratosis"), because this area is now edentulous and becomes traumatized from mastication. Such frictional keratoses should resolve when the source of irritation is eliminated and should not be mistaken for true leukoplakia.

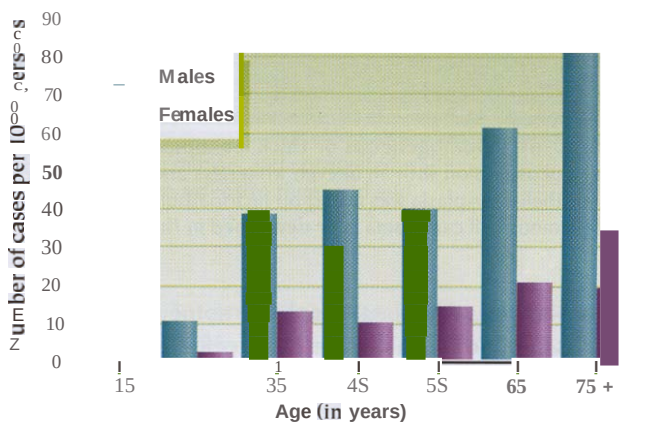

Figure 10-58 • leukoplakia. Age-specific prevalence (number of new cases per 1000 adults examined at various ages) for oral leukoplakia demonstrates increasing prevalence with increasing age. especially for men.

Approximately 70% of oral leukoplakias are found on the lip vermilion, buccal mucosa, and gingiva. Lesions on the tongue, lip vermilion, and oral floor, however, account for more than 90% of those that show dysplasia **or carcinoma.** Individual lesions **may have a varied clin**ical appearance and tend to change over time. Early and mild lesions appear as slightly elevated gray or gray-

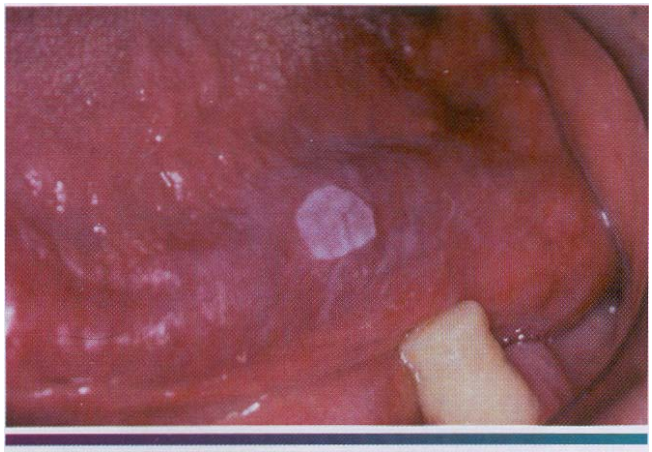

figure 10-59 • Early or thin leukoplakia. This early lesion of the ventral tongue is smooth. white. and well demarcated from the surrounding normal mucosa.

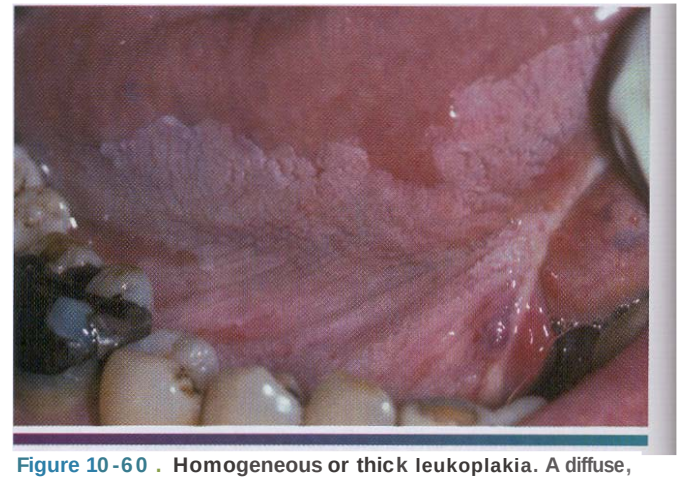

Figure 10-60 . Homogeneous or thick leukoplakia. A diffuse, corrugated white patch on the right ventral surface of the tongue and floor of mouth.

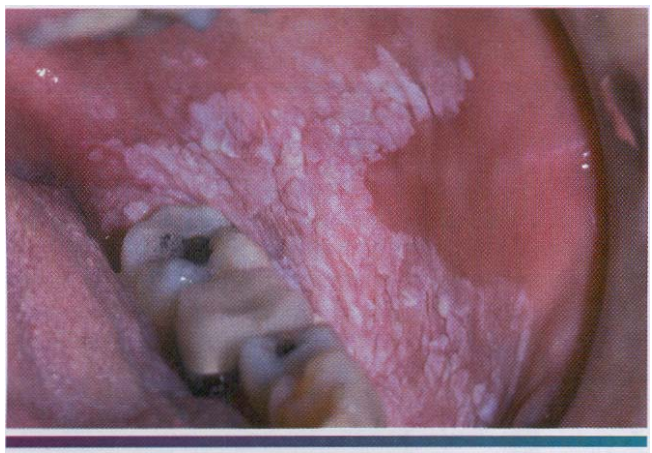

Figure 10-61 • Homogeneous or thick leukoplakia. Extensive buccal mucosa lesion with an uneven whiteness and fissures. Moderate epithelial dysplasia was noted on histopathologic evaluation, and squamous cell carcinoma later developed in this area.

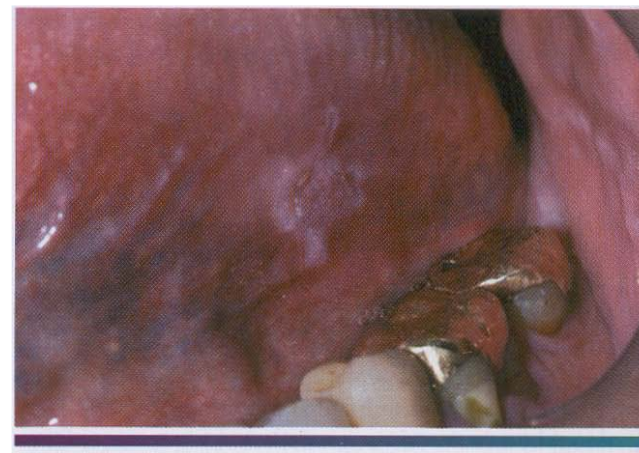

Figure 10-62 • Granular leukoplakia. Focalleukoplakic lesion with a rough, granular surface on the posterior lateral border of the tongue. Biopsy of the lesion revealed an early invasive squamous cell carcinoma.

white plaques, which may appear somewhat translucent, fissured, or wrinkled and are typically soft and flat (Figure 10-59), They usually have sharply demarcated borders but occasionally blend gradually into normal mucosa.

Mild or thin leukoplakia, which seidom shows dysplasia on biopsy, may disappear or continue unchanged, For tobacco smokers who do not reduce their habit, as many as two thirds of such lesions slowly extend laterally, become thicker, and acquire a distinctly white appearance. The affected mucosa may become leathery to palpation, and fissures may deepen and become more numerous. At this stage or phase, the lesion is often called a homogeneous or thick leukoplakia (Figures 10-60 and iO-61). Most thick, smooth lesions remain indefinitely at this stage. Some, perhaps as many as one third, regress or disappear; a few become even more severe, deveiop increased surface irregularities, and are then called granular or nodular leukoplakia (Figures iO-62 and 10-63), Some iesions demonstrate sharp or blunt projections and have been called verrucous or verruciform leukoplakia (Figure iO-64),

A special high-risk form of leukoplakia, proliferative verrucous leukoplakia (PVL), is characterized by the development of multiple keratotic plaques with roughened surface projections (Figure 10-65). The relationship of PVL to cases described as verrucous leukoplakia is uncertain. The multiple PVL plaques tend to slowly spread and involve additional oral mucosal sites. Although the lesions typically begin as simple, flat hyperkeratoses that are indistinguishable from ordinary leukoplakic lesions, PVL exhibits persistent growth, eventually

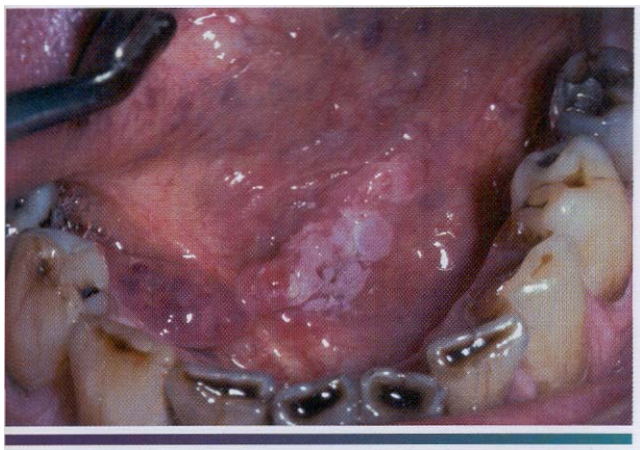

Figure 10-63 • **Granular leukoplakia.** Irregular white patch in the floor of the mouth of a heavy smoker. Early invasive squamous cell carcinoma was found upon biopsy.

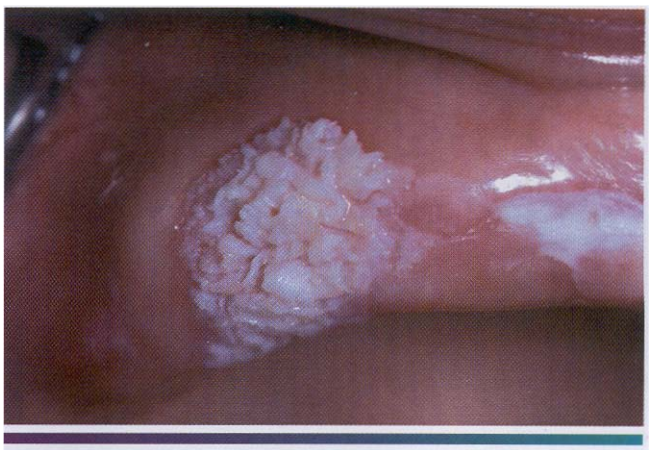

figure 10-64 • **Verruciforrn leukoplakia.** Exophytic papillary lesion of the anterior maxillary alveolar ridge. Biopsy revealed a well-differentiated squamous cell carcinoma.

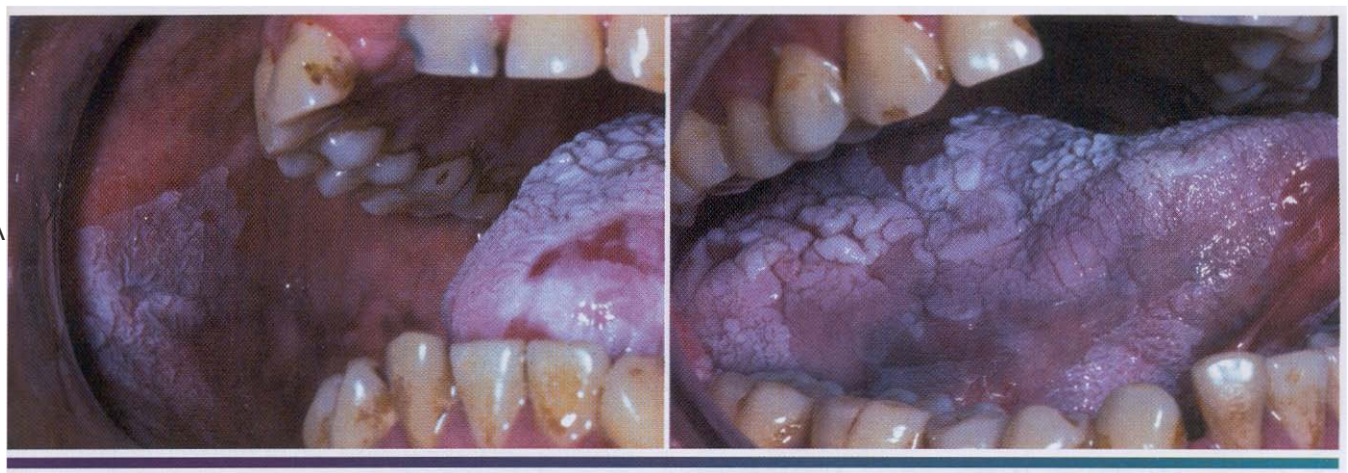

Figure 10-65 • **Proliferative verrucous leukoplakia (PVl). A.** large. diffuse, and corrugated white lesions of the buccal mucosa and tongue. **B,** Same patient showing the extensive thickened and fissured alteration of the tongue.

becoming exophytic and verrucous in nature. As the lesions progress, they may go through a stage indistinguishable from verrucous carcinoma (see page 367), but they later usually develop dysplastic changes and transform into full-fledged squamous cell carcinoma (usually within 8 years of initial PVL diagnosis). These lesions rarely regress 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, even invasive, **with no change in its clinical appearance.** However, some lesions eventually demonstrate scattered patches of redness, called erythroplakla (sec page 345). Such areas usually represent sites in which epithelial cells arc so immature or atrophic that they can no longer produce keratin. This intermixed red-and-white lesion, called erythroleukoplakia or speckled leukoplakia, represents a pattern of leukoplakia that frequently reveals advanced dysplasia upon biopsy (Figure 10-66).

Of course, many leukoplakic lesions are a mixture of the previously mentioned phases or subtypes. Because it is important to perform a biopsy of the lesional site with the greatest potential to contain dysplastic cells. Figures 10-67 and 10-68 provide a clinical and graphic representation of such a lesion. Biopsy sites should be taken from areas with clinical lesional appearances that are most similar to those toward the right in Figure 10-68.

In recent years. attempts have been made to develop **new techniques to aid in the identification and diagnosis of premalignant and malignant** oral lesions. **However, at** the present time, careful clinical evaluation with directed

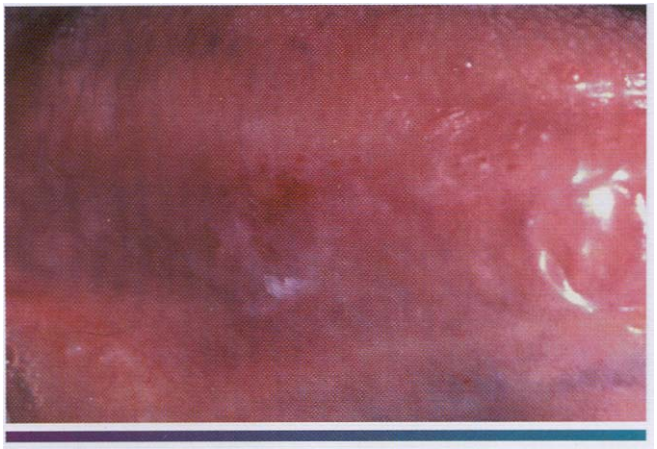

Figure 10-66 • Erythroleukoplakia. Mixed red-and-white lesion of the lateral border of the tongue. Biopsy revealed carcinoma in *situ*.

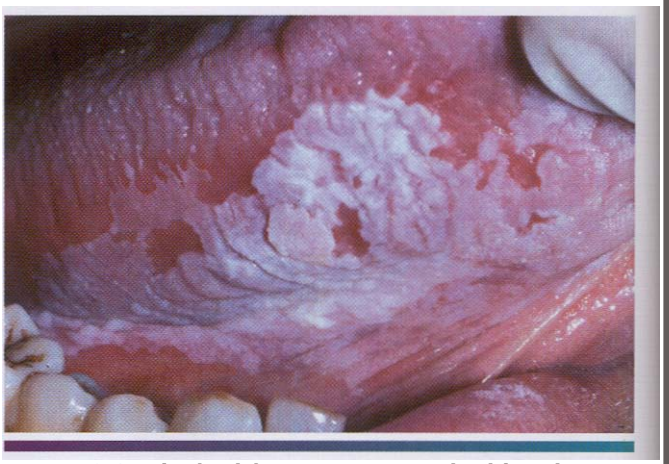

Figure 10-67 • leukoplakia. Extensive ventral and lateral tongue lesion containing multiple areas representing various possible phases or clinical appearances (compare with Figure 10-68).

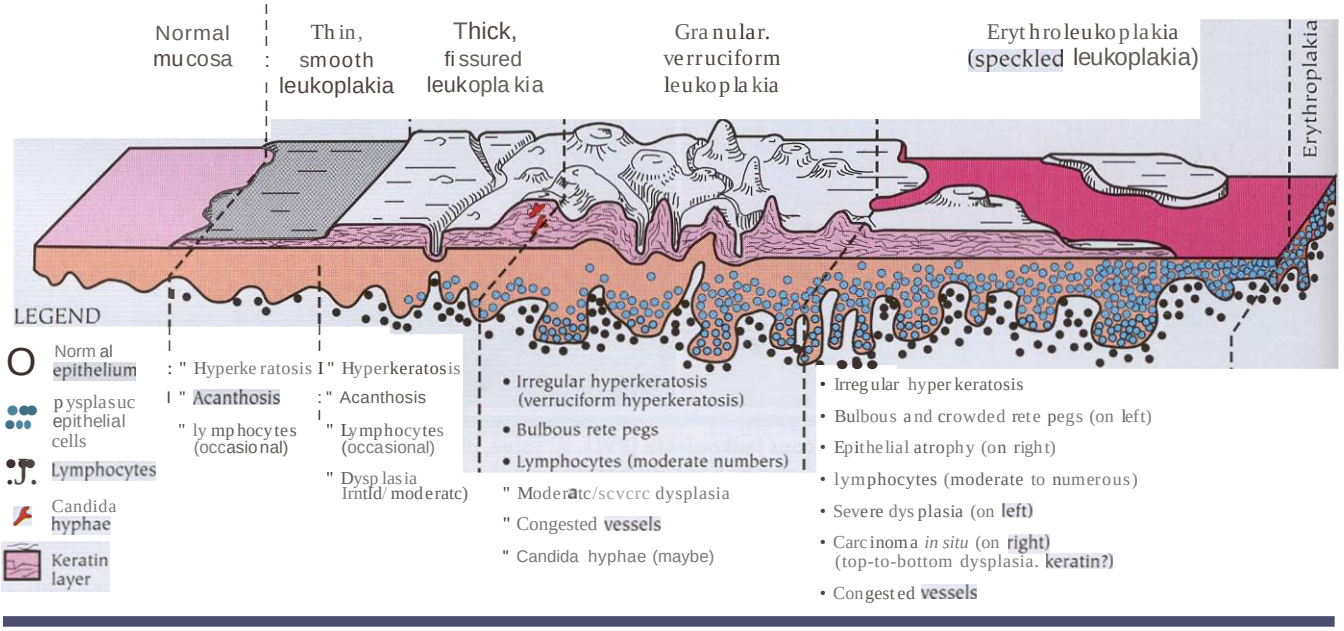

Figure 10-68 • Leukoplakia. Composite representation of the various phases or clinical appearances of oral leukoplakia. with anticipated underlying histopathologic changes. Lesions have increasing malignant transformation potentials as their appearances approach those toward the right. (From Bouquot JE, Gnepp DR: laryngeal precancer-a review of the literature, commentary and comparison with oral leukoplakia. *Head Neck* 13:488-497, 1991.)

conventional biopsy remains the best and most accurate means of assessing oral leukoplakic lesions. In their excellent article, Alexander, Wright, and Thiebaud support this approach when they state, "Noninvasive screening techniques such as cytologic testing (including brush biopsy) and lesion staining with supravital dyes have many pitfalls and should not be considered as substitutes *tor* biopsy when there is concern about malignancy,"

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 arc noted within the subjacent connective tissue.

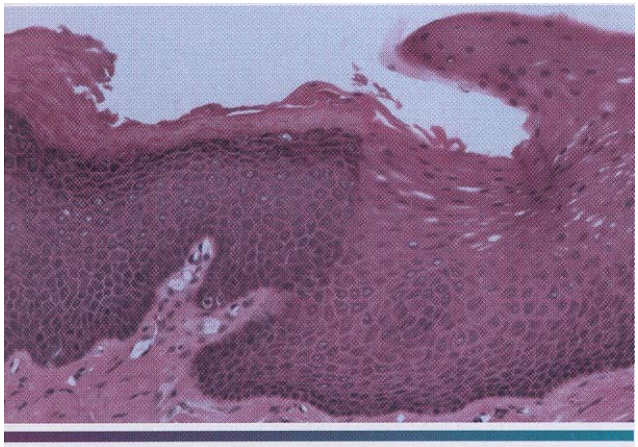

Figure 10-69 • Hyperorthokeratosis. This medium-power photomicrograph demonstrates hyperorthokeratosis with a well-defined granular cell layer on the left side. The right side shows normal parakeratinized epithelium without a granular cell layer.

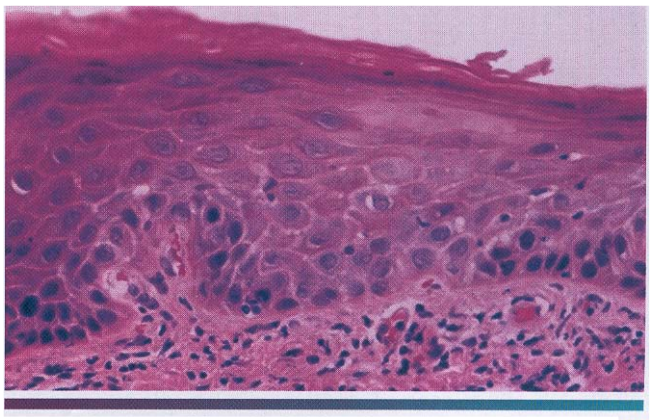

Figure 10-70 . Mild epithelial dysplasia. Hyperchromatic and slightly pleomorphic nuclei are noted in the basal and parabasal cell layers of this stratified squamous epithelium.

The keratin layer may consist of parakeratin (hyperparakeratosis), orthokeratin (hypcrorthokeratosts). or a combination of both (Figure 10-69). 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 it **from early verrucous carcinoma.**

PVL shows a variable microscopic appearance, depending on the stage of the lesions. Early PVL appears as a benign hyperkeratosis that is indistinguishable from other simple leukoplakic lesions. 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 hyper**plasia). In later stages, this papillary proliferation exhibits downgrowth of well-differentiated squamous epithelium with broad, blunt rete ridges. This epithelium demonstrates **invasion into the underlying lamina propria; at this stage, it is indistinguishable from verrucous carci**noma. In the final stages, the invading epithelium becomes less differentiated, transforming into a full-fledged squa**mous cell carcinoma. Because of the variable clinical and** histopathologic appearance of PVL, careful correlation of the clinical and microscopic findings is required for **diagnosis.**

Most leukoplakic lesions demonstrate no dysplasia on biopsy. Evidence of epithelial dysplasia is found in **only 5% to 25% of cases if all oral sites are considered.** When present, these 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:

- 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

When epithelial dysplasia is present, the pathologist provides a descriptive adjective relating to its "severity" or intensity. Mild epithelial dysplasia refers to alterations limited principally to the basal and parabasal layers (Figure 10-70). Moderate epithelial dysplasia **demonstrates involvement from the basal layer to the** midportion of the spinous layer (Figure 10-71). Severe epithelial dysplasia demonstrates alterations from the basal layer to a level above the midpoint of the epithelium (Figure 10-72). Sometimes dysplasia will be seen to extend down the duct of a minor salivary gland, especially in lesions of the floor of the mouth (Figure 10-73).

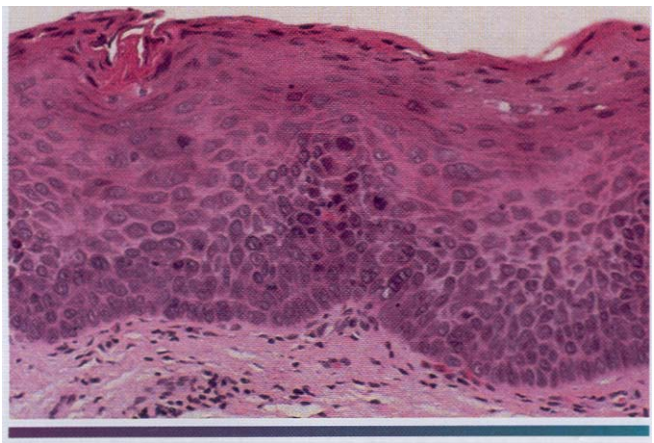

Figure 10-71 • Moderate epithelial dysplasia. Dysplastic changes extend to the midpoint of the epithelium and are characterized by nuclear hyperchromatism, pleomorphism, and cellular crowding.

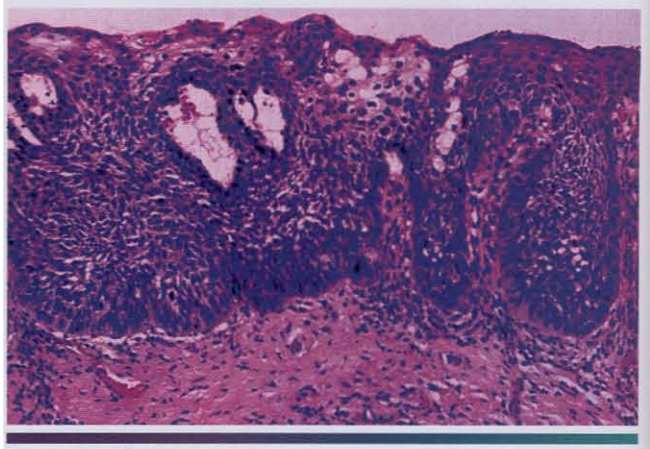

Figure 10-72 • Severe epithelial dysplasia. Cellular crowding and disordered arrangement are noted throughout most of the epithelial thickness, although slight maturation and flattening of the cells appears to be present at the epithelial surface.

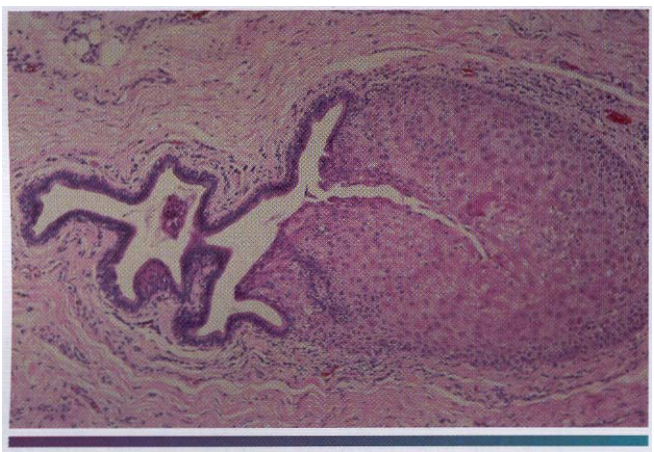

Figure 10-73 • Ductal dysplasia. Salivary gland duct exhibiting squamous metaplasia and dysplasia that originated from an overlying surface epithelial dysplasia.

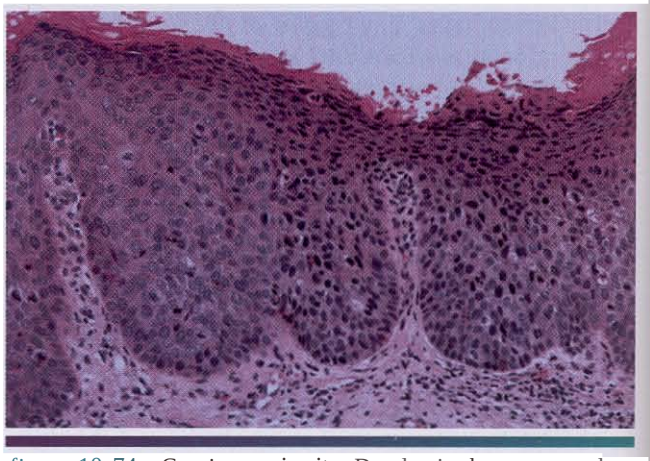

figure 10-74 . Carcinoma *in situ.* Dysplastic changes extend throughout the entire thickness of the epithelium.

When the entire thickness of the epithelium is involved, the term carcinoma *in situ* is used. Carcinoma *in situ* is defined as dysplastic epithelial cells that extend from the basal layer to the surface of the mucosa (rtop-to-bottom" change) (Figure 10-74). There mayor may not be a thin layer of keratin on the surface. The epithelium may be hyperplastic or atrophic. This entity is considered by some authorities to be a precancerous lesion: others believe that it represents a genuine malignancy discovered before invasion. Regardless of the concept preferred, the important feature of carcinoma *in situ* is that no invasion has occurred, despite the fact that the atypical epithelial cells look exactly like those of squamous cell carcinoma (see page 356). Without invasion, the most serious aspect of malignant transformation, metastasis, cannot occur. in this light. it should be mentioned that keratin pearl formation is rare in carcinoma *in situ* and may indicate the presence of a focus of invasive squamous cell carcinoma in the adjacent tissue.

Sometimes dysplasia will be seen extending down the ducts of the minor salivary glands. especially in lesions in the floor of the mouth. When ductal dysplasia occurs in a precancerous surface dysplasia. the recurrence rate is increased. The depth of ductal dysplasia does not appear to be a significant factor.

Treatment and Prognosis

Because leukoplakia represents a clinical term only, the first step in treatment is to arrive at a definitive histopathologic diagnosis. Therefore, a biopsy is mandatory and will guide the course of treatment. Tissue obtained for biopsy, moreover, should be taken from the

clinically most "severe" areas of involvement (with features toward the right side of Figure 10-68). Multiple biopsies of large or multiple lesions may be required.

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 size of the lesion and the response to more conservative measures, such as smoking cessation.

Complete *removal* can be accomplished with equal effectiveness by surgical excision, electrocautery, cryosurgery, or laser ablation. Long-term follow-up after removal is extremely important because recurrences are frequent and because additional leukoplakias may develop. This is especially true for the verruciform or granular types, 83% of which recur and require additional removal or destruction.

Leukoplakia not exhibiting dysplasia often is not excised, but clinical evaluation every 6 months is recommended because of the possibility of progression toward epithelial dysplasia. Additional biopsies are recommended if smoking continues or if the clinical changes increase in severity.

overall, 4% of oral leukoplakias become squamous cell carcinoma after diagnosis, according to follow-up studies. As previously stated, this figure, and those mentioned later, may be artificially low because so many followed cases are treated early in an investigation. Not to do so, of course, raises certain ethical questions; hence, more accurate data may never become available. Other confounding features of leukoplakia follow-up investigations include variations in diagnostic definitions and periods of observation. Typically, the latter extend for 5 to 10 years, but several studies have observed patients with lesions for more than 20 years-one study for more than half a century.

With these caveats in mind, follow-up investigations have demonstrated that carcinomatous transformation usually occurs 2 to 4 years after the onset of the white plaque, but it may occur within months or after decades. Transformation does not appear to depend on the age of the affected patient.

Although dysplasia may be present in any leukoplakia, each clinical appearance or phase of leukoplakia has a different malignant transformation potential. Thin leukoplakia seldom becomes malignant without demonstrating a clinical change. Homogeneous, thick leukoplakia undergoes malignant transformation in 1% to 7% of cases. Once the surface becomes granular or verruciform, the malignant transformation potential becomes 4% to 15%. Erythroleukoplakia carries an average transformation potential of 28%, but the rates have varied from 18% to 47% in different investigations.

The increased frequency of transformation of the different phases of leukoplakia is related closely to the degree of dysplasia present. The greater the clinical *severity,* the greater the chance of significant dysplasia and malignant transformation. Estimates of the malignant potential for histopathologically proven dysplastic lesions are, unfortunately, open to question because so many are excised completely. Thus, their true biologic behavior in an unaltered state may not be appreciated fully. With this understanding, however, lesions diagnosed as moderate and severe dysplasia reportedly have malignant transformation potentials of 4% to 11% and 20% to 35%, respectively. Cancers from dysplastic lesions usually develop within 3 years of the dysplasia diagnosis, but can occur much later. Additionally, one in three dysplasias will recur after complete *removal.*

In addition to the clinical and histopathologic appearance at diagnosis, several factors may increase the risk for cancer in leukoplakic lesions. These include persistence over several years, occurrence in a female patient, occurrence in a nonsmoker, and occurrence on the oral floor or ventral tongue. Leukoplakia of the latter two locations has shown malignant transformation in 16% to 39% of all cases and 47% of those occurring in females.

Some smoking-related leukoplakias with no or minimal dysplasia may disappear or diminish in size within 3 months after the patient stops smoking. Thus habit cessation is recommended. Chemoprevention also may be useful, but remains primarily experimental. High doses of isotretinoin (13-cis-retinoic acid, a form of vitamin A) followed by a course of low-dose isotretinoin or beta-carotene have been reported to reduce or eliminate some leukoplakic lesions in short-term studies. Toxic reactions to systemic retinoids are frequent, however, as is lesion recurrence after the conclusion of therapy.

ERYTHROPLAKIA (ERYTHROPLASIA; ERYTHROPLASIA OF QUEYRAT)

As with leukoplakia, erythroplakia is defined as a red patch that cannot be clinically or pathologically diagnosed as any other condition. The term *erythroplasia* originally was used by Queyrat to describe a precancerous red lesion that develops 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 unknown, but they are presumed to be the same as those associated with invasive squamous cell carcinoma of the mouth (see page 356).

The point prevalence rate (number of persons with active lesions at a given point in time) of oral erythroplakia has been estimated as 1 per 2500 adults. The inci-

dence is not known. but the average annual incidence for microscopically proven oral carcinoma *in situ,* which represents the great majority of erythroplakias, has been estimated to be 1,2 per 100,000 population (2.0 in males and 0.5 in females) in the United States.

Erythroplakia also may occur in conjunction with leukoplakia (see page 337l 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 invasive malignancy at a later time.

Clinical Features

Erythroplakia is predominantly a disease of older men, with a peak prevalence at 65 to 74 years. The floor of mouth, tongue, and soft palate are the most common sites of involvement, and multiple lesions may be present.

The altered mucosa appears as a well-demarcated erythematous macule or plaque with a soft, velvety texture (Figure 10-75). It is usually asymptomatic and may be associated with an adjacent leukoplakia (erythroleukoplakia) (see Figure 10-67l. Nonspecific mucositis, candidiasis. psoriasis, or vascular lesions may clinically mimic erythroplakia, and biopsy often is required to distinguish between them.

Histopathologic Features

According to one large clinicopathologic investigation, 90% of erythroplakic lesions histopathologically represent either severe epithelial dysplasia (sec page 343), carcinoma *in situ* (see page 344), or superficially invasive squamous cell carcinoma (see page 365). The epithelium shows a lack of keratin production and often is atrophic, but it may be hyperplastic. This lack of keratinization, especially when combined with epithelial thinness, allows the underlying microvasculature to show through, thereby explaining the red color. The underlying connective tissue often demonstrates chronic inflammation.

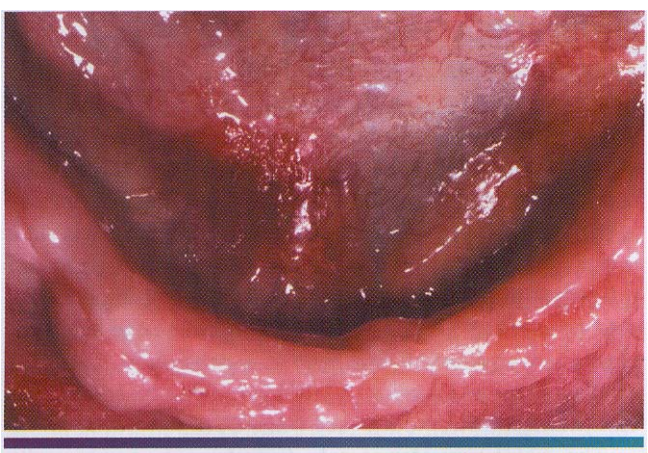

Figure 10-75 • Erythroplakia. An erythematous macular lesion is seen on the right floor of the mouth with no associated leukoplakia. Biopsy showed early invasive squamous cell carcinoma.

Treatment and Prognosis

Red lesions of the oral mucosa, especially those of the oral floor and ventral or lateral tongue, should be viewed with suspicion, and a biopsy should be performed. If a source of irritation can be identified and removed, biopsy of such a lesion 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 definitive diagnosis obtained by biopsy. Lesions exhibiting moderate dysplasia or worse must be removed completely or destroyed by the methods used for leukoplakia (see page 344). It is best, however, to preserve most of the specimen for microscopic examination because of the possibility that a focal invasive carcinoma might be missed in the initial biopsy material. Recurrence and multifocal oral mucosal involvement are common with erythroplakia; hence, long-term follow-up is suggested for treated patients.

SMOKELESS TOBACCO USE AND SMOKEIESS TOBACCO KERATOSIS (SNUFF POUCH; SNUFF DIPPER'S IESION; TOBACCO POUCH KERATOSIS; SPIT TOBACCO KERATOSIS)

The habit of chewing coarsely cut tobacco leaves (chewing tobacco) or holding finely ground tobacco leaves (snuff) in the mandibular vestibule was once almost universal in the United States and is still common among certain populations around the world, most notably in India and Southeast Asia. Either habit is referred to as smokeless tobacco use or spit tobacco use. The latter term is preferred by the U.S. federal government in its attempt to diminish the appeal of the habit. At present, the proportion of adult men in the United States who regularly use spit tobacco approximates 6%. Among young men it is more than 10%, and the proportion is as high as 21 % in some Southeastern and Midwestern states. The habit is started early in life, usually at 8 to 14 years of age, and rarely is initiated after 20 years of age. A recent national survey detected smokeless tobacco lesions of all types in 1.5% (2.9% in males, 0.1% in females) of U.S. adolescents and teenagers.

Clinical Features

Several health and addiction hazards may be associated with the use of spit tobacco because of the ready absorption of nicotine and other molecules through the oral

mucosa. A variety of local oral alterations also arc found in chronic users. One of the most common local changes is a characteristic painless loss of gingival and periodontal tissues in the area of tobacco contact (Figure 10-76). This gingival "recession" frequently includes destruction of the facial surface of the alveoiar bone and correlates well with the quantity of daily use and the duration of the smokeless tobacco habit.

Dental caries also has been reported to be more prevalent in spit 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 persons employed in dusty environments. A brown-black extrinsic tobacco stain is typically found on the enamel and cementum surfaces of the teeth adjacent to the tobacco. In addition, halitosis is a frequent finding in chronic users.

A characteristic white plaque. the smokeless tobacco keratosis. also is produced on 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. The development of this lesion is most strongly influenced by habit duration and also by the brand of tobacco used, early onset of spit tobacco use, total hours of daily use, amount of tobacco consumed daily. and number of sites routinely used for tobacco placement. In India, smokeless tobacco keratosis (which is often mistakenly referred to as leukoplakia) is much more prevalent, presumably because of the Increased hours of daily use and the use of different tobacco leaves combined in a quid with other products. such as betel leaves, areca nuts, and slaked lime (see the discussion of oral submucous fibrosis on page 349).

Smokeless tobacco keratosis in many western cultures is usually noted in young adult men and in men older than 65 years of age, because the habit has not been popular among the generation that is now middle-aged. In some populations. the prevalence of smokeless tobacco keratosis (and the smokeless tobacco habit) is most frequent 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 lesion is confined to areas in direct contact with spit tobacco. It is typically a thin. gray or gray-white. almost "translucent," plaque with a border that blends gradually into the surrounding mucosa (Figure to-77). Sometimes mild peripheral erythema is present.

The altered mucosa typically has a soft velvety feel to palpation. and stretching of the mucosa often reveals a distinct "pouch" (snuff pouch. tobacco pouch) caused by flaccidity in the chronically stretched tissues in the area of tobacco placement. Because the tobacco is not in the mouth during a clinical examination. the usually stretched 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 are held chronically in the vestibule (e.g.. hard candy), Induration. ulceration, and pain are not associated with this lesion.

Smokeless tobacco keratosis usually takes I 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 white lesion gradually becomes thickened to the point of appearing leathery or nodular (Figure 10-78).

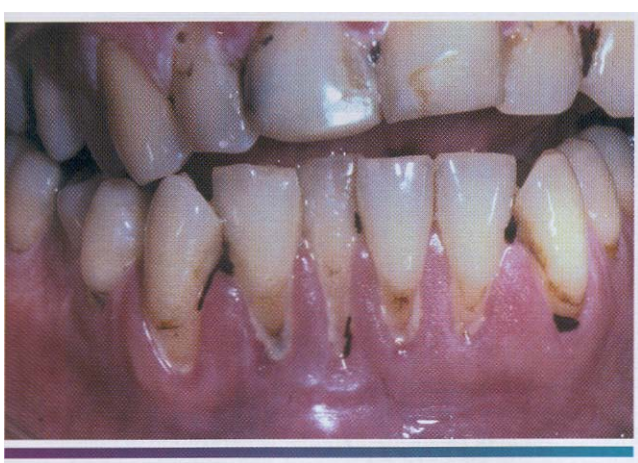

Figure 10-76 • Smokeless tobacco-related gingival recession. Extensive recession of the anterior mandibular facial gingiva.

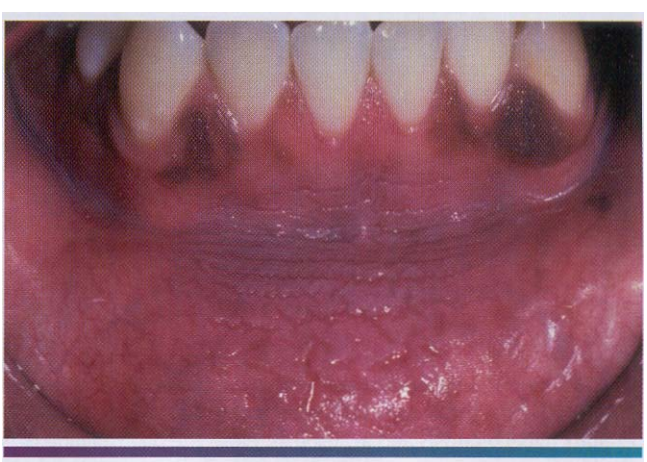

Figure 10-77 . Tobacco pouch keratosis, mild. A soft. fissured. gray-white lesion of the lower labial mucosa located in the area of chronic snuff placement. The gingival melanosis is racial pigmentation and not associated with the keratosis.

Histopathologic Features

The histopathologic appearance of smokeless tobacco keratosis is not specific. The squamous epithelium is hyperkeratinized and acanthotic, with or without intracellular vacuolization or "edema" of glycogen-rich superficial cells (Figure 10-79). Parakeratin chevrons may be seen as pointed projections above or within superficial epithelial layers (Figure 10-80). Increased subepithelial vascularity and vessel engorgement often are seen. In some cases, an unusual deposition of amorphous eosinophilic material is noted within the subjacent connective tissue and salivary glands (Figure 10-81). Epithelial dysplasia is uncommon in smokeless tobacco keratosis and, when present, is typically mild. Occasionally, *however,* significant dysplasia or squamous cell carcinoma may be present.

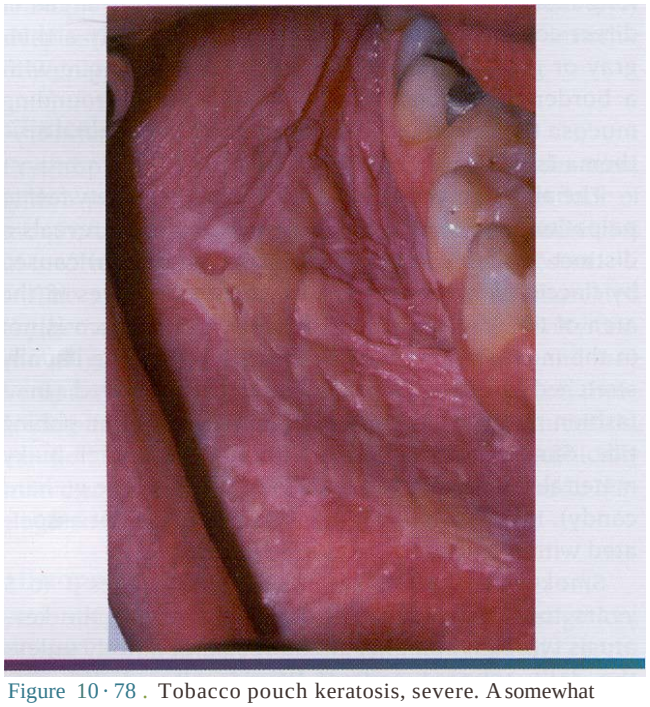

Figure 10·78. Tobacco pouch keratosis, severe. A somewhat leathery, white, fissured plaque of the posterior mandibular vestibule, which is located in the area of chronic chewing tobacco placement.

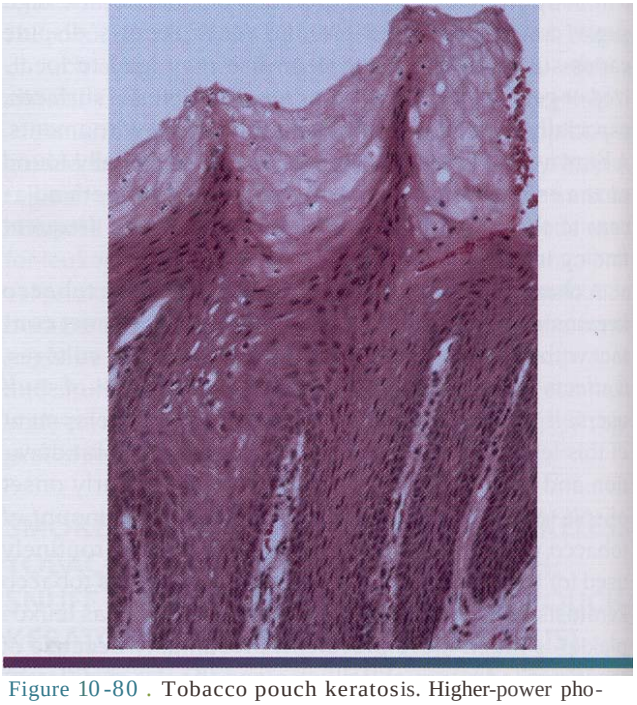

Figure 10-80. Tobacco pouch keratosis. Higher-power photomicrograph of Figure 10·79 showing hyperkeratosis with "chevron" formation.

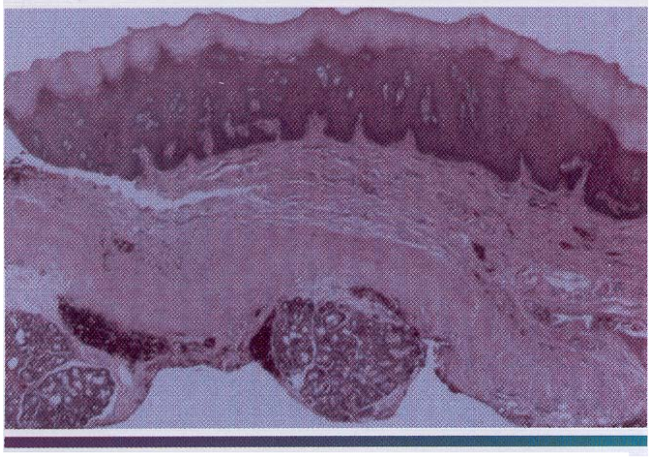

Figure 10-79 • Tobacco pouch keratosis. The epithelium exhibits hyperkeratosis and acanthosis. Note the pale staining of the keratin.

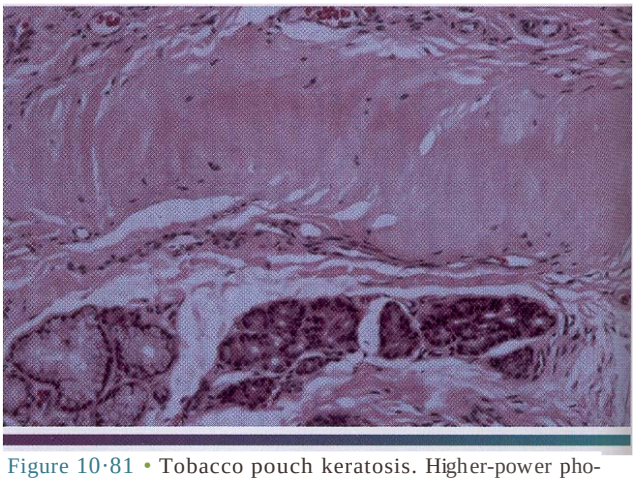

Figure 10·81 • Tobacco pouch keratosis. Higher-power photomicrograph of Figure 10-79 showing deposition of homogeneous eosinophilic material above the minor salivary glands.

Treatment and Prognosis

Chronic use of smokeless tobacco in the United States is considered to be carcinogenic. Fortunately, the clinical **appearance of smokeless tobacco keratosis is distinct** enough and the malignant transformation potential is low enough so that biopsy is needed for only the more severe **lesions** (i.e., **those demonstrating an intense whiteness. agranular or verruciform clinical appearance. ulceration.** mass formation, induration, or hemorrhage). Obviously, treatment would then depend on the histopathologic diagnosis. Without microscopic evidence of dysplasia or malignancy, keratoses are not treated. Alternating the tobaccochewing sites between the left and right sides will **eliminate or reduce the keratotic lesion** but **may result in** epithelial alteration or gingival and periodontal difficul**ties in two sites** rather **than one.**

One U.S. study showed that the risk of developing oral **cancer was about four times greater in chronic smokeless tobacco users than in nonusers. Recent** studies **from** Sweden, however, have failed to show an increased risk for users of Swedish moist snuff. On the Indian subcontinent, the long-term risk of oral cancer for betel quid users is much higher (8%); 2% of biopsied keratotic lesions in those users already have evidence of malignancy. Even without tobacco in the betel quid, the risk of malignant transformation is approximately 10 times higher than normal.

Squamous cell carcinoma is the most common malignancy resulting from this habit, but an uncommon and **relatively unique low-grade oral malignancy. verrucous** carcinoma ("snuff dipper's" cancer), may also be associated with spit tobacco use (see page 367).

Significantly, habit cessation leads to a normal mucosal appearance (usually within 2 to 6 weeks) in 98% of smokeless tobacco keratosis lesions that are not intensely white (Figure 10-82). A lesion that remains after 6 weeks without smokeless tobacco contact should be considered to be a true leukoplakia and should be sampled for biopsy and managed accordingly.

ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis is a chronic, progressive, scarring, high-risk precancerous condition of the oral mucosa seen primarily on the Indian subcontinent and in Southeast Asia. It has been linked to the chronic placement in the mouth of a betel quid or *paan* and is found in 0.4% of India's villagers. The quid consists typically of areca nut and slaked lime, usually with tobacco and **sometimes with sweeteners and condiments. wrapped in** a betel leaf. The slaked lime acts to release an alkaloid (arccaidlne) from the areca nut, producing a feeling of euphoria and well-being in the user, Villagers habitually chew betel quids from an early age, frequently for 16 to 24 hours daily.

The condition is characterized by a mucosal rigidity of varied intensity caused by a fibroelastic hyperplasia and modification of the superficial connective tissue. The **submucosal changes may be a response to the areca nut;** the epithelial alterations and carcinogenesis may be the **result of tobacco contact. Nutritional deficiency increases the risk and severity of fibrosis, and some persons seem** to have a genetic predisposition to it. A few individuals have developed the disease after only a few contacts with **areca nut.**

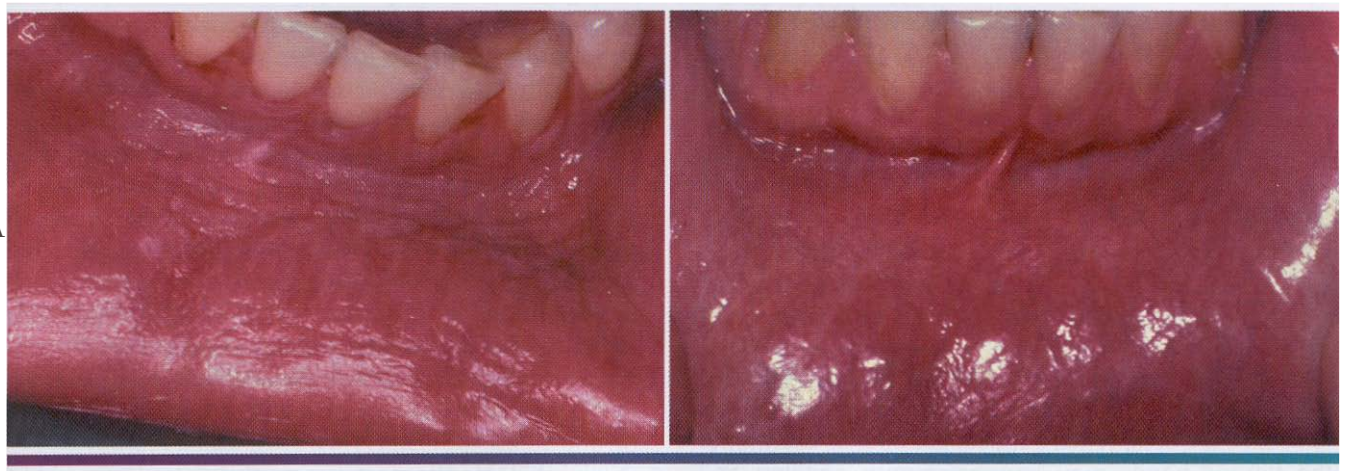

Figure 10-82 • Tobacco pouch keratosis. A, Moderately severe lesion of the lower anterior vestibule and lip in a 15-year-old male, which demonstrates a grayish-white surface change and fissuring. The patient had been placing snuff in the area for several years. B, Two weeks after cessation of the tobacco habit the mucosa has returned to an almost normal appearance.

Clinical Features

Oral submucous fibrosis often is first noted in young adult betel quid users. whose chief complaint is an inability to open the mouth (trismus). often accompanied by mucosal pain while eating spicy foods. An interincisal distance of less than 20 mm is considered severe; in advanced cases, the jaws may actually be inseparable. Females are more susceptible to these changes than males.

Vesicles, petechiae, melanosis. xerostomia, and a generalized oral burning sensation (stomatopyrosls) are usually the first signs and symptoms. The buccal mucosa, retromolar area, and soft palate are the most commonly affected sites. The mucosa in these regions develops a blotchy. rnarblchke pallor and a progressive stiffness of subepithelial tissues (Figure 10-83), When the tongue is involved, it becomes rather immobile. is frequently diminished in size. and may be devoid of papillae. Submucosal fibrous bands are palpable on the buccal mucosa. soft palate. and labial mucosa of fully developed cases. Leukoplakia of the surface mucosa often is noted.

Betel quid chewers also may exhibit a brownish-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.

Histopathologic Features

Oral submucous fibrosis is characterized by the submucosal deposition of extremely dense and avascular collagenous connective tissue with variable numbers of chronic inflammatory cells. sometimes imparting a lichenoid appearance. 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.

The lesions of so-called betel chewer's mucosa are histopathologically similar to morsicatlo buccarum (see page 253). except that the ragged keratinaceous surface is covered by encrustations of betel quid ingredients.

Treatment and Prognosis

Unlike tobacco pouch keratosis. oral submucous fibrosis does not regress with habit cessation. Patients with mild cases may be treated with intralesional corticosteroids to reduce the symptoms: surgical splitting or excision of the fibrous bands may improve mouth opening and mobility in the later stages of the disease. One recent study showed that intralesional injections of interferon *gamma* improved maximum mouth opening. reduced mucosal burning. and increased suppleness of the buccal tissues.

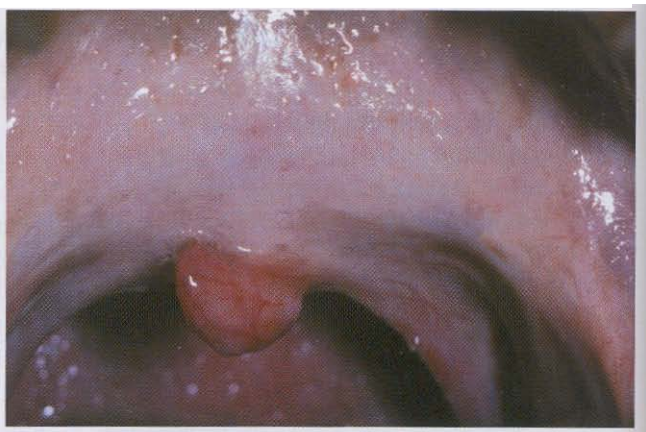

Figure 10-83 • Oral submucous fibrosis. Pallor and fibrosis of the soft palate in a betel quid chewer. The uvula has retained its normal color.

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 as cigar and pipe smoking have lost popularity. Although this lesion is a white keratotic change obviously 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. Because pipe smoking generates more heat on the palate than other forms of smoking, nicotine stomatitis has been associated most often with this habit. Similar changes can also 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 carcinorna.

Clinical Features

Nicotine stomatitis most commonly is found in men older than 45 years of age. 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 (Figures 10-84 and 10-85). Such papules represent inflamed minor salivary glands

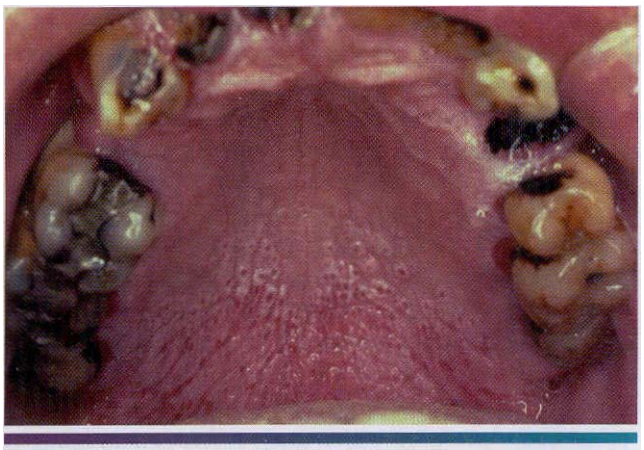

Figure 10-84 • Nicotine stomatitis. This extensive leathery, white change of the hard palate in a pipe smoker is sprinkled throughout with numerous red papules. which represent inflamed salivary duct openings. The gingival mucosa also is keratotic.

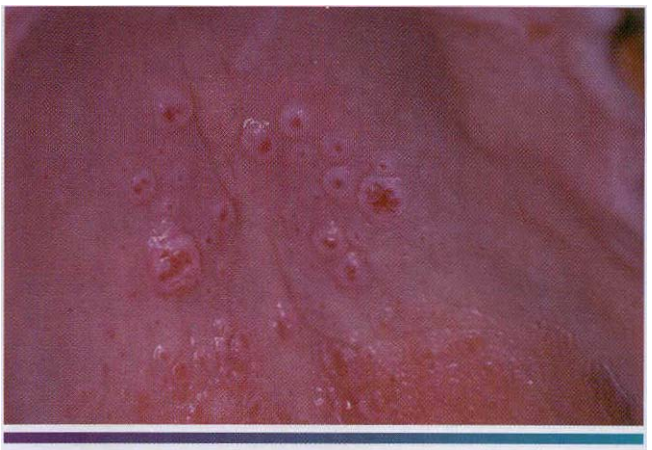

Figure 10-85 • Nicotine stomatitis. Close-up of the inflamed ductal openings of involved salivary glands of the hard palate. Note the white keratotic ring at the lip of many of the Inflamed ducts.

and their ductal orifices. The mucosa that covers the papules frequently appears whiter than the surrounding epithelium.

The palatal keratin may become so thickened that a fissured or "dried mud" appearance is imparted. The whiteness usually involves marginal gingiva and interdental papillae. and leukoplakia of the buccal mucosa is occasionally 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 (Figure 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 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 returns to normal. usually within I to 2 weeks of smoking cessation. Although this is not a precancerous lesion and no treatment is needed. 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 I month of habit cessation should be considered a true leukoplakia and managed accordingly (see page 344).

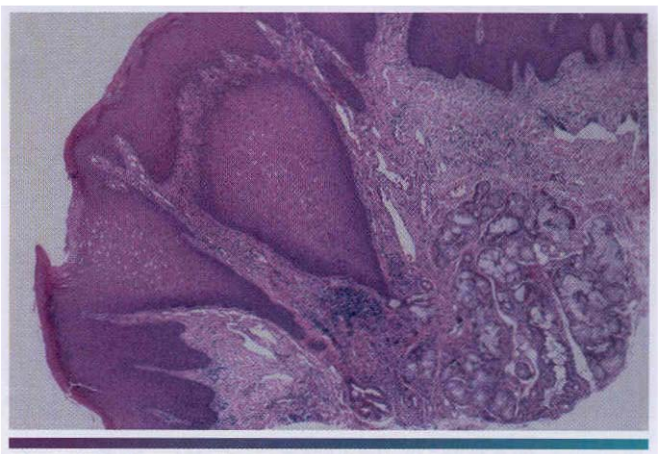

Figure 10-86 • Nicotine stomatitis. There is hyperkeratosis and acanthosis of the palatal epithelium. Note the squamous metaplasia of the minor salivary gland ducts.

ACTINIC KERATOSIS (SOLAR KERATOSIS)

Actinic keratosis is a commoncutaneous **premalignant lesion that is caused by cumulative ultraviolet radiation** to sun-exposed skin. especially in fair-skinned people. Ultraviolet light exposure can produce mutations in the p53 tumor suppressor gene. an alteration found frequently in this and other precancers and cancers of the head and neck region. A similar phenomenon. actinic cheilosis. is associated with sun damage to the lower lip vermilion (see page 353>'

The lesion will develop on the skin of more than 50% of all white adults with significant lifetime sun exposure. and in the U.S. white population the prevalence rate is 15% for older men and 6% for older women. The prevalence increases with advancing age. Although the exact

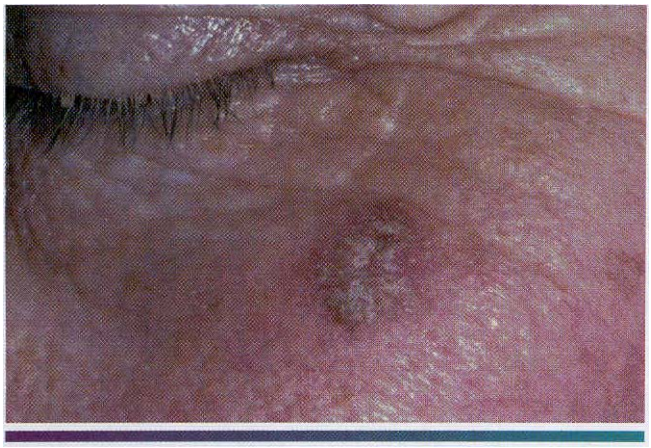

Figure 10-87 • Actinic keratosis. A plaque of the skin of the face with a rough, sandpaper-like surface.

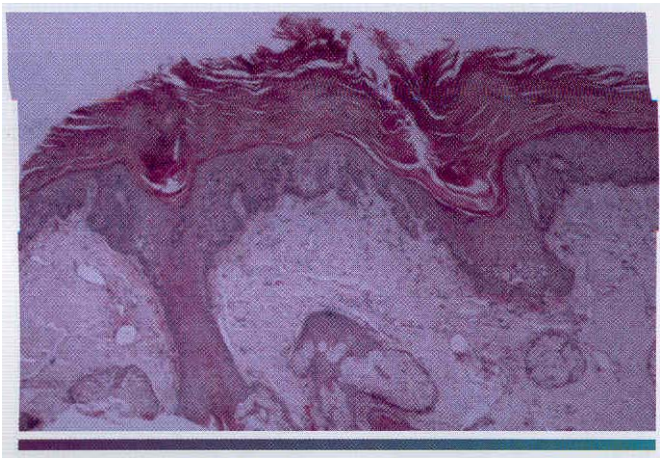

Figure 10-88 • Actinic keratosis. An extremely excessive amount of parakeratin is noted on the epidermal surface.

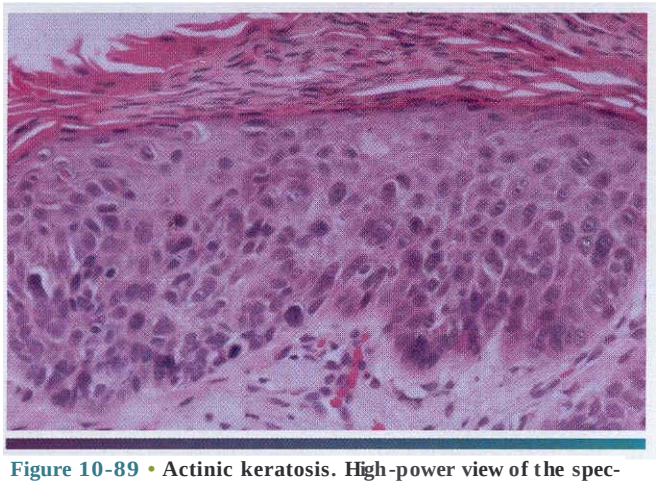

Figure 10-89 • Actinic keratosis. High-power view of the specimen depicted in Figure 10-88. Note the hyperchromatism and pleomorphism of the epidermal cells.

frequency of malignant transformation is unknown, it has been estimated that only one in a thousand individual lesions will become invasive. In high-risk populations, however, at least 13% of affected patients will develop invasive squamous cell carcinoma from at least one of their actinic keratoses.

Clinical Features

Actinic keratosis seldom is found in persons younger than 40 years of age. The face and neck, the dorsum of the hands, the forearms, and the scalp of bald-headed men are the most common sites of occurrence. Individual lesions are irregular scaly plaques, which vary in color from normal to white, gray, or brown, and may be superimposed on an erythematous background (Figure 10-87). The keratotic scale peels off with varying degrees of difficulty. Palpation reveals a "sandpaper," roughened texture, and some lesions can be felt more easily than they can be seen. Typically, a lesion is smaller than 7 mm in diameter but may reach a size of 2 cm, usually with minimal elevation above the surface of the skin. Occasional lesions, however, produce so much keratin that a "horn" may be seen arising from the central area. 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 (Figure 10-88). Teardrop-shaped rete ridges typically extend down from the epithelium; by definition, some degree of epithelial dysplasia is present (Figure 10-89). When full-thickness dysplasia is noted, this is termed bowenoid actinic keratosis. Suprabasilar acantholysis may be seen, as may melanosis and a lichenoid inflammatory infiltrate. The dermis exhibits a band of pale basophilic change, which represents 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 is increased with increased exposure to actinic rays. Variable numbers of chronic inflammatory cells are typically present.

Treatment and Prognosis

Because of its precancerous nature, it is usually recommended that actinic keratosis be destroyed by cryotherapy with liquid nitrogen, topical application of 5-fluorouracil, curettage, electrodesiccation, or surgical excision. Recurrence is rare, but additional lesions frequently arise in adjacent sun-damaged skin. Long-term follow-up, therefore, is recommended.

ACTINIC CHEILOSIS (ACTINIC CHEILITIS)

Actinic cheilosis is a common premalignant alteration of the lower lip vermilion that results from long-term or excessive exposure to the ultraviolet component of sunlight. It is a problem confined predominantly to light-complexioned people with a tendency to sunburn easily. Outdoor occupation obviously is associated with this problem, leading to the popular use of terms such as farmer's **lip** and sailor's lip. A person with chronic sunlight exposure and compromised immunity, especially a transplant recipient, has an elevated risk of developing a cancer of the lower lip vermilion.

Actinic cheilosis is similar to actinic keratosis of the skin (see previous topic) in its pathophysiologic and biologic behavior.

Clinical Features

Actinic cheilosis seldom occurs in persons younger than 45 years of age. It has a strong male predilection, with a male-to-female ratio as high as 10:1 in some studies.

The lesion develops so slowly that patients often are not aware of a change. The earliest clinical changes include atrophy of the lower lip vermilion border, characterized by a smooth surface and blotchy pale areas. Blurring of the margin between the vermilion zone and the cutaneous portion of the lip is typically seen (Figure 10-90). As the lesion progresses, rough, scaly areas develop on the drier portions of the vermilion. These areas thicken and may appear as leukoplakic lesions, especially when they extend near the wet line of the lip. The patient may report that the scaly material can be peeled off with some difficulty, only to reform again within a few days.

With further progression, chronic focal ulceration may develop in one or more sites, especially at places of mild trauma from cigarettes or pipe stems (Figure 10-91). Such ulcerations may last for months and often suggest **progression to early squamous cell carcinoma.**

Histopathologic Features

Actinic cheilosis is usually characterized by an atrophic stratified squamous epithelium, often demonstrating marked keratin production. Varying degrees of epithelial dysplasia may be encountered. A mild chronic inflammatory cell infiltrate commonly is present subjacent to the dysplastic epithelium. The underlying connective tissue invariably demonstrates a band of amorphous, acellular, basophilic change known as solar (actinic) elastosis, an ultraviolet light-induced alteration of collagen and elastic fibers (Figure 10-92).

Treatment and Prognosis

Many of the changes associated with actinic cheilosis are probably irreversible, but patients should be encouraged

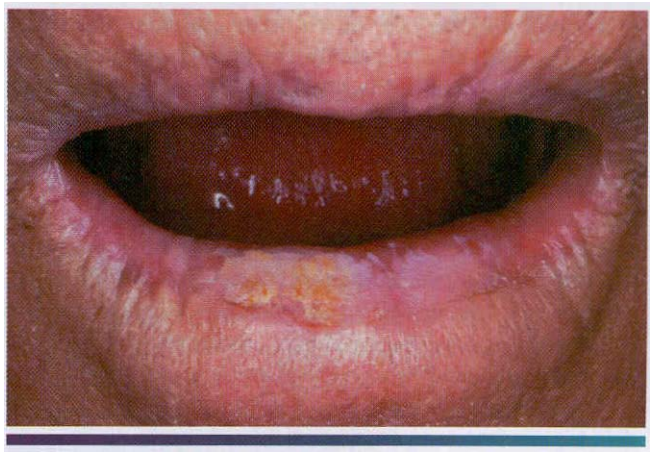

Figure 10-90 • Actinic cheilosis. A blurring of the interface between the vermilion mucosa and the skin of the lip is especially noted in this case.

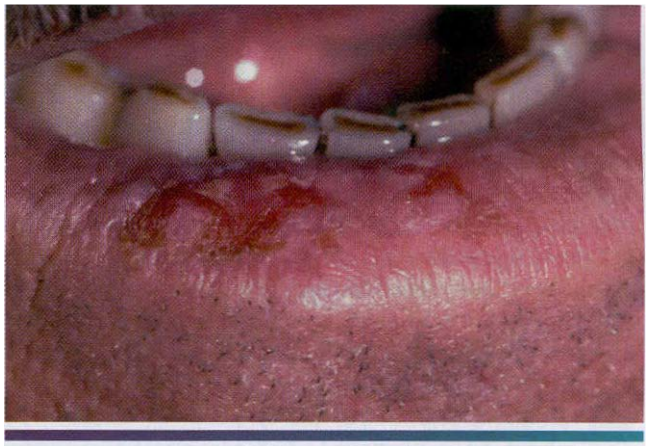

Figure 10-91 • Actinic cheilosis. Crusted and ulcerated lesions of the lower lip vermilion.

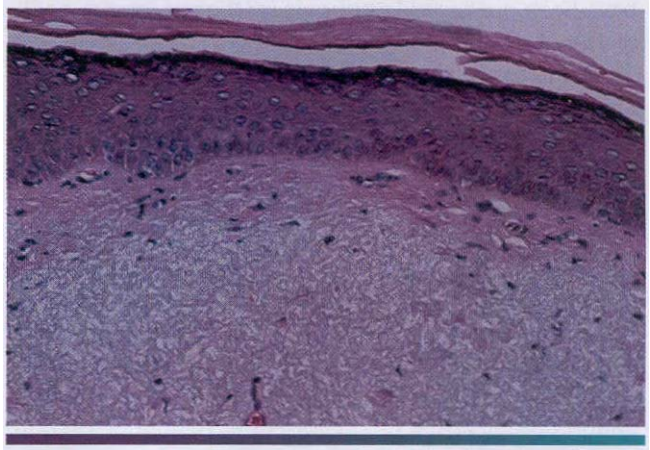

Figure 10-92 • Actinic cheilosis. Hyperorthokeratosis and epithelial atrophy. Note the striking underlying solar elastosis.

to use lip balms with sunscreens 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 malignancy. 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. Alternative treatments include CO, laser ablation and electrodesiccation. Long-term follow-up is recommended. Of course, if a squamous cell carcinoma is identified. the involved lip is treated accordingly.

Squamous cell carcinoma. usually well differentiated. develops over time in 6% to 10% of actinic cheilosis cases reported from medical centers. Such malignant transformation seldom occurs before 60 years of age, with the resulting carcinoma typically enlarging slowly and metastasizing only at a late stage.

KERATOACANTHOMA ("SELF-HEALING" CARCINOMA; PSEUDOCARCINOMA)

Keratoacanthoma is a self-limiting. epithelial proliferation with a strong clinical and histopathologic similarity to well-differentiated squamous cell carcinoma. In fact. some authorities consider it to represent an extremely well-differentiated form of squamous cell carcinoma. Cutaneous lesions presumably arise from the infundibulum of hair follicles. Intraoral lesions have been reported. but they are rare and. in fact. some authorities do not accept keratoacanthoma as an intraoral disease.

The cause of this lesion is unknown. but sun damage and human papillomavirus (HPV). possibly subtypes 26 or 37. have been proposed. The association with sun damage is suggested by the fact that most solitary lesions are found on sun-exposed skin. predominantly in the elderly. In addition. 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 immunosuppressed patients and those with Muir-Terre syndrome (sebaceous neoplasms. keratoacanthomas. and gastrointestinal carcinomas).

Clinical Features

Keratoacanthoma rarely occurs in patients before 45 years of age and shows a male predilection. Almost 95% of solitary lesions are found on sun-exposed skin. and 8% of all cases are found on the outer edge of the vermilion border of the lips. with equal frequency on both the upper and lower lips.

Keratoacanthoma appears as a firm. nontendcr, well-demarcated. sessile. dome-shaped nodule with a central plug of keratin (Figures 10-93 and 10-94), although lesions reported as intraoral keratoacanthoma usually have lacked the central plug. The outer portion of the nodule has a normal texture and color but may be erythematous. The central keratin plug is yellowish. brown. or black and has an irregular. crusted. often verruciform surface.

Rapid enlargement is typical. with the lesion usually attaining a diameter of 1 to 2 cm within 6 weeks. This critical feature helps to distinguish it from the more slowly enlarging squamous cell carcinoma. Most lesions regress spontaneously within 6 to 12 months of onset, frequently leaving a depressed scar in the area (Figure 10-95).

Occasional patients demonstrate large numbers of keratoacanthomas. One multiple-lesion variant. the Ferguson Smith type. manifests in early life and appears to

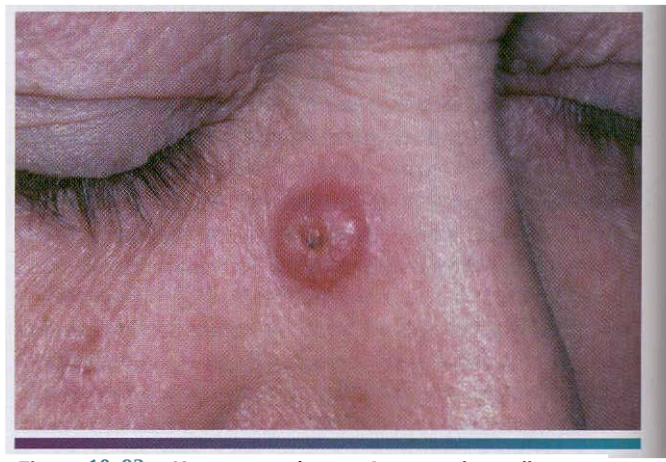

Figure 10-93 • Keratoacanthoma. A nontender, well-demarcated nodule of the skin of the nose in an older woman. The nodule demonstrates a central keratin plug.

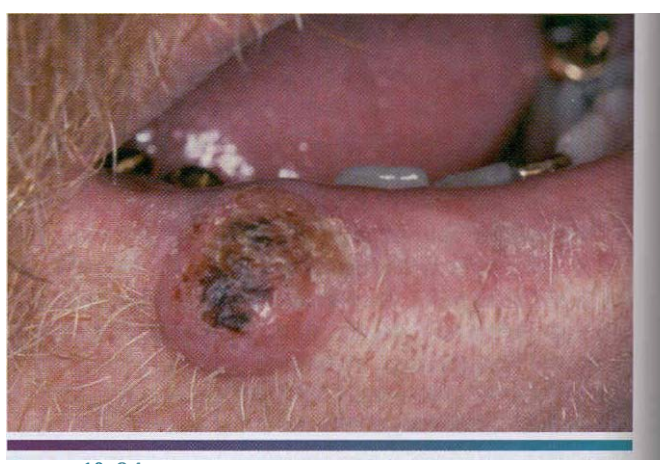

Figure 10-94. Keratoacanthoma. This lesion. which is located at the outer edge of the vermilion border of the lip, demonstrates a prominent core or plug of keratin.

behereditary; the lesions are not likely to involute spontaneously. Another variant manifests as hundreds of small papules of the skin and upper digestive tract (eruptive Grzybowski type) and may be associated with internal malignancy.

Histopathologic Fcaturcs

Keratoacanthoma of the skin and lip vermilion warrants excisional or large incisional biopsy with inclusion of adjacent. clinically normal epithelium for proper histopathologic interpretation; this is because the overall pattern of the tumor is diagnostically more important than the appearance of individual cells. The cells appear mature. although considerable dyskeratosis (abnormal or premature keratin production) is typically seen in the form of deeply located individually keratinizing lesional cells and keratin pearls similar to those found in well-differentiated squamous cell carcinoma.

The surface epithelium at the lateral edge of the tumor appears normal; at the lip of the central crater. however, **a characteristic acute angle 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 (Figure 10-96). This action often elicits a pronounced chronic inflammatory cell response. Downward proliferation does not extend below the level of the sweat glands in skin lesions or into underlying **muscle in vermilion lesions. late-stage lesions show** considerably more keratinization of the deeper aspects of the tumor than do early lesions.

Treatment and Prognosis

Despite the propensity of keratoacanthoma to involute **of its own accord, surgical excision of large lesions is** indicated for optimal aesthetic appearance because **significant scarring may otherwise occur. After excision. 2% of treated patients experience recurrence. *Aggressive* behavior and malignant transformation into carcinoma** have been reported in a small proportion of keratoacanthomas. but the close histopathologic similarities **between this lesion and squamous cell carcinoma make** it difficult to rule out the possibility of misinterpretation **of the microscopic section.**

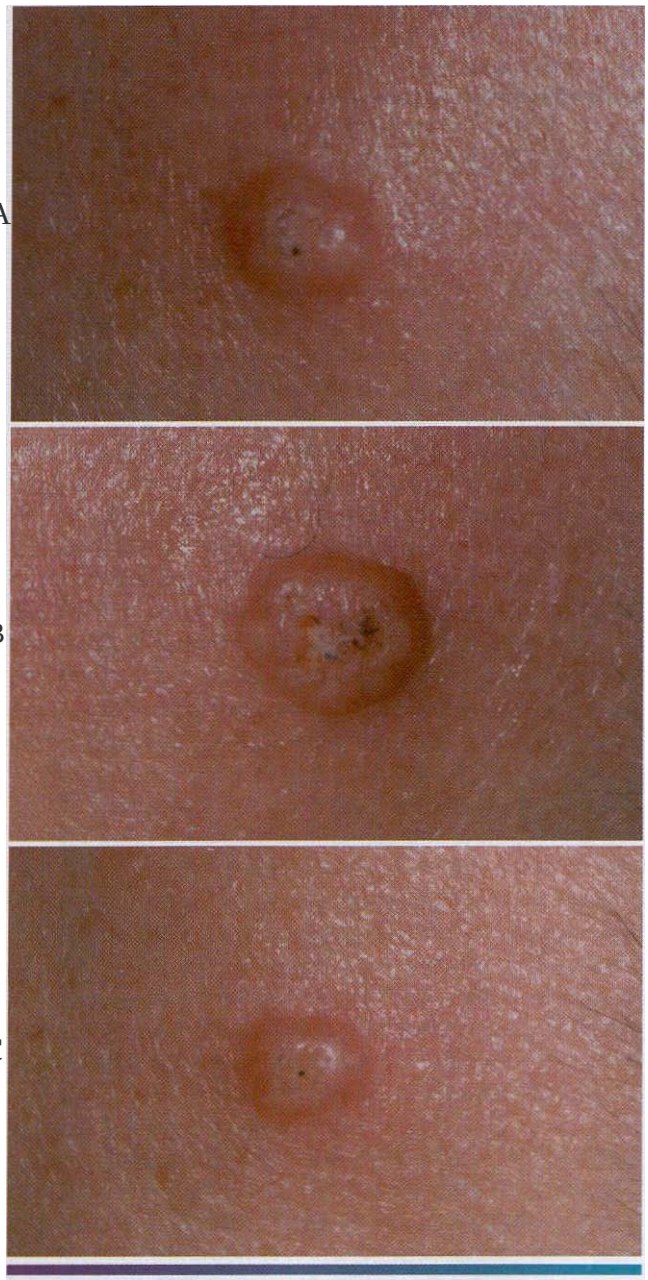

Figure 10-95 • Keratoacanthoma. A. Appearance on initial presentation. Note central keratin-filled invagination. B. Same lesion 1 week later showing dramatic enlargement. C. The lesion has begun to involute 3 weeks after initial presentation. All three photographs were taken at the same magnification. (Courtesy of Dr. John Iovas.)

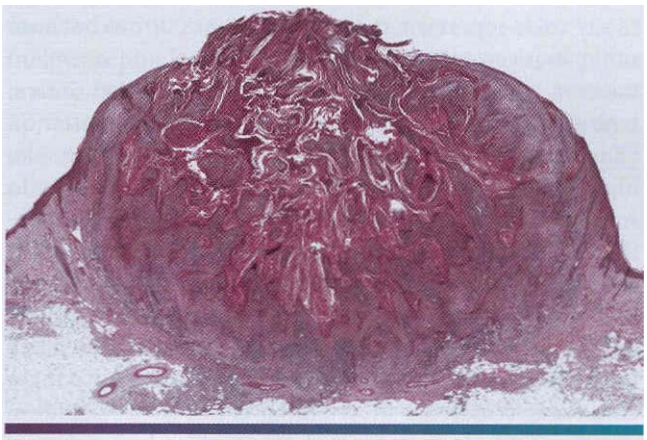

figure 10-96 • Keratoacanthoma. low-power microscopic view showing extensive epidermal proliferation with a central keratin plug.

SQUAMOUS CELL CARCINOMA

In approximately one of every three Americans now living, a malignancy will develop at some point. During 2000, more than 1,220,000 persons in the United States had at least one malignancy, in addition to an equal number with nonmelanoma skin cancers. Although 54% of affected persons now survive their disease, cancer still causes 552,200 deaths each year in the United States and accounts for more than 20% of all deaths. Also, the current annual death rate from nondermal cancers (170 per 100,000 persons) has increased by 19% since 1930, partially because of a considerable increase in the incidence of lung cancer and partially because people are now less likely to die at an early age of other common disorders, such as cardiovascular disease and infection. During the 1990s, however, this trend was reversed, and the average annual incidence and mortality rates for all cancers combined (excluding nonmelanoma skin cancers) began to decline.

Oral cancer accounts for less than 3% of all cancers in the United States, but it is the sixth most common cancer in males and the twelfth most common in females. In some countries, such as India, it is the most common cancer. Approximately 94% of all oral malignancies are squamous cell carcinoma. Within the adult population of the United States, oral carcinoma has been reported to be one of the 25 most common oral mucosal lesions, and approximately 21,000 new cases are diagnosed annually. Slightly more than 6000 Americans die of this disease each year. The average annual incidence and mortality rates, however, vary considerably between different races, genders, and age groups.

As with so many carcinomas, the risk of intraoral cancer increases with increasing age, especially for males. The annual incidence rate (the number of newly diagnosed cases per 100,000 persons each year) for this disease is 7.7 per 100,000 in the United States, although many texts report an 11 to 15 per 100,000 rate because of the inadvertent inclusion of pharyngeal and vermilion cancers with the intraoral cases. In the United States, white men have a higher risk of intraoral cancer after 65 years of age than does any other group. However, the highest annual incidence rate in middle age is seen in American males of African ancestry (Figure 10-97). Furthermore, the incidence of intraoral cancer is increasing dramatically over time for black males in the United States; for nonblack males in the United States, the annual incidence rate has been decreasing slowly since the 1980s. In other countries, the rate of intraoral cancer continues to increase more slowly for all races. Females, whether white or nonwhite, have a much lower annual incidence rate than males at all age levels. The overall male-to-female gender ratio is 3:1.

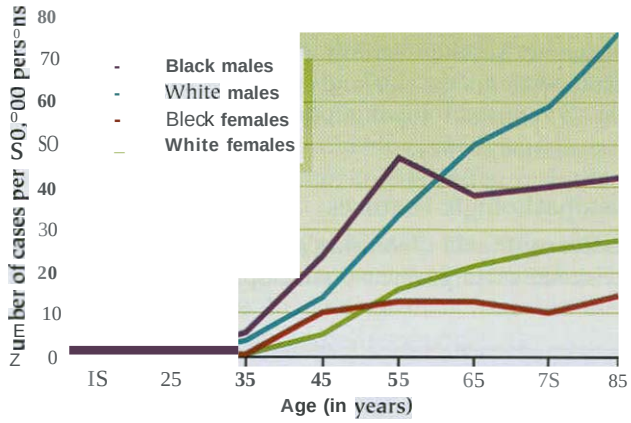

Figure 10-97 • Oral carcinoma. Age-specific incidence rates for intraoral squamous cell carcinoma (number of new cases diagnosed per 100,000 persons each year). Separate rates are provided for white and black males and females in the United States.

Carcinoma of the lip vermilion is somewhat different from intraoral carcinoma. It has a pathophysiology more akin to squamous cell carcinoma of the sun-exposed skin. The average annual incidence rate for white males in the United States is 4 per 100,000, but the rate increases dramatically with age, to almost 30 per 100,000 for men older than 75 years of age. Once the most common oral cancer, the cumulative lifetime risk for developing lip cancer today is only 0.15% for men and 0.07% for women. There was a considerable decrease in the annual incidence rate of this cancer in white males in the United States during the latter half of the twentieth century, because fewer and fewer of them held outdoor occupations. Few females or nonwhite males develop lip carcinoma; there has been little change in the incidence over time for these groups.

Outside the United States, exceptionally wide differences in annual incidence and mortality rates for oral carcinoma are found. These rates vary by as much as twentyfold among different countries. Many of these differences are undoubtedly caused by differing population habits, life expectancies, preventive education, and the quality of medical records in various countries. Despite the difficulties involved in interpreting such data, however, the data 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 at work. It is likely that more than a single factor is needed to produce such a malignancy (cocarcinogenesis). ***Extrinsic*** factors include such

external agents as tobacco smoke. alcohol. syphilis. and (for vermilion cancers onlyl sunlight. *Intrinsic* factors include systemic or generalized states, such as general malnutrition or iron-deficiency anemia. Heredity does not appear to play a major causative role in oral carcinoma. Many oral squamous cell carcinomas have been documented to be associated with or preceded by a precancerous lesion. especially leukoplakia (Table 10-1).

Tobacco smoking. Tobacco smoking reached its greatest popularity in the United States during the 1940s. when at least 65% of white males smoked and other population subgroups were beginning to smoke in large numbers. Today less than 24% of u.s. adults. males and females alike. smoke cigarettes. Unfortunately. remaining smokers appear to be the heavier users; therefore. the effects on the mouth may be *even* greater than the typical effects noted in the past.

Much indirect clinical evidence implicates the habit of tobacco smoking in the development of oral squamous ceil carcinoma. The proportion of smokers (80%) among patients with oral carcinoma is two to three times greater than the general population. 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 thosewho quit after diagnosis.

In addition. case control studies *have* shown that pipe and cigar smoking carries a greater oral cancer risk than does cigarette smoking. and that the relative risk (smoker's risk for oral cancer compared with that of a nonsmoker) is dose dependent for cigarette smokers. 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. furthermore. increases the longer the person smokes.

The greatest risk of all probably is found in certain isolated 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. This habit considerably elevates one's risk for oral cancer. 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.

It should be mentioned that there may be distinct differences between head and neck cancers that develop in smokers compared with those that develop in nonsmokers. although these differences do not appear to affect survival. Tumors in nonsmokers contain a lower frequency of common genetic alterations and have certain clinical differences. For example, affected nonsmokers are more likely to be female. to *have* oral (especially tongue) rather than pharyngeal or laryngeal.

Table 10-1 *Precancerous Lesions of the oral, Pharyngen], and Luryngeal Mucosa, fCli" ical Terms Only)*

Disease Name	*Malignant Transformation Potential*
Proliferative verrucous leukoplakia (PVl) 1	******
Nicotine palatinus in reverse smokers/	*****
Eryth roplakia	*****
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) 3	* 1
Smooth. thin leukoplakia	+/-

1PVI: High-risk. high-recurrence form of oral leukoplakia affecting multiple sites.
2Rcverse smoking: smoking with the lit end of the cigarette In one's mouth.
-Prccancer character is ccnrroverstal.
(From Speight PM. Farthing PM. Bouquet IE: The pathology of oral cancer and precancer. *CUff Diag Path* J:165-167. 1997.)

disease, to be *very* young. and to demonstrate mutations of the p53 and other tumor suppressor genes.

Smokeless (sptt) tobacco. Smokeless or "spit" tobacco use in Western cultures may increase a chronic user's risk for oral carcinoma by a factor of four (relative risk = 4). This apparent increased risk. which is based on a single epidemiologic (case control) study of female textile workers, is supported by clinicopathologic investigations that have found an abnormal mole-to-female sex ratio for oral carcinoma (greater than I:1.5) in geographic areas where the habit is more popular among women than among men, and by the fact that approximately 50% of all oral cancers in spit tobacco users occur at the site where the tobacco is habitually placed.

Betel 'l"id (paan). The betel or paan quid is a compound of natural substances (I.e., areca palm nuts, betel leaf. slaked lime. perhaps tobacco leaf) chewed for their psychostimulating effects. The slaked lime enhances absorption of molecules from the other products. Among betel quid users in Asia, the lifetime risk of developing oral cancer is a remarkable 8%. This habit is also associated with significant development of precanccrs, such as leukoplakia. More than 200 million persons worldwide chew these quids on a regular basis.

Alcohol. Alcohol consumption and abuse. in and of itself. has not been definitively proven to be capable of initiating oral cancer, and oral cancer has not yet been produced by the systemic or topical application of alcohol in animals. This habit does. however, appear to be a significant potentiator or promoter for other causative factors. especially tobacco. and its effects are significant when it is understood that most heavy drinkers are also heavy smokers.

Case control studies have concluded that the risk is dose dependent and time dependent. and the combination of alcohol and tobacco abuse over long periods may increase a person's risk for oral cancer by a factor of 15 or more (relative risk = 15). In this light. it may be significant that the lowest annual oral cancer incidence rate in the United States is found in Utah. where 75% of the population follow Mormon doctrines that forbid the use of tobacco and alcohol.

Indirect evidence for alcohol's role in oral cancer production includes the fact that approximately one third of male patients with oral cancer are heavy alcohol users; less than 10% of the general population can be classified as such. Cirrhosis of the liver. likewise, is found in at least 20% of male patients with oral cancer,

Phenols. Recent evidence has pointed to an increased oral cancer risk for workers in the wood products industry chronically exposed to certain chemicals, such as phenoxyacctic acids. Moreover. it has long been known that these workers are at increased risk for nasal and nasopharyngeal carcinoma.

Radiatlon, The effects of ultraviolet radiation on the lips are discussed elsewhere (actinic cheilosis. see page 353J. but it is well known that another form of radiation. x-irradiation, decreases immune reactivity and produces abnormalities in chromosomal material. It should not seem surprising, then. that radiotherapy to the head and neck area increases the risk of the later development of a new primary oral malignancy. either a carcinoma or a sarcoma. This effect is dose dependent. but even low-dose radiotherapy for benign entities may increase the local risk to some extent. However. the small amount of radiation from routine diagnostic dental radiographs has not been associated with oral mucosal carcinomas.

iron ***deficiency.*** Iron deficiency, especially the severe, chronic form known as the Plummer-Vinson or Paterson-Kelly syndrome (see page 715) 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. People who are deficient in iron tend to have impaired cell-mediated immunity. and iron is essential to the normal functioning of epithelial cells of the upper digestive tract. In deficiency states, these epithelial cells turn over more rapidly and produce an atrophic or immature mucosa. Intertwining fibrous bands of scar tissue also may develop within the esophagus of severely affected patients (esophageal webs). Patients with such esophageal webbing seem to be especially susceptible to malignant transformation.

Vilamill A ***deficiency.*** Vitamin A deficiency produces excessive keratinization of the skin and mucous membranes. and it has been suggested that the vitamin may play a protective or preventive role in oral precancer and cancer. Blood levels of retinol and the amounts of dietary betacarotene ingested are believed by some to be inversely proportional to the risk of oral squamous cell carcinoma and leukoplakia. Long-term therapy with rctinoic acids and betacarotene also has been associated with a regression of at least some leukoplakic lesions and a concomitant reduction in the severity of dysplasia within such lesions.

Syphilis. Syphilis (tertiary stage) has long been accepted as having a strong association with the development of dorsal tongue carcinoma. The relative risk ratio approximates four. Conversely, a person with a lingual carcinoma is five times more likely to have a positive serology test for syphilis than someone without such a cancer. The arsenicals and heavy metals that were used to treat syphilis before the advent of modern antibiotics have carcinogenic properties themselves and may have been responsible for some of the earlier cancer development in this disease. Regardless of the pathophysiologic mechanism at work. however, syphilis-associated oral malignancies are rare today because the infection is typically diagnosed and treated before the onset of the tertiary stage.

Candldal infection. Hyperplastic candidiasis (see page 194) 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 albtcans* have produced hyperkeratotic lesions of the dorsal rat tongue without any other contributing factor. In other studies, certain strains have been shown to produce nitrosamines, chemicals that have been implicated in carcinogenesis. Some candidal strains may have the potential to promote the development of oral cancer; to date, however, the evidence to suggest this role is largely circumstantial.

Oncogenic *viruses.* Oncogenic (tumor-producing) viruses may play a major role in a wide variety of cancers, although no virus has definitively been proven to cause oral cancer so far. Viral agents capable of inte-

gration into the host's genetic material may be particularly dangerous and potentially could commandeer the host's ability to regulate normal growth and proliferation of the infected cell. The oncogenic viruses may immortalize the host cell, thereby facilitating malignant transformation. In the past, retroviruses, adcnovlruscs, herpes simplex viruses (HSVs). and human papillomaviruses IHPVs) all have been suggested as playing a role in the development of oral carcinoma. It appears. however. that HPV is the only one still implicated. not only in oral cancer but also in carcinoma of the pharyngeal tonsil. larynx. esophagus. uterine cervix. vulva. and penis. HPV subtypes 16. 18. 3i. and 33 are the strains most closely associated with dysplasia and squamous cell carcinoma.

HSV. especially type 2. once was thought to produce a large proportion of cancers of the uterine cervix. and it has been suggested as a causative factor in oral carcinoma. Evidence now suggests that it may be no more than a common companion infection in persons with HPV infections. and that the latter virus plays a much more important carcinogenic role than does HSV. Currently. the evidence gathered to prove a causal relationship between HSV and oral carcinoma is insufficient.

immunosnppression. Immunosuppression may play a role in the development of at least some malignancies of the upper acrodigcstive tract. Without effective immunologicsurveillance and attack. it is thought that newly created malignant cells cannot be recognized and destroyed at an early stage. Persons with acquired immunodeficiency syndrome (AIDS) 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. Oncogenes and tumor suppressor genes are chromosomal components capable of being acted on by a variety of causative agents. Normal genes or proto-oncogenes are transformed into activated oncogenes in certain malignancies through the actions of viruses. irradiation. or chemical carcinogens. Once oncogenes are activated. they may stimulate the production of an *excessive* amount of new genetic material through amplification or overexprcsslon of the involved gene. Oncogenes probably are involved in the initiation and progression of a wide variety of neoplasms. including oral squamous cell carcinoma.

Tumor suppressor genes. on the other hand. allow tumor production indirectly when they become inactivated or mutated. Thus far. abnormalities of the *ras*, *myc*, and *c-etbb* oncogenes. and the p53. pRb. and E-cadherin tumor suppressor genes. have been identified in oral carcinomas. although a cause-and-effect relationship is not yet *proven.* Most authorities feel that an accumulation of several of these various genetic aberrations is necessary before the affected cell expresses a malignant phenotype.

Clinical and Radiographic Features

Persons with oral squamous cell carcinoma arc most often older men who have been aware of an alteration in an oral cancer site 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. and this may explain the delay in seeking professional care. If the health care professional does not have a high index of suspicion. an additional *several* weeks or months may elapse before a biopsy is performed.

Oral squamous cell carcinoma has a varied clinical presentation. including:

- Exophytic (mass-forming; fungating. papillary. verruciform)
- Endophytic (Invastvc. burrowing. ulcerated)
- Leukoplakic (white patch)
- Erythroplakic (red patch)
- Erythroleukoplakic <Combined red-and-white patch)

The */eukop/akic* and *erythroplak«:* 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 337 and 345). These mucosal surface changes typically are destroyed by the developing exophytic or endophytic carcinoma. but many cases are diagnosed before their complete destruction and show residual precancerous lesions involving adjacent mucosa (Figure 10-98).

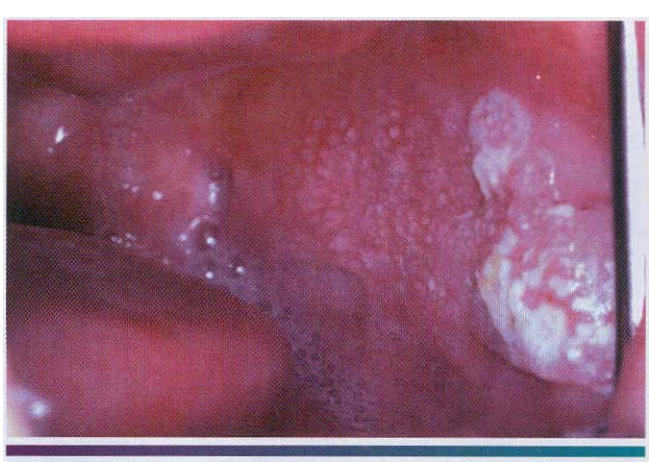

figure 10-98 • Squamous cell carcinoma. A buccal lesion with a granular. erythematous surface is destroying the prior leukoplakic lesion from which it appeared to arise. Only the anterior-most portion of the white precancerous lesion remains.

An *exophytic* lesion typically has a surface that is irregular, fungating, papillary, or verruciform. and its color may vary from normal to red to white. depending on the amount of keratin and vascularity (Figures to-99 and 10-tOO). The surface is often ulcerated, and the tumor feels hard (indurated) on palpation (Figure 10-lOt).

The *endophytic* growth pattern is characterized by a depressed. irregularly shaped, ulcerated, central area with a surrounding "rolled" border of normal. red or white mucosa (Figure 10-102). The rolled border results from invasion of the tumor downward and laterally under adjacent epithelium. This appearance is not unique to **oral carcinoma because granulomatous lesions. such as** deep fungal infections. tuberculosis, tertiary syphilis. oral lesions of Wegener's granulomatosis or Crohn's dis**ease, and chronic traumatic ulcers. may look similar.**

Destruction of underlying bone. when present, may be painful or completely painless, and it appears on radiographs as a "moth-eaten" radiolucency with ill-defined **or ragged margins (an appearance similar to osteomye**litis) (Figure 10-t03). Carcinoma also can extend for **many centimeters along a nerve (perineural invasion) without breaking away to form a true metastasis.**

Lip vermilion carcinoma. **Carcinoma of the lip ver**milion is typically found in light-skinned persons with either long-term exposure to ultraviolet radiation from sunlight or a history of acute sun damage (sunburn) early in life. Seventy percent of affected individuals have out**door *occupations.* It is usually associated with actinic** cheilosis (see page 353) and may arise at the site where a cigarette, cigar. or pipe stem is held by the patient. Almost 90% of lesions arc located on the lower lip.

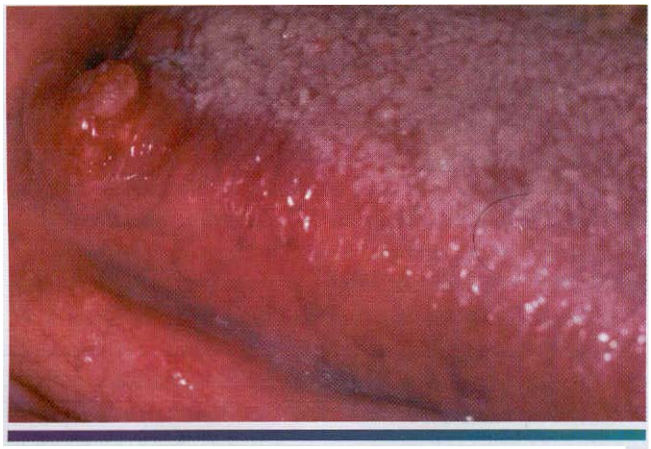

Figure 10·99 • Squamous cell carcinoma. An exophytic lesion of the posterior lateral tongue demonstrates surface nodularity and minimal surface keratin production. It is painless and indurated.

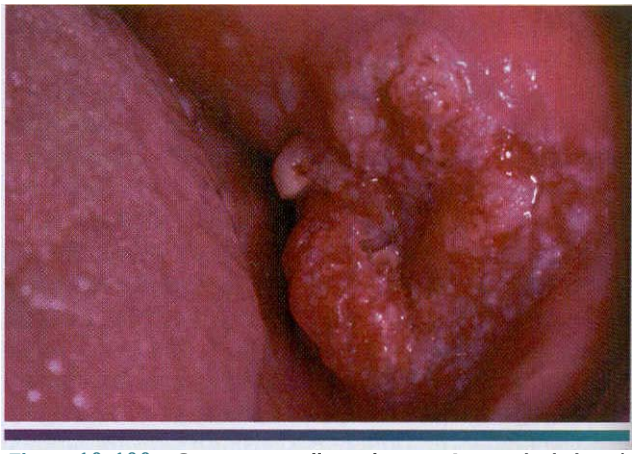

Figure 10-100. Squamous cell carcinoma. An exophytic buccal lesion shows a roughened and irregular surface with areas of erythema admixed with small areas of white keratosis. Surface ulceration is evident.

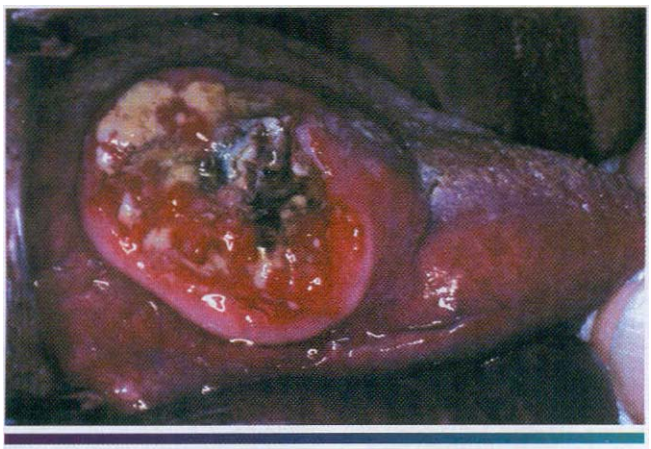

Figure 10-101 • Squamous cell carcinoma. A posterior lateral tongue lesion is exophytic but also demonstrates extensive surface ulceration and nodularity. Such lesions are sometimes referred to as "fungating" carcinomas.

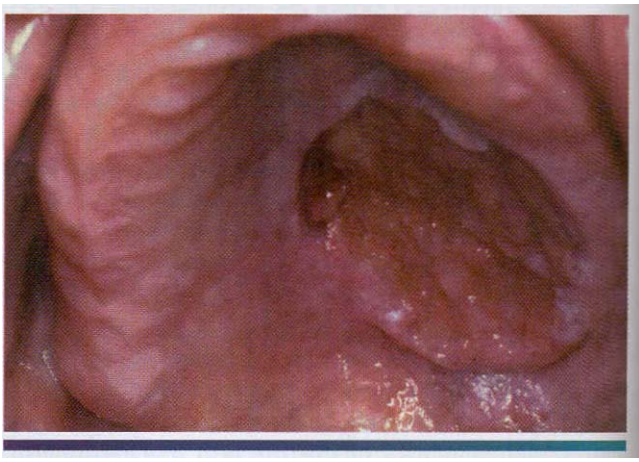

Figure 10-102 • Squamous cell carcinoma. An ulcerated or endophytic lesion of the hard palate demonstrates rolled borders and a necrotic ulcer bed. This cancer was painless, although it had partially destroyed underlying palatal bone.

The typical vermilion carcinoma is a crusted. oozing. nontender, indurated ulceration that is usually iess than l cm in greatest diameter when discovered {Figures 10-104 and 10-IOS}.The tumor is characterized by a slow **growth rate. and most patients have been aware of a** -problem" in the area for 12 to 16 months before a formal diagnosis is made. Metastasis is a late event; at diag- **nosis. fewer than 2% of patients have metastatically** involved lymph nodes. usually in the submental region. **Perineural invasion may result in extension of the tumor** into the mandible through the mental foramen. Although this tumor is typically diagnosed and treated at an early stage. patient neglect can result in considerable destruc- tion of normal tissue (Figure 10-106).

tntmoral carcinoma. **The most common site for intra-** oral carcinoma is the tongue. usually the posterior lateral and ventral surfaces. The oral floor is affected almost as frequently in males but is involved much less commonly in females. Other sites of involvement are (in descending order of frequency): soft palate. gingiva. buccal mucosa. labial mucosa. and hard palate.

Carcinoma of the tongue accounts for marc than SO% of intraoral cancers in population studies in the United States (Figures 10-107 and 10-108: see also Figures 10-62. 10-99. and 10-101). 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. The tongue especially is the site of involvement in young patients and. in fact. is the site of the only congenital oral squamous cell carcinoma reported.

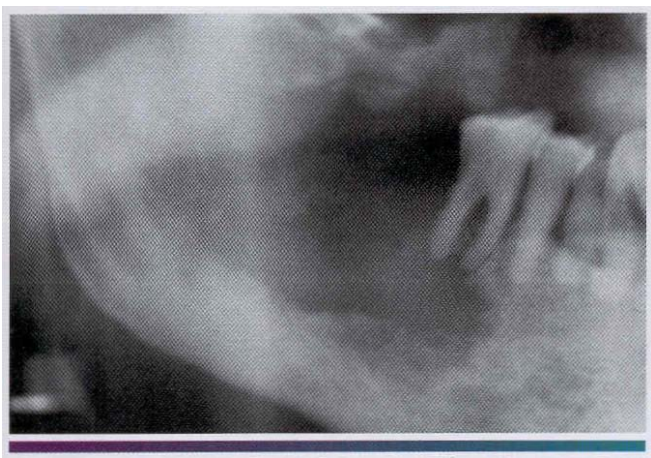

Figure 10-103 • Squamous cell carcinoma. Bone involvement is characterized by an irregular, "moth-eaten" radiolucency with ragged margins-an appearance similar to that of osteomyelitis.

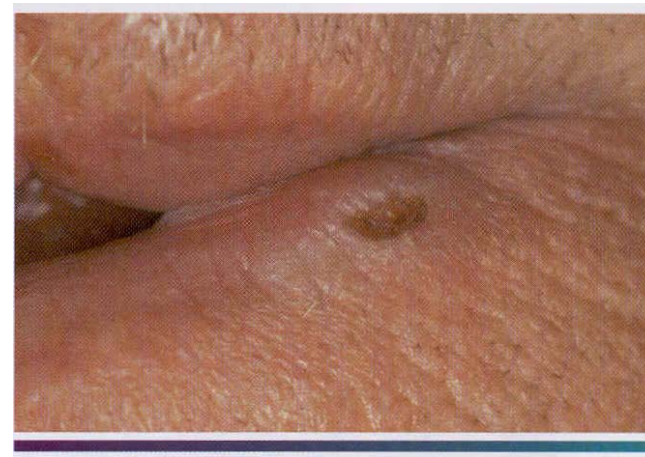

Figure 10-104 • Squamous cell carcinoma. Small, crusted ulcer of the lower lip vermilion.

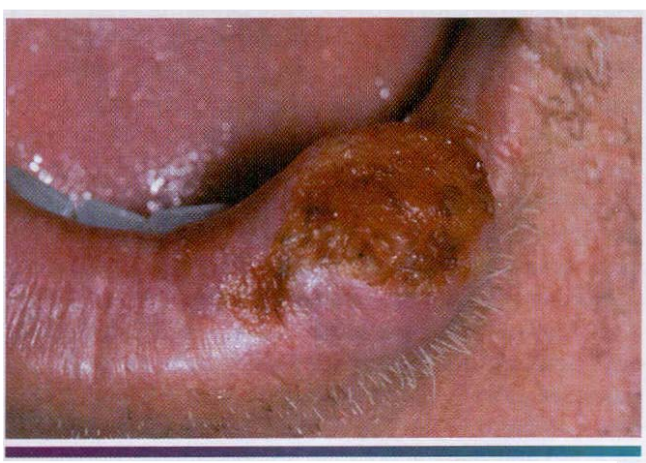

Figure 10-105 • Squamous cell carcinoma. Ulcerated mass of the lower lip vermilion.

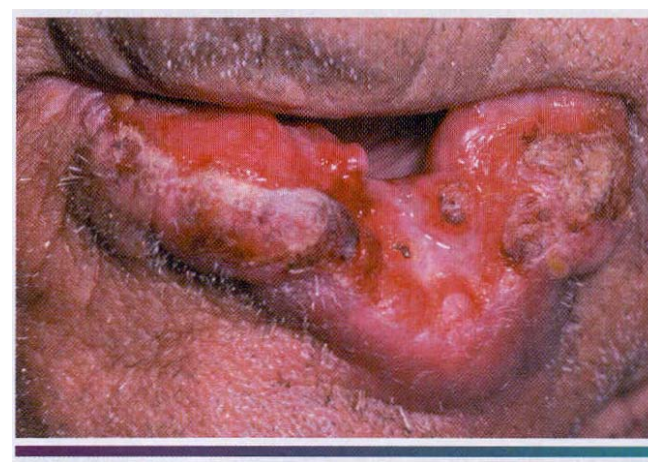

Figure 10-106 . Squamous cell carcinoma. Patient neglect can result in extensive involvement. even in a readily visible site such as the lip vermilion. This ulcerating lesion of the lower lip had been present for more than 1 year before diagnosis.

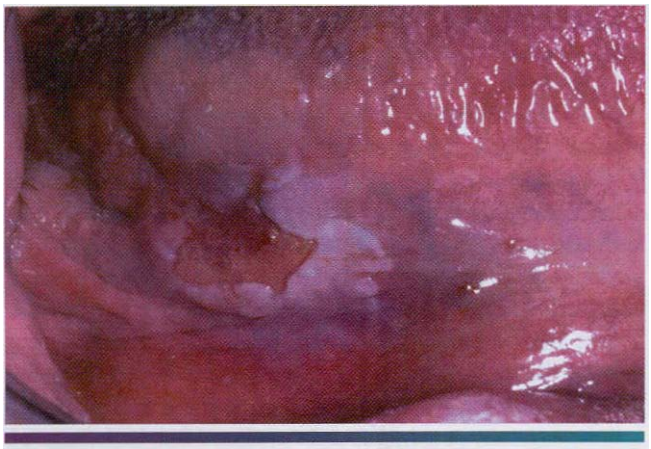

Figure 10-107 . Squamous cell carcinoma. Ulcerated lesion with surrounding leukoplakia on the posterior lateral and ventral tongue.

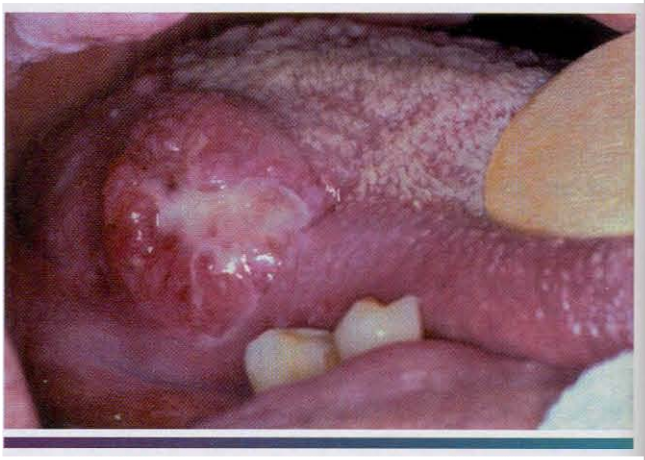

Figure 10-108 • Squamous cell carcinoma. Ulcerated. exophytic mass of the posterior lateral border of the tongue.

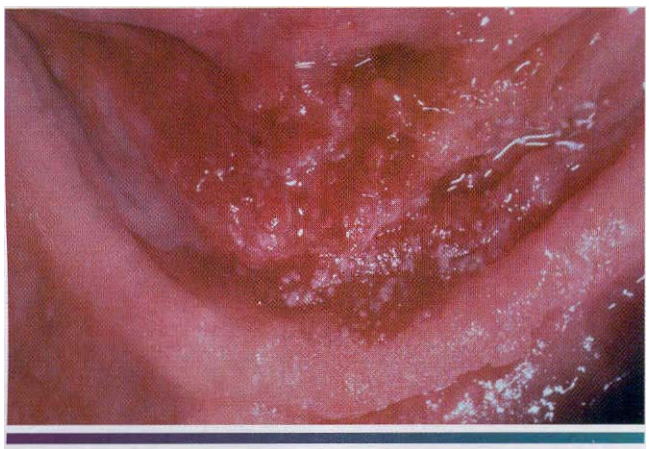

figure 10-109 • Squamous cell carcinoma. Oral floor lesions are typically ulcerated or present as an admixed red-and-white. pebbled-surface change (as depicted here).

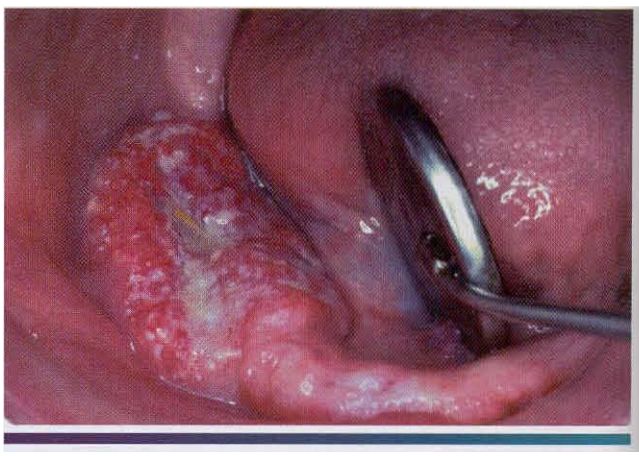

Figure 10-110 . Squamous cell carcinoma. An exophytic lesion with an irregular and pebbled surface has a linear indentation along its facial aspect resulting from pressure from the patient's lower denture. Underlying alveolar bone was extensively destroyed.

Carcinoma of the oral floor represents 35% of all intraoral cancers in epidemiologic surveys and appears to be **increasing in frequency among** females. It **occurs a decade** earlier in females than in males but is still usually a disease of elderly people. Of all intraoral carcinomas. oral floor lesions are the most likely to arise from a preexisting leukoplakia or erythroplakia (Figure 10-t09; see also Figures 10-63 and to-75). It is also the oral cancer site most often associated with the development of a second primary malignancy of another aerodigestive tract location or of a distant organ. The most common site of involvement **is the midline near the frenum.**

Gingivai and alveolar carcinomas are usually painless **and most frequently arise from keratinized mucosa in a** posterior mandibular site. This tumor has a special propensity to mimic the benign inflammatory and reactive lesions. such as pyogenic granuloma. that are so **common to the gingiva.** when **the cancer develops in an** edentulous area. it may give rise to a mass that "wraps around" a denture flange and superficially resembles inflammatory fibrous hyperplasia (epulis fissuratum) (Figure 10-110). Tumors of the maxillary alveolar ridge may extend onto the hard palate (Figure to-l t). if the tumor is adjacent to a tooth (Figure 10-t121. it may mimic periodontal disease or a pyogenic granuloma. Gingival carcinoma often destroys the underlying bone structure. causing tooth mobility. This lesion may not become clinically evident until after tooth extraction. when it proliferates out of the socket to mimic the hyperplastic granulation tissue of epulis granulomatosa. Of ali the intraoral **carcinomas. this one is least associated with tobacco** smoking and has the greatest predilection for females.

***Oropharyngeal carcinoma*. Carcinoma of** the soft palate and oropharyngeal mucosa has the same basic

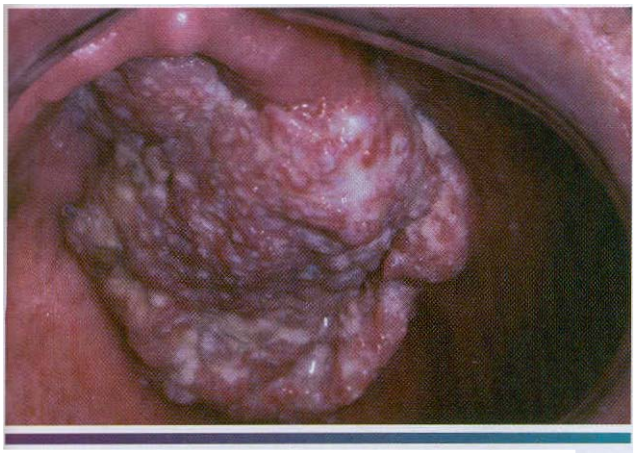

Figure 10-111 • Squamous cell carcinoma. large fungating tumor of the maxillary alveolar ridge and hard palate.

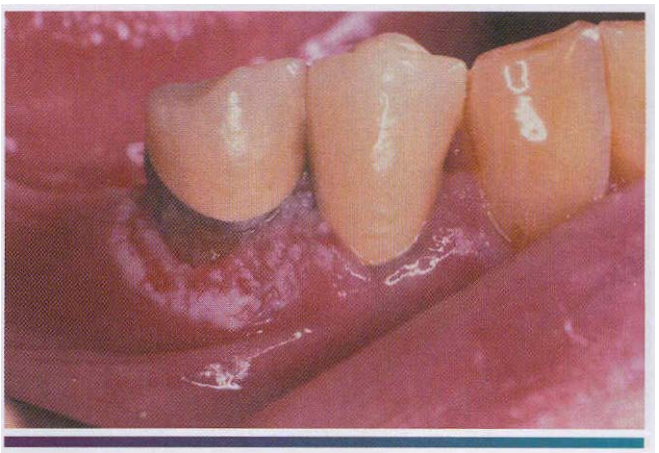

Figure 10-112 • Squamous cell carcinoma. An innocuous pebbled-surface change of the attached and marginal gingiva was interpreted as an inflammatory change until multifocal white keratoses occurred.

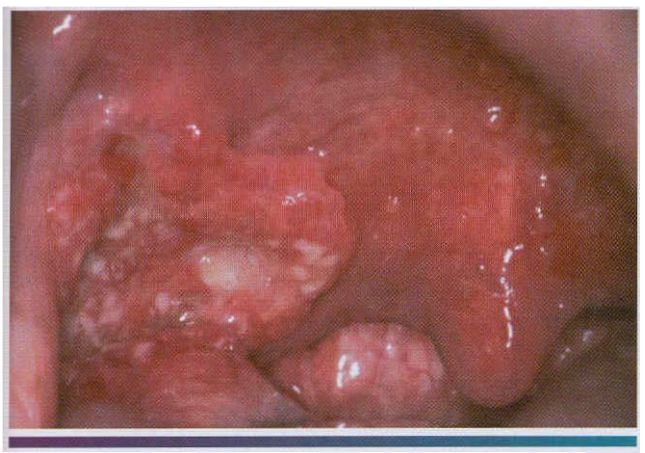

Figure 10-113. Squamous cell carcinoma. large. ulcerated lesion of the right lateral soft palate.

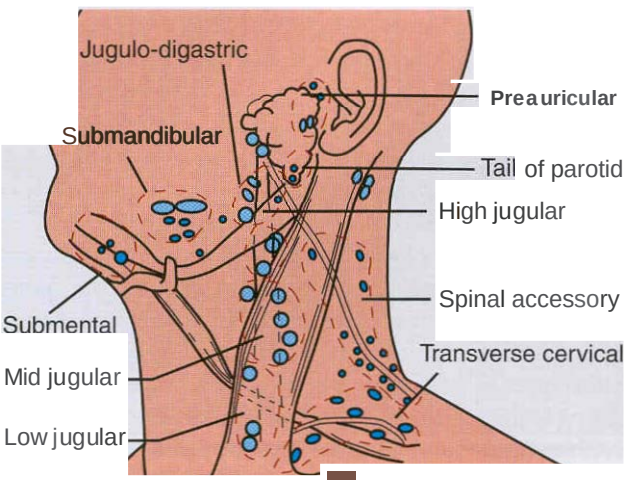

Figure 10-114 • Squamous cell carcinoma. metastatic spread. Diagram demonstrating potential sites for metastatic spread of oral carcinoma to regional lymph nodes.

clinical appearance as more anterior carcinomas. except that, in this posterior location. the patient often is unaware of its presence and the diagnosis may be delayed. Tumor size is typically greater than that of more anterior carcinomas, and the proportion of cases with cervical and distant metastasis at diagnosis is higher (Figure 10-113). Three of every four oropharyngeal carcinemas arise from the tonsillar area or soft palate: most of the others originate on the base of the tongue. The initial symptoms are usually pain or difficuity in swallowing (dysphagia). The pain may be dull or sharp and frequently is referred to the ear.

As a general rule. the more posterior or inferior the oropharyngeal tumor location. the larger the lesion and the greater the chance for lymphatic spread by the time of diagnosis. A soft palate lesion may present as a localized turner, but 80% of posterior oropharyngeal wall lesions have metastasized or extensively involved surrounding structures by the time of diagnosis.

Metastasis

The metastatic spread of oral squamous cell carcinoma is largely through the lymphatics to the ipsilateral cervical lymph nodes (Figure 10-114). A cervical lymph node that contains a metastatic deposit of carcinoma is usually firm to stony hard. nontender, and enlarged (Figure 10-115). If the malignant cells have perforated the capsule of the node and invaded into surrounding tissues. the node will feel "fixed." or not easily movable.

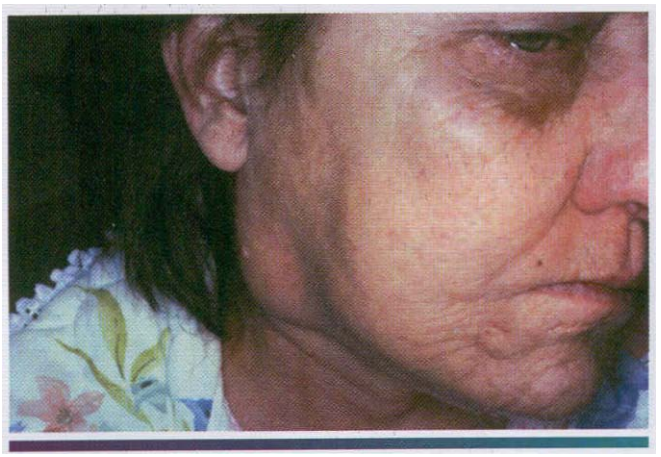

figure 10-115 • Squamous cell carcinoma. Metastatic deposits within cervical lymph nodes present as firm, painless enlargements as seen in this patient with metastasis to a superior jugular node from a posterior lateral tongue carcinoma.

Occasionally, contralateral or bilateral metastatic deposits are seen, and at least 2% of patients have distant (vbclow 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 travel to the superior jugular and digastric nodes. Lymphatic drainage from the oropharynx leads to the jugulodigastric chain of lymph nodes or to the retropharyngeal nodes, and metastatic deposits from oropharyngeal carcinoma are usually found there.

Metastasis is not an early event for carcinomas of the oral cavity proper. However. because of delay in the diagnosis, approximately 21% of patients have cervical metastases at diagnosis (60% in reports from tertiary care medical centers). In contrast. tumors that arise more posteriorly in the oropharynx are prone to early metastasis. More than 50% of all affected persons in population studies have positive cervical nodes at diagnosis, and I in 10 already have distant metastasis by that time.

Staging

Tumor size and the extent of metastatic spread of oral squamous cell carcinoma are the best indicators of the patient's prognosis. Quantifying these clinical parameters is called staging the disease. Table 10-2 summarizes the most popular staging protocol. the tumor-node-metastasis (TNM) system. Individualized TNM classifications are used for most human cancers, with each system pertaining exclusively to a specific anatomic site and a specific tumor type. This staging protocol depends on three basic clinlcal features:

1. T = size of the primary tumor, in centimeters
2. N = involvement of local lymph nodes
3. M = distant metastasis

Once the three parameters are determined, they are tallied together to determine the appropriate stage. The higher the stage classification, the worse the prognosis (Table 10-3). In other words, a stage IV lesion is associated with a much worse prognosis than a stage I lesion. Most head and neck staging protocols do not use histopathologic or immunohistochemical findings beyond those needed for a determination of the diagnosis.

Table 10-2 *Tumor-Node-Metastasls (TNM) Staging System for Oral Carcinoma*

PRIMARY TUMOR SIZE (T)	
TX	No available information on primary tumor
TO	No evidence of primary tumor
T1S	Only carcinoma *in situ* at primary site
TI	Tumor is less than 2 em in greatest diameter
T2	Tumor is 2 to 4 em in greatest diameter
T3	Tumor is more than 4 em in greatest diameter
T4	Massive tumor greater than 4 em in diameter. with involvement of antrum. pterygoid muscles. base of tongue, or skin
REGIONAL LYMPII NODE INVOLVEMENT IN)	
NX	Nodes could not be or were not assessed
NO	No clinically positive nodes
NI	Single clinically positive homolateral node less than 3 em in diameter
N2	Single clinically positive homolateral node 3 to 6 em in diameter or multiple clinically positive homolateral nodes, none more than 6 em in diameter
N2a	Single clinically positive homolateral node 3 to 6 cm in diameter
N2b	Multiple clinically positive homolateral nodes. none more than 6 em in diameter
N3	Massive homolateral node or nodes, bilateral nodes, or contralateral node or nodes
N3a	Clinically positive homolateral node or nodes, one more than 6 em in diameter
N3b	Bilateral clinically positive nodes
N3c	Contralateral clinically positive node or nodes
INVOLVEMENT BY DISTANT METASTASES (M)	
MX	Distant metastasis was not assessed
MO	No evidence of distant metastasis
M1	Distant metastasis is present

Table 10-3 TNM Clinical Staging Categories for Oral Squamous Cell Carcinoma

STAGE	TNM CLASSIFICATION	5-YEAR SURVIVAL RATE
Stage I	T1 NO MO	85%
Stage II	T2 NO MO	66%
Stage III	n NO MO, or ri. rz, or rs. N1 MO	41%
Stage IV	Any T4 lesion, or Any N2 or N3 lesion, or Any M1 lesion	9%

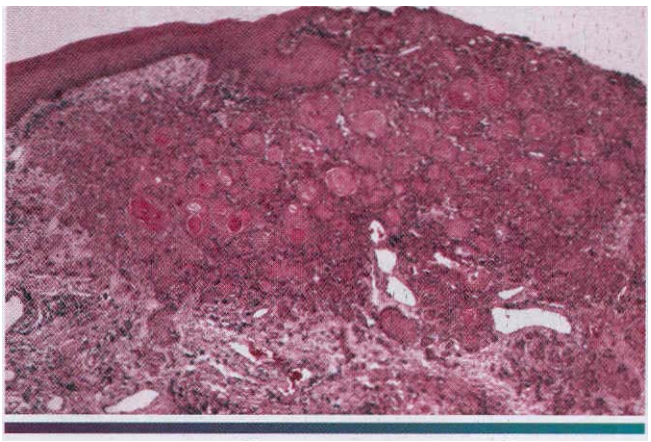

Figure 10-116 • Well-differentiated squamous cell carcinoma. Low-power photomicrograph showing islands of malignant squamous epithelium invading into the lamina propria.

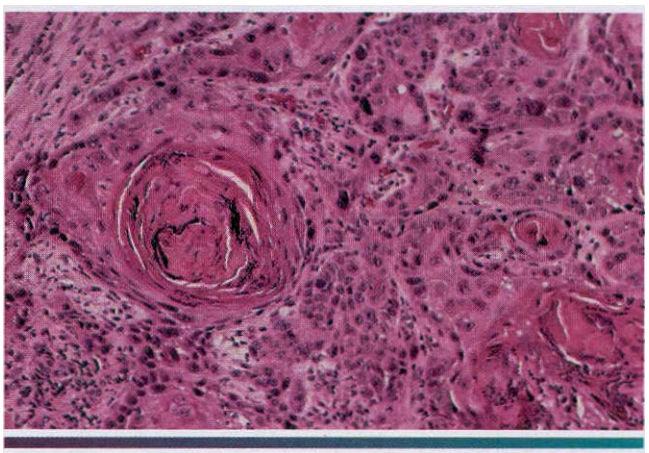

Figure 10-117 . Well-differentiated squamous cell carcinoma. High-power view showing dysplastic epithelial cells with keratin pearl formation.

Histopathologic Features

Squamous cell carcinoma arises from dysplastic surface epithelium and is characterized histopathologically by invasive islands and cords of malignant squamous epithelial cells. When the tumor is sampled fortuitously 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 pertaining to leukoplakia (see page 342).

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 are seen to be thriving as independent entities within the connective tissues, without attachment to the surface epithelium. Invading cells and cell masses may extend deeply into underlying adipose tissue, muscle, or bone, destroying the original tissue as they progress. Lesional cells may surround and destroy blood vessels, and may invade into the lumina of veins or lymphatics. There is often a strong inflammatory or immune cell response to invading epithelium, and focal areas of necrosis may be present. The lesional epithelium is capable of inducing the formation of new small blood vessels (angiogenesis) and, occasionally, dense fibrosis (desmoplasia or scirrhous change).

Whether the tumor is superficially or deeply invasive, 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. Single cells also may undergo individual cell keratinization.

Histopathologic evaluation of the degree to which these tumors resemble their parent tissue (squamous epithelium) and produce their normal product (keratin) is called grading. 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 tumor that is mature enough to closely resemble its tissue of origin seems to grow at a slightly slower pace and to metastasize later in its course. Such a tumor is called *low-grade*, *grade* I, or *well-differelltiated* squamous cell carcinoma (Figures 10-116 and 10-117). In contrast, a tumor with much cellular and nuclear pleomorphism and with little or no keratin production may be so immature that it becomes difficult to identify the tissue of origin. Such a tumor often enlarges rapidly, metastasizes early in its course, and is termed *high-grade*, *grade* III/IV, *poorly dif-*

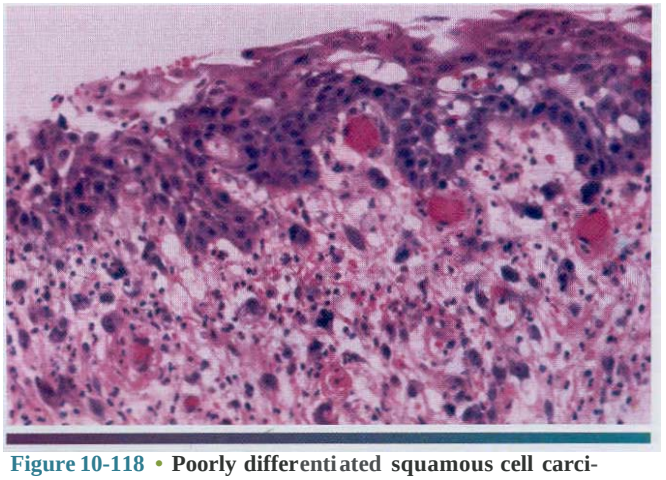

Figure 10-118 • Poorly differentiated squamous cell carcinoma. The numerous pleomorphic cells within the lamina propria represent anaplastic carcinoma.

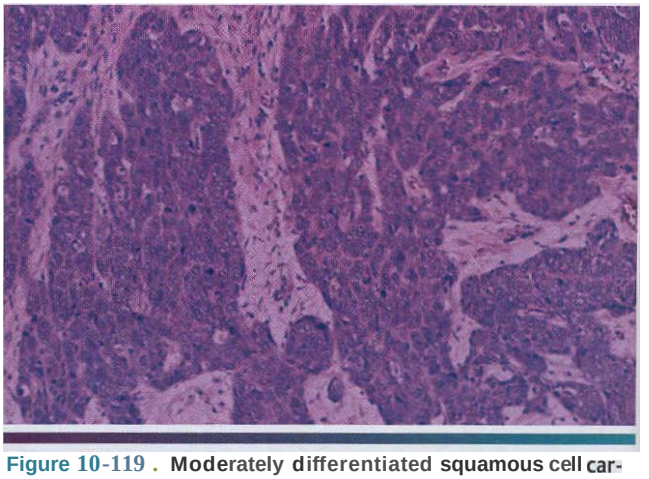

Figure 10-119 . Moderately differentiated squamous cell carcinoma. Although no keratinization is seen in this medium-power view, these malignant cells are still easily recognizable as being of squamous epithelial origin.

[erentiated. or *anaplastic* (Figure 10-118). A tumor with a **microscopic appearance somewhere between these two** extremes is labeled a "moderately differentiated" carcinoma (Figure 10-119).

To a certain extent, the grading of squamous cell carcinoma is a subjective process, depending on the area of the tumor sampled and the individual pathologist's criteria **for evaluation. Moreover. clinical staging seems to correlate much better with the prognosis than microscopic** grading.

The diagnosis of squamous cell carcinoma almost always is made with routine light microscopy. Special studies that use monoclonal antibodies directed against cytokeratins may. however. be needed to distinguish high-grade or poorly differentiated squamous cell carcinoma **from other malignancies.**

Treatment and Prognosis

Carcinoma of the vermilion zone of the lip is usually treated by surgical excision. typically a wedge resection, with excellent results. Only 8% recur. and 5-year survival rates are 95% to 100%. In one study that evaluated **all vermilion cancers diagnosed in a population over** 6 decades. not one patient died of his or her disease. Squamous cell carcinomas of the upper lip vermilion appear to have a different biologic behavior than do those of the lower lip. The 5-year survival rate is only 58%, **and 25% of lesions recur after treatment. Fortunately,** upper **lip carcinoma is considerably less common than lower lip carcinoma.**

The treatment of intraoral squamous cell carcinoma is guided by the clinical stage of the disease and consists of wide (radical) surgical excision. radiation therapy. or a combination of surgery and radiation therapy. The tumor's location may influence the treatment plan. Oropharyngeal lesions usually receive radiation therapy. A variety of chemotherapeutic agents are used as adjunctive therapy: some can temporarily reduce the size of **a tumor mass, but none has improved survival rates** significantly.

For the small intraoral carcinoma. a single treatment modality is usually chosen. Patients with larger lesions or lesions with clinically palpable lymph nodes typically require combined therapy. With suspected local lymph node metastasis, either a radical or modified radical neck dissection is performed. Radical neck dissection is essentially an *en bloc* removal of all fibrofatty tissues of the lateral triangle of the neck, including the superior, middle. and inferior jugular nodes. the supraclavicular group of nodes. and variable portions of the surrounding **musculature.**

The prognosis for survival from oral cancer depends on tumor stage (see Table 10-3). The 5-year disease-free **survival rate for intraoral carcinoma is 76% if metastasis** has not occurred by the time of diagnosis (stage i and lii, 41 % when the cervical nodes are involved (stage Iii), and only 9% when metastasis below the clavicle is present (stage *IV).* 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 various molecular markers associated with carcinoma. such as mutation of the p53 tumor suppressor **gene, have shown equivocal results as** prognostic **indicators.** The presence or absence of HPV, including subtypes 16 and 18. also docs not seem to affect prognosis.

The overall 5-year survival rate for intraoral carcinoma in whites in the United States and Europe has increased from 40% in the 19505 to 58% today. During

the same period. however. the rate for black Americans decreased from 36% to 32%. The latter trend is thought to result from a combination of delayed diagnosis and inadequate initial therapy and is partially responsible for an 8% increase in the oral and pharyngeal cancer-related mortality rate (number of cancer deaths per 100,000 persons) in black Americans since 1960. The oral cancer mortality rate for whites has decreased by 20% since that time.

Multiple Carcinomas

Patients with one carcinoma of the mouth or throat arc at increased risk for additional conc urrent (synchronous) or later (rnetachronous) primary surface epithelial malignancies of the upper aerodigestive tract, the esophagus. the stomach. the lungs. and other sites. This risk has been estimated to be as low as 6% and as high as 44% in affected individuals. The highest figures are associated with male patients who continue to smoke and abuse alcohol after therapy. Overall, in 9% to 25% of **patients with oral carcinoma. additional mouth or throat** malignancies develop.

In patients with more than one upper aerodigestive tract malignancy, approximately one third of the tumors arise simultaneously. of the rest, the second lesion usually develops within 3 years after the Initial cancer. This tendency toward the development of multiple mucosal **cancers. sometimes called "field cancerization." may** reflect diffuse exposure to local carcinogens. a process that increases the malignant transformation potential of all exposed epithelial cells. At least one investigation has shown positive p53 (tumor suppressor gene) reactivity for all synchronous tumors of the mouth, esophagus. and **stomach. indicating a common predisposition toward malignant development. Another recent investigation** has demonstrated that the additional tumors are not clones of the original (hence. they have not migrated from the original tumor cells).

VERRUCOUS CARCINOMA (SNUFF DIPPER'S CANCER; ACKERMAN'S TUMOR)

Verrucous carcinoma is a low-grade variant of oral squamous cell carcinoma. Reported first by Ackerman **in 1948 as a spit tobacco-associated malignancy. it has** been diagnosed since then at several extraoral sites, including laryngeal. vaginal. and rectal mucosa. and skin from the breast. axilla, ear canal. and soles of the feet. **Tumors at anatomic sites other than the mouth arc unrelated** to tobacco use. Several investigators have identified HPV subtypes 16 and 18 in some oral verrucous carcinomas. **but the significance of this is unclear.**

Verrucous carcinoma represents 1% to 10% of all oral squamous cell carcinomas, depending on the local popularity of spit tobacco use. The only epidemiologic assess**ment of this tumor in a western culture reported an average annual incidence rate of one oral lesion per 1** million population each year.

Many verrucous carcinomas arise from the oral mucosa in people who chronically use chewing tobacco or snuff. typically in the area where the tobacco is habitually placed. Cases also may occur in nonusers. but the exact figure is difficult to assess because patients will often deny the tobacco habit. In spit tobacco users, a regular squamous cell carcinoma is 25 times more likely to develop than this low-grade variant.

Clinical Features

Verrucous **carcinoma is found predominantly in men** older than 55 years of age (average age, 65 to 70 years). **In areas where women are frequent users of spit tobacco.** however. elderly females may predominate. The most **common sites of oral mucosal involvement include the** mandibular vestibule, the buccal mucosa. and the hard palate. The site of occurrence often corresponds to the site of chronic tobacco placement. In cultural groups who keep spit tobacco in the maxillary vestibule or under the tongue, these **locations are the most commonly involved sites,**

Oral **verrucous carcinoma is usually extensive by the** time of diagnosis. and it is not unusual for a tumor to be present in the mouth 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 (Figures 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. 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 340). Both 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 (Figure 10-122). Lesions usually show abundant keratin (usually parakeratin) production and a papillary or verruciform surface. Parakeratin typically fills the numerous clefts or crypts (parakeratin plugs) between the surface projections. These projections may be long and pointed or short and blunted. The lesional epithelial cells generally show a normal matu-

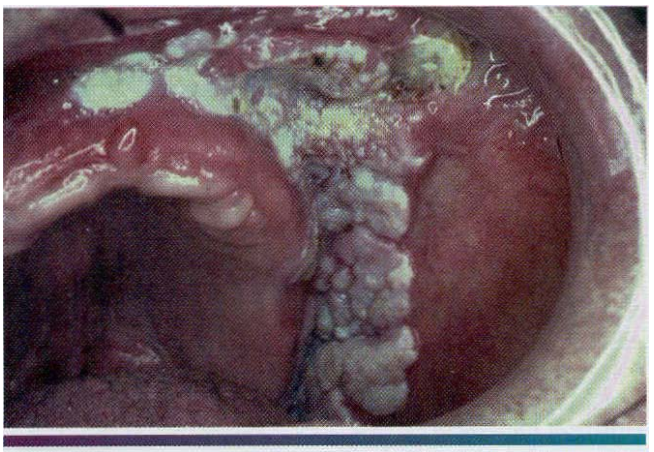

Figure 10-120 • Verrucous carcinoma. Extensive papillary, white lesion of the maxillary vestibule.

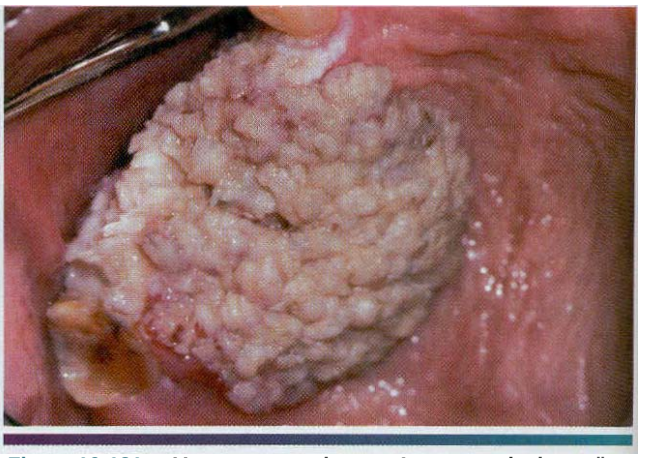

Figure 10-121 • Verrucous carcinoma. Large, exophytic, papillary mass of the maxillary alveolar ridge.

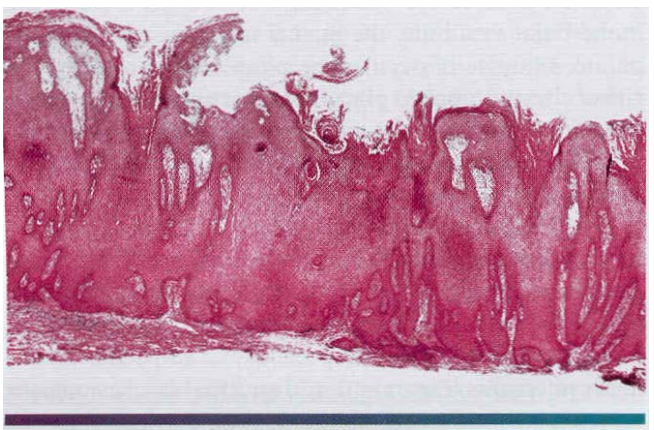

Figure 10-122 • Verrucous carcinoma. Low-power photomicrograph showing marked epithelial hyperplasia with a rough, papillary surface and keratin plugging.

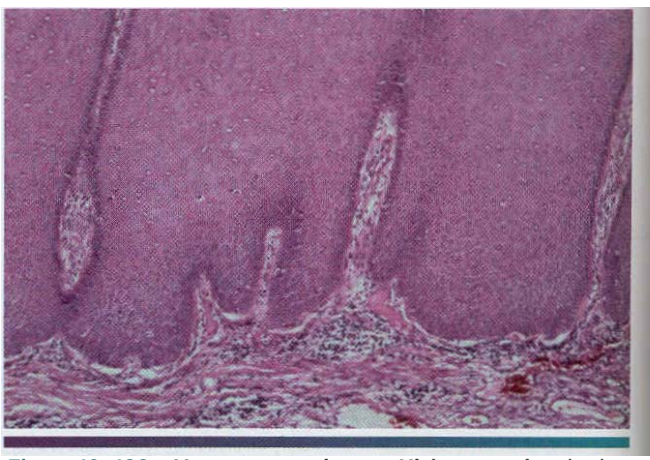

Figure 10-123 • Verrucous carcinoma. High-power view showing bulbous rete ridges without significant dysplasia.

ration pattern with no significant degree of cellular atypia (Figure 10-123). There is frequently an intense infiltrate of chronic inflammatory cells in the subjacent connective tissue.

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 arrive at an appropriate diagnosis. Adequate sampling also is important because as many as 20% of these lesions have a routine squamous cell carcinoma developing concurrently within the verrucous carcinoma.

Treatment and Prognosis

Because metastasis is an extremely rare event in verrucous carcinoma, the treatment of choice is surgical excision without radical neck dissection. The surgery generally need not be as extensive as that required for routine squamous cell carcinoma of a similar size. With this treatment, 90% of patients are disease free after 5 years, although 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 a focal squamous cell carcinoma arising concurrently within the less aggressive lesion.

Radiotherapy is effective, but has been less popular because of published reports of poorly differentiated or anaplastic carcinoma developing within the lesion after radiotherapy. A recent analysis suggests that this threat is seriously overexaggerated, and that similar dediffer-

entlation can occur in verrucous carcinomas treated surgically, Chemotherapy may temporarily reduce the size ofverrucous carcinoma, but it is not considered a definitive, stand-alone treatment.

SPINDLE CELL CARCINOMA (SARCOMATOID SQUAMOUS CEIL CARCINOMA; POLYPOID SQUAMOUS CEIL CARCINOMA)

Spindle cell carcinoma is a rare variant of squamous cell carcinoma characterized by dysplastic surface squamous epithelium in conjunction with an invasive spindle cell element. It may be indistinguishabie from connective tissue sarcomas or other spindle cell malignancies at the ievel of the light microscope,

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 be Simply an anaplastic type of carcinoma cell. Electron microscopy and immunohistochemicai analysis support the concept that these lesional cells are of epltheiial origin with the ability to produce mesenchymai intermediate filaments, More than one third of all mucosal cases develop as recurrences after radiotherapy for a more differentiated squamous cell carcinoma, a phenomenon known as dedifferentiation.

Clinical Features

The mean age at diagnosis for spindle cell carcinoma is 57 years (range: 29 to 93 years), There is no sex predilection, The neoplasm occurs predominantly in the upper aerodigestive tract, especially the larynx, oral cavity, and esophagus, Within the mouth, the lower lip, lateral posterior tongue, and alveolar ridges are common sites, but other areas may be involved.

In contrast to other oral cancers, the spindle cell carcinoma typically appears as a pedunculated, polypoid mass, but it may occasionally appear as a sessile, nodular or fungating mass, or an ulcer (Figure to-124), Pain and paresthesia are prominent features. The tumor grows rapidly, tends to metastasize early, and is typically diagnosed in a late stage (stages ill and iV), Lower lip lesions seem to have a special propensity to travel along nerves through the mental foramen and into the mandibular canal.

Histopathologic Features

The spindle cell carcinoma is composed predominantly of fascicles of anaplastic spindle-shaped cells (Figure 10-125), Some spindie 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 480) except for the often inconspicuous squamous element.

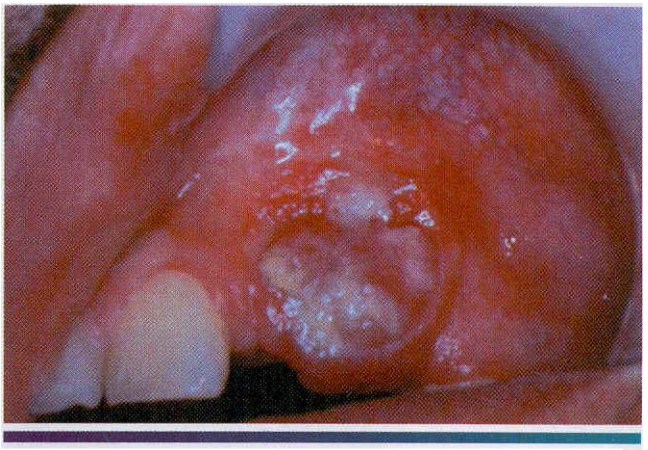

Figure 10-124 • Spindle cell carcinoma. Ulcerated mass of the maxillary alveolar ridge. (Courtesy of Dr. Michael Robinson.)

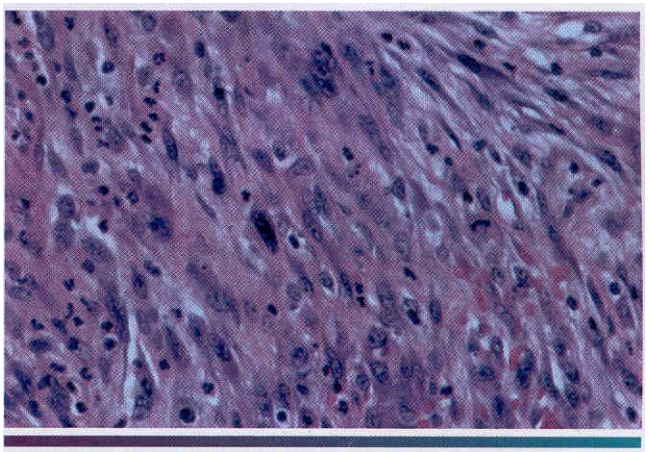

Figure 10-125 • Spindle cell carcinoma. Streaming fascicles of pleomorphic spindle cells that represent anaplastic epithelial cells.

The squamous component usually consists of carcinoma *in* situ of the overlying surface epithelium but may appear as islands of dysplastic squamous epithelium among the spindle cells, Direct transition between the two cell types may be seen. 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 distinguishlng this tumor from mesenchymal spindle cell malignancies, The lesional cells of most mesenchymal tumors typically produce vimentin but not cytokeratin, Approximately two thirds of the cases of spindle cell car-

cinema react with antibodies directed against cytokeratin, and an equivalent number show vimentin immunoreactivity. Some cases also will be positive for carcinoembryonic antigen (CEA).

Treatment and Prognosis

The treatment of choice for spindle cell carcinoma is radical surgery, with neck dissection when clinically positive nodes are present. Radiotherapy and chemotherapy are ineffective. The 5-year disease-free survival rate is approximately 30% for oral lesions, with most deaths occurring within 1 year of diagnosis. This is somewhat worse than the prognosis for the tumor when it occurs in other anatomic sites, but it is similar to the prognosis for high-grade oral squamous cell carcinoma. Surprisingly, tumor size seems to have little effect on the prognosis, although there is some *evidence* that the microscopic depth of invasion is a strong prognostic indicator in oral lesions, with superficial tumors demonstrating a better prognosis.

ADENOSQUAMOUS CARCINOMA

Adenosquamous carcinoma is a rare variant of squamous cell carcinoma 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 419). The cause is unknown.

Clinical Features

Cases of adenosquamous carcinoma have been reported from the tongue, oral floor, and other mucosal surfaces, usually in older adults. There is no sex predilection. The clinical appearance is that of a painless, nodular, broad-based mass with or without surface ulceration. Eighty percent of patients have metastatic deposits within the neck nodes at diagnosis.

Histopathologic Features

Adenosquamous carcinoma appears as an admixture of a surface squamous cell carcinoma and an underlying ductal adenocarcinoma. Intracytoplasmic mucin is noted by mucicarmine staining 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

Radical surgical excision, with or without radiation therapy, is the treatment of choice for patients with adenosquamous carcinoma. The prognosis is poor, with 60% of patients dying of disease, usually within 2 years of diagnosis.

BASALOID SQUAMOUS CARCINOMA (BASALOID SQUAMOUS CELL CARCINOMA)

Basaloid squamous carcinoma is a lesion found primarily in the upper aerodigestive tract mucosa and represents the most recently described variant of squamous cell carcinoma. It has a tendency to develop in the hypopharynx, but dozens of oral lesions have been reported.

Clinical Features

Basaloid squamous carcinoma occurs predominantly in men, in persons 40 to 85 years of age, and in abusers of alcohol and smoked tobacco. It occurs most commonly in the larynx and tongue base, but any region of the upper aerodigestive tract may be affected. The individual lesion clinically appears as a fungating mass or ulcer and may be painful or interfere with swallowing (dysphagia). Almost 80% of patients have cervical metastases at the time of diagnosis of this high-grade, aggressive cancer.

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, necrosis of central regions, and occasional squamous differentiation (Figure 10-126). 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 transition from squamous to basaloid cells may occasionally be seen. Basaloid cells and islands of cells often are surrounded by mucoid stroma (basal lamina material).

Treatment and Prognosis

Basaloid squamous carcinoma is an aggressive malignancy. Affected patients have a mean survival time of only 23 months. Surgery followed by radiotherapy is the recommended treatment, usually with adjuvant chemotherapy for the distant metastases.

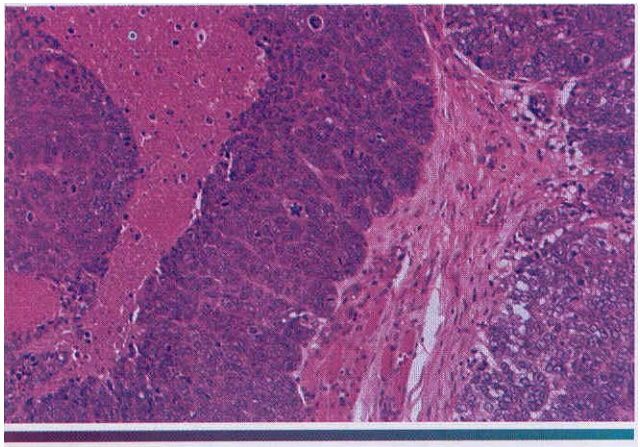

Figure 10-126 . Basaloid squamous carcinoma. Sheets of basaloid squamous epithelium exhibiting a high mitotic index and tumor necrosis.

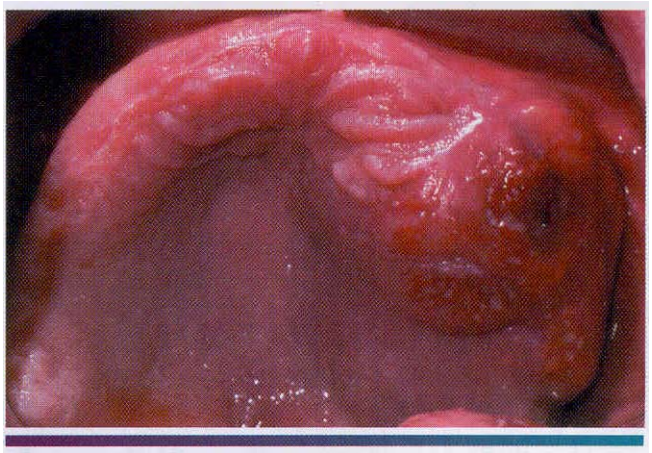

Figure 10-127 . Carcinoma of the maxillary sinus. The tumor has produced a bulge of the posterior maxillary alveolar ridge and is beginning to ulcerate through the surface mucosa.

CARCINOMA OF THE MAXILLARY SINUS

Carcinoma of the maxillary sinus or antrum is an uncommon malignancy of unknown cause. It does not appear to be related to sinusitis, nasal polyps, or tobacco **use. Most lesions remain asymptomatic 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.

Clinical and Radiographic Features

Typically, carcinoma of the maxillary sinus is a disease of elderly persons. There Is a slight predilection for males. More than 80% of cases are advanced (stage III and stage IV) at the time of diagnosis, Affected patients generally **complain of a chronic unilateral nasal stuffiness or notice an ulceration or mass of the hard palate or alveolar bone** (Figure iO-i27). 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, Teeth in the area of the tumor may become loosened, 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, although the extent of the tumor is visualized best by computed tomography (CT) or magnetic resonance imaging (MRil.

If the tumor perforates the lateral wall of the sinus, unilateral facial swelling and pain are usually present. If **the extension is medial, nasal obstruction or hemorrhage** usually occurs. Extension superiorly results in displacement or protrusion of the eyeball. Approximately 4% of patients have cervical or submandibular lymph node **metastasis at the time of diagnosis. Distant metastasis is quite uncommon** until late **in the progression of disease.**

A recently recognized form of undifferentiated tumor, the sinonasal undifferentiated carcinoma (SNUC), should be considered in the differential diagnosis of carcinomas **of the sinus. Some undifferentiated sinus tumors may show neuroendocrine differentiation. These aggressive** neoplasms develop within the nasal cavity and **paranasal sinuses, usually appearing with nasal obstruction**, facial pain, epistaxis, or perforation through the **sinus wall. There appears to be no sex predilection, and** the majority of patients are adults.

Histopathologic Features

Although the antrum is lined by respiratory epithelium, the great majority of maxillary sinus carcinomas are squamous cell carcinoma, usually moderately or poorly differentiated.

Sinonasal undifferentiated carcinoma is characterized by trabeculae and nests of polygonal lesional cells with minimal cytoplasm and pleomorphic, hyperchromatic **nuclei. Mitotic figures are numerous and the deep tumor** may be associated with carcinoma *in situ* of the overlying **surface epithelium. Vascular invasion and tissue necrosis often are extensive. Immunohistochemical staining for** cytokeratin or epithelial membrane antigen is typically **positive.**

Treatment and Prognosis

Carcinoma confined within the maxillary sinus is treated by hemimaxillectomy; those that have perforated through the surrounding bone are treated by radiotherapy or combined radical surgery and radiotherapy. **Even with radical treatment, however, the prognosis is** poor. Only 10% to 30% of patients survive 5 years after therapy. The presence of metastatic deposits in local

lymph nodes reduces the survival rate to less than 8%, as does involvement of the pterygopalatine fossa. With or without cervical node involvement, death usually occurs from local destruction and the inability to control the primary disease.

Aggressive multimodal therapy, including complete surgical excision when feasible, is the treatment of choice for sinonasal undifferentiated carcinoma. The prognosis for this lesion, however, is extremely poor. Cisplatin chemotherapy and bone marrow transplantation may extend the life of the patient.

NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma refers to 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's tonsillar tissue or Waldeyer's ring.

Nasopharyngeal carcinoma is rare in most areas of the world. The average annual incidence rate in the United States is less than one case per 100,000 population. In southern Chinese males, however, the rate is a startling 20 to 55 cases per 100,000. Among southern Chinese males who migrate to the United States, the rate is intermediate, which suggests an environmental causative agent. Infection with Epstein-Barr virus, diets deficient in vitamin C, and consumption of salt fish that contains potentially carcinogenic N-nitrosamines have been implicated as contributory factors.

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 when the area is examined endoscopically. The first sign of disease for 50% to 60% of patients is an enlarged, firm to hard, cervical lymph node, which represents metastatic tumor (Figure 10-128). Symptoms related to the ear are described by slightly less than half of these patients. If the tumor arises near the eustachian tube, unilateral serous otitis media, otalgia, or hearing loss from obstruction may be the presenting complaint.

Epistaxis, nasal obstruction, and pharyngeal pain may be present. The tumor may invade through the foramen lacerum into the brain, producing central nervous system (CNS) symptoms, or it may involve cranial nerves in the area, causing specific symptoms related to those nerves.

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 of nasopharyngeal carcinoma clinically, and multiple, systematic biopsy samples of the nasopharyngeal mucosa may be necessary for tumor identification and diagnosis. Microscopic examination of a nasopharyngeal carcinoma typically shows one of three histopathologic patterns:

1. Squamous cell carcinoma (keratinizing squamous cell carcinoma)
2. Differentiated nonkeratinizing carcinoma (nonkeratinizing squamous cell carcinoma)
3. Undifferentiated nonkeratinizing carcinoma (poorly differentiated carcinoma, anaplastic carcinoma, lymphoepithelioma)

More than one histopathologic type may be present in the same biopsy sample, in which case the tumor is classified according to the predominant histologic type.

The histopathologic features of the keratinizing squamous cell carcinoma are identical to those of squamous cell carcinoma of other head and neck regions (see page 365). Evidence of keratinization must be seen at the light microscopic level.

The lesional cells of differentiated nonkeratinizing carcinoma are relatively mature and somewhat squa-

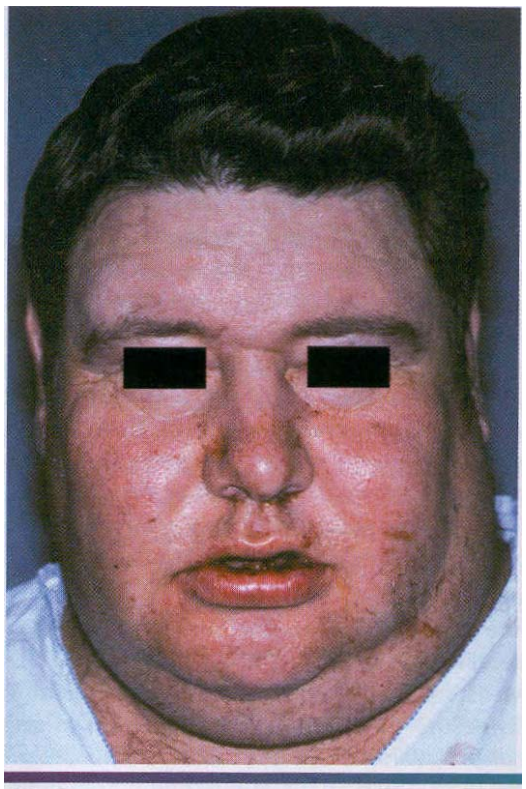

Figure 10-128 • Nasopharyngeal carcinoma. This patient initially appeared with metastatic carcinoma in the left lateral neck. Further evaluation revealed a primary tumor of the nasopharynx. (Courtesy of D. D. E. Kenady.)

mous 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 lesional cells with less distinct margins that show virtually no differentiation in most instances (Figure 10-129). They have very little cytoplasm and large vesicular nuclei. These tumor cells are often intermixed with the lymphoid cells normaiiy 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 light microscopy alone. and immunohistochemical studies often are used to demonstrate cytokeratins within the carcinoma cells. Some of these undifferentiated tumors currently are classified as sinonasal undifferentiated carcinomas (SNUC), Occasional neoplasms show neuroendocrine differentiation.

The less-differentiated lesions tend to occur in younger individuals. In fact, virtually all nasopharyngeal carcinomas in people younger than 40 years of age are poorly differentiated.

Treatment and Prognosis

Because of the inaccessibility of the nasopharynx and the high frequency of metastasis at diagnosis. nasopharyngeal carcinoma is treated most frequently with radiotherapy to the nasopharynx and neck. This may be combinedwith chemotherapy, but this addition has not been shown to improve survival. The prognosis ranges from good to poor. depending on the stage of the disease. The overall 5-year disease-free survival rate reported in one large series of cases in the United States was 45.5%, For stage I patients. a 100% 5-year survival rate has been demonstrated. Stage II is associated with a 67% 5-year survival rate; stage III. 44%; and stage IV, 34%. Patients with two or more clinical symptoms tend to have a worse prognosis. Persons treated for nasopharyngeal carcinoma are also at increased risk of developing a second primary malignancy of the head and neck mucosa.

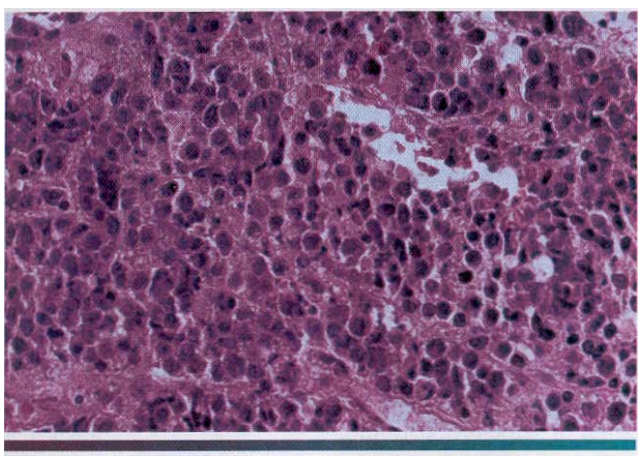

Figure 10-129 • Nasopharyngeal carcinoma. Poorly differentiated tumor exhibiting sheets of rounded tumor cells.

BASAL CELL CARCINOMA (BASAL CELL EPITHELIOMA; RODENT ULCER)

Basal cell carcinoma, the most common skin cancer (and the most common of all cancers), is a locally invasive. slowly spreading primary epithelial malignancy that arises from the basal cell layer of the skin and its appendages. About 85% are found on the skin of the head and neck. More than 800.000 new cases of basal cell carcinoma are diagnosed annually in the United States, representing 80% of all skin cancers. and the number of new cases is increasing by 3% to 7% each year. Incidence increases with increasing age.

This cancer results from chronic exposure to ultraviolet radiation. Oral lesions have been reported but are usually considered to be cases of misdiagnosed salivary or odontogenic neoplasms.

Clinical Features

Basal cell carcinoma is a disease of adult whites, especially those with fair complexions. Although most patients are older than 40 years of age at the time of diagnosis, some lesions are detected as early as the second decade of life, particularly in patients with red hair and blue eyes.

The most common form of this lesion, the nodular (noduloulcerauve) basal cell carcinoma. begins as a firm. painless papule that slowly enlarges and gradually develops a central depression and an umbilicated appearance. One or more telangiectatic blood vessels are usually seen coursing over the rolled border surrounding the central depression (Figures 10-130 and iO-131). When the iesion is pressed, a characteristic pearly opalescent quality is discerned. Expanding ulceration often develops in the central depressed area and the patient may give a history of intermittent bleeding followed by healing. Untreated lesions continue to enlarge slowly over months and years. with ulceration and destruction of underlying structures, hence their historical name, rodent ulcer. Destruction of underlying bone or cartilage may occur, but metastasis is extremely rare.

Several other clinicopathologic varieties of this tumor have also been described. Pigmented basal cell carcinoma is seen occasionally and represents a noduloulcerative tumor colonized by benign melanocytes {Figure

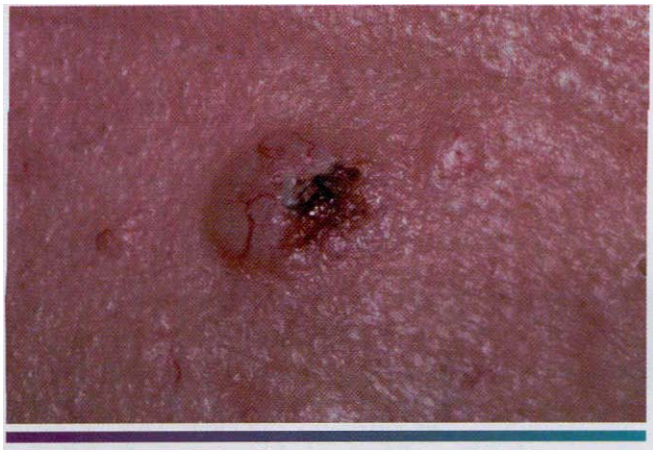

Figure 10-130 • **Basal cell carcinoma.** Early noduloulcerative basal cell carcinoma of the forehead showing raised. rolled borders and focal ulceration. Fine. telangiectatic blood vessels can be seen on the surface.

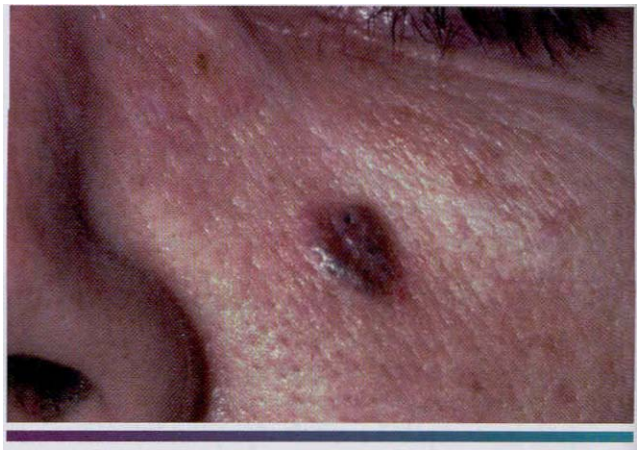

Figure 10-132 • **Basal cell carcinoma. Pigmented basal cell carcinoma of the cheek.**

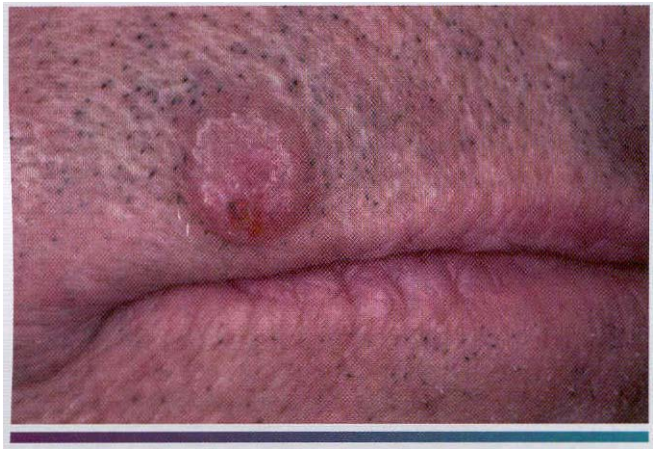

Figure 10-131 • **Basal cell carcinoma. Noduloulcerative lesion of the upper lip demonstrating telangiectasia and small ulceration.**

10-132). The melanin production imparts a tan, brown, black, or even bluish color to the lesion, and usually the pigment is not distributed uniformly. as it would be in a melanocytic nevus (see page 332).

Sclerosing (morpheaforml 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 edges of the tumor. Often a great deal of invasion has occurred before the **patient becomes aware of a problem.**

The 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. A fine, elevated, "threadlike" border is seen at the margins.

Some investigators believe that the basal cell carcinoma **associated with the nevoid basal cell carcinoma** syndrome (see page 598) 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 a significant degree of tissue destruction.

Histopathologic Features

The basal cell carcinoma displays a considerable diversity of appearances under the microscope: nodulocystic (noduloulcerativel. superficial, adenoid. pigmented, infiltrative, morpheaform, and keratotic. The noduloulcerative. pigmented, and syndrome-related basal cell **carcinomas are comprised of uniform ovoid. dark**-staining basaloid cells with moderate-sized nuclei and relatively little cytoplasm (Figure 10-133). The cells are arranged into well-demarcated islands and strands, which appear to arise from the basal cell layer of the overlying epidermis and invade into the underlying dermal connective tissue. Epithelial islands typically demonstrate palisading of the peripheral cells: fre**quently, a clear zone of artifactual retraction is** seen between the epithelial islands and the connective tissue. Although most of these neoplasms show no differentia**tion. some exhibit areas of keratin production, sebaceous** differentiation. or interlacing strands of lesional cellsthat resemble duct formation (vadenotd"). 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 den**dritic melanocytes within tumor islands. and** melano-

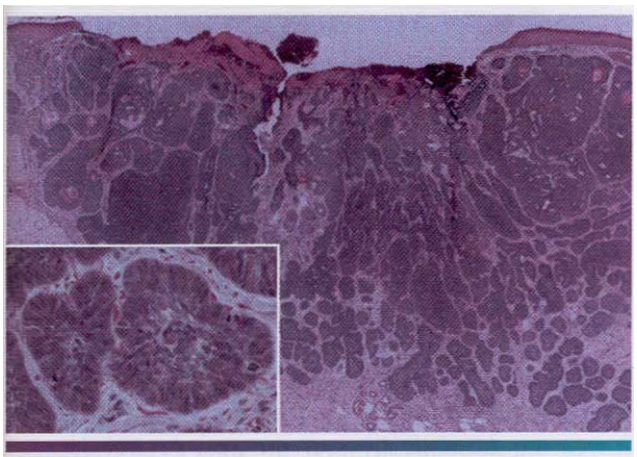

Figure 10-133 • Basal cell carcinoma. low-power photomicrograph showing ulceration of the epidermal surface associated with an invading tumor of hyperchromatic epithelial cells. Inset demonstrates islands of basophilic epithelium with peripheral palisading.

phages may be seen in the surrounding stroma. Sclerosing basal cell carcinoma is characterized by infiltrating thin strands of basaioid tumor celis set in a densely coliagenous background. Superficiai basal celi carcinoma includes lobules of tumor cells that drop from theepidermis in a multifocal pattern. Occasionally, basal cell carcinoma is seen admixed with an independent primary squamous cell carcinoma of the skin. The resulting "collision" tumor is called basosquamous carcinoma. Some authorities consider the basosquarnous carcinoma to bea simple basal celi carcinoma with abundant squamous metaplasia.

Treatment and Prognosis

The treatment of basal cell carcinoma often depends on the size and site of the lesion. Smali lesions « I em) are treated by routine surgical excision. laser ablation, or electrodesiccation and curettage. with 5 mm margins of clinicaliy normal-appearing skin beyond the visible lesion. These methods result in a cure rate of 95% to 98%. Radical surgical excision and radiation therapy are recommended for large or aggressive lesions. For sclerosing-type lesions. recurrent lesions. or lesions situated near embryonic planes of fusion (along which these tumor cells lend to invade), a procedure called Mohs micrographic surgery should be used. This technique essentially uses frozen-section evaluation of specially mapped and marked surgical specimens to determine whether tumor tissue has been left behind. If it has, the surgeon can return immediately to that particular area and remove more tissue. repeating the process until the patient is free of disease.

Recurrence of a properly treated basal cell carcinoma is uncommon. and metastasis is exceptionally rare. In patients with uncontrollable disease, death is usually the result of 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 a 30% chance of a second lesion developing within 3 years of the treatment of the initial tumor.

MERKEL CELL CARCINOMA (MERKEL CELL TUMOR; NEUROENDOCRINE CARCINOMA OF SKIN; SMALL CELL CARCINOMA OF SKIN; TRABECULAR CARCINOMA OF SKIN)

The Merkel cell carcinoma. first described in 1972. is a rare, aggressive primary malignancy with neuroendocrine features. It occurs primarily on the skin of the head and neck region. Lesional cells contain cytoplasmic granules that resemble the neurosecretory granules found within the epidermal Merkel cells of touch receptor regions. Intraoral and lip vermilion cases have been reported but are rare.

Clinical Features

Merkel cell carcinoma typically appears in older people. It occurs primarily on the sun-exposed areas of fair-skinned individuals. most commonly (75%) all the skin of the face. The vermilion border of the lower lip is also a susceptible site. The tumor usually appears as a slowly enlarging. dome-shaped nodule with a smooth surface and prominent surface vessels (telangiectasias), It is red or violaceous and ranges in size from 0.5 to S.O em. Ulceration rarely is seen. Occasional lesions grow rapidly, and 25% demonstrate local metastasis at diagnosis. belying its innocuous clinical appearance.

Histopathologic Features

Merkel cell carcinoma consists of infiltrating sheets and anastomosing strands of moderately sized. uniform. undifferentiated basophilic cells in the dermis and subcutaneous fat (Figure 10-134). Pseudoglandular. trabecular, and cribriform ("Swiss cheese") patterns may be seen. The surface epithelium is usually intact and otherwise unremarkable unless secondarily ulcerated by the tumor. Mitotic figures are abundant. and tumor cells have prominent nuclei, scant cytoplasm. and indistinct cell borders. Intracytoplasmic argyrophilic granules may be demonstrated by the Grimelius stain, and Icslonal cells are consistently reactive with antibodies directed against cytokeratin 20 (CK20),

At times. this entity is difficult to differentiate histopathologically from amelanotic melanoma. metastatic esthesioneuroblastoma, metastatic small cell car-

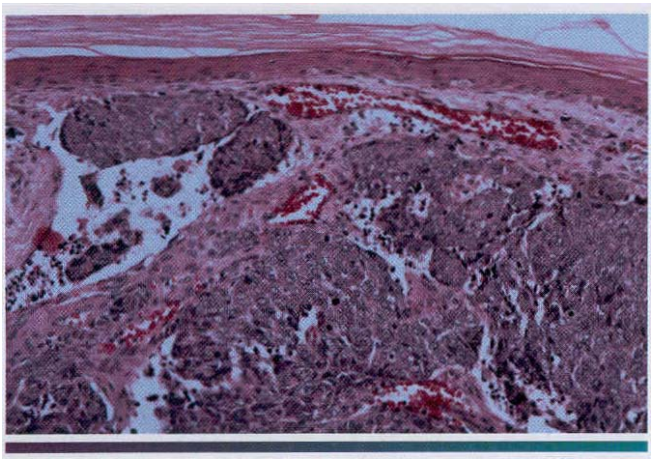

Figure 10-134 • Merkel cell carcinoma. A sheet of undifferentiated basophilic cells is seen beneath the epidermal surface.

cinoma of the lung, malignant lymphoma, and other undifferentiated malignancies. In this situation, a panel of immunohistochemical studies should be used to exclude these other diagnostic possibilities. Careful physical examination of the patient also may provide useful diagnostic information.

Treatment and Prognosis

Merkel cell carcinoma is treated with wide local excision, which is combined with lymph node dissection when clinically palpable nodes are found. The addition of postoperative radiotherapy improves the prognosis.

Recurrence develops in 55% of cases, most commonly within the draining lymph nodes. The overall 5-year disease-specific survival rate was 74% in one recent study.

MELANOMA (MALIGNANT MELANOMA; MELANOCARCINOMA)

Melanoma is a malignant neoplasm of melanocytic origin that arises *from* a benign melanocytic lesion or *de novo* from melanocytes within otherwise normal skin or mucosa. Although most melanomas occur on the skin, they may develop at any site where melanocytes are present. Damage from ultraviolet radiation is considered a major causative factor, as suggested by the fact that the incidence of melanoma increases for light-complexioned populations as they approach the equator, but chronic sun exposure does not seem to be as significant as *it* is for other cutaneous cancers, such as basal and squamous cell carcinoma. Acute sun damage may be of greater causative importance than chronic exposure in melanoma. Lesions of the intraoral mucosa, of course, are not related to sun exposure.

The risk of melanoma development is two to eight times greater when a relative has a history of the cancer. Additional risk factors include a fair complexion and light hair, a tendency to sunburn easily, a history of painful or blistering sunburns in childhood, an indoor occupation with outdoor recreational habits, a personal history of melanoma, and a personal history of dysplastic or congenital nevus.

Melanoma is the third most common skin cancer, but it accounts for only 5% of the total. Most deaths that are due to skin cancer, however, are caused by melanoma. In the United States, 48,000 new cases are diagnosed each year, and 7700 persons die of the disease. The average annual incidence rate for skin melanoma (9.3 per 100,000 males and 8.7 per 100,000 females) has been increasing dramatically over the past several decades. Today, it is estimated that one in 75 white persons born in the year 2000 will develop cutaneous melanoma in his or her lifetime.

Almost 25% of cutaneous melanomas arise in the head and neck area, 40% occur on the extremities, and the rest occur on the trunk.

Oral mucosal melanoma is rare in the United States, where it occurs in only one of every two million persons annually and comprises much less than 1% of all melanomas. It is more frequent in other countries, such as Japan and Uganda. The mucosal melanoma tends to appear at a higher stage and is much more aggressive than its cutaneous counterpart. At least one in three patients with oral melanoma have a history of a pigmented macule in the region of the tumor for some time before melanoma diagnosis. Melanoma occasionally affects the parotid gland, usually as a metastatic deposit from a scalp, conjunctival, or paranasal tumor.

Clinical Features

Most melanomas are seen in white adults. The average age of affected persons is 50 to 55 years, but cases are rather evenly distributed over the 30- to 80-year age bracket. A few melanomas occur in the second and third decades of life. Four clinicopathologic types of melanoma have been described:

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 of melanoma development, the radial growth phase tends to predominate in lentigo maligna melanoma, superficial spreading melanoma, and acral lentiginous melanoma. In these lesions, the malignant melanocytes tend to spread horizontally through the basal layer of the epidermis. Even-

Box 10-4 *The "ABCD" Clinical Features of Melanoma*

- Asymmetry (because of its uncontrolled growth pattern)
- Border irregularity (often with notching)
- Color variegation (which varies from shades of brown to black, white, red, and blue, depending on the amount and depth of melanin pigmentation)
- Diameter greater than 6 mm (which is the diameter of a pencil eraser)

tually, however, the malignant cells begin to invade the underlying connective tissue, thus initiating the vertical growth phase. With noduiar melanoma, the radial growth phase is very short or nonexistent and the vertical growth phase predominates.

Because many clinical similarities exist between melanoma and its benign counterpart, the melanocytic nevus, an "ABCD" system of evaluation has been developed to help distinguish a melanoma clinically from a melanocytic nevus (Box 10-4).

*Superficial **spreading** melanoma.* Superficial spreading melanoma is the most common form of melanoma, representing 70% of cutaneous lesions (Figure 10-135). The most common sites of origin are the interscapular area of males and the back of the legs of females. This form of melanoma appears as a macule with a variety of potential colors (i.e., tan, brown, gray, black, blue, white, pink). Typically, the lesion is smaller than 3 em in greatest diameter at diagnosis, but it may be several times that size. Many lesions are slightly elevated. Clinically, invasion is indicated by the appearance of surface nodules or induration, and usually occurs within 1 year of discovery of the precursor macule. Satellite macules or nodules of malignant cells 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 area. Nodular melanoma is thought to begin almost immediately in the vertical growth phase and, therefore, typically appears as a nodular elevation that rapidly invades into the connective tissue. Nodular melanoma is usually a deeply pigmented exophytic lesion, although sometimes the melanoma cells are so poorly differentiated that they no longer can produce melanin, resulting in a nonpigmented amelanotic melanoma.

Lentlgo maligna melanoma. Lentigo malign a melanoma, which accounts for 5% to 10% of cutaneous rnela-

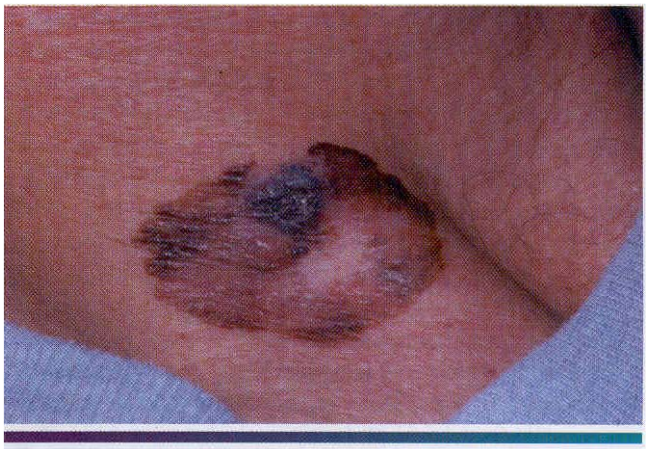

Figure 10-135 • Superficial spreading melanoma. This lesion on the neck demonstrates the ABe D warning signs of melanoma: Asymmetry, Border irregularity, Color variegation, and Diameter larger than a pencil eraser. (Courtesy of Dr. Mark Bowden.)

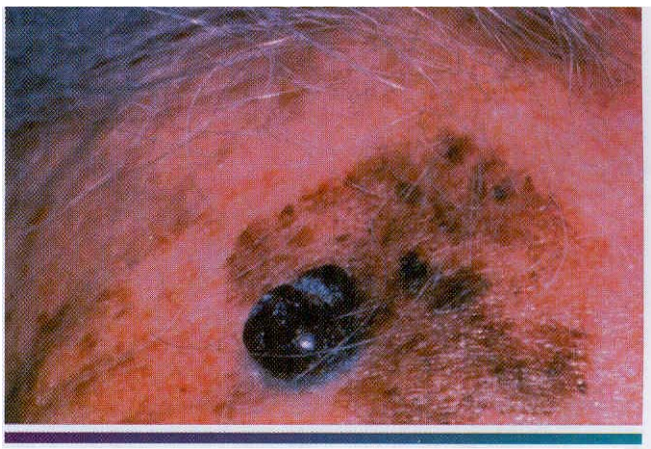

Figure 10-136 • lentigo maligna melanoma. A slowly evolving pigmented lesion ofthe facial skin in an elderly man.

nomas, develops from a precursor lesion called lentigo maligna (Hutchinson's freckle). Lentigo maligna occurs almost exclusively on the sun-exposed skin of fair-complexioned elderly persons, particularly in the midfacial region, and represents a melanoma *ln 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 (Figure 10-1 36). 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.

***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 darkly pigmented, irregularly marginated macule. which later develops a nodular invasive growth phase. Recently, **some authorities have separated this lesion into two entities:** (I) acral lentiginous melanoma and (2) mucosal **lentiginous melanoma.**

Oral melanoma is often nodular at the time of diagnosis, but early lesions may be flat. Affected persons are usually in their sixth or seventh decade of life. Two thirds of patients are male. Four of every five oral melanomas are found on the hard palate or maxillary alveolus.

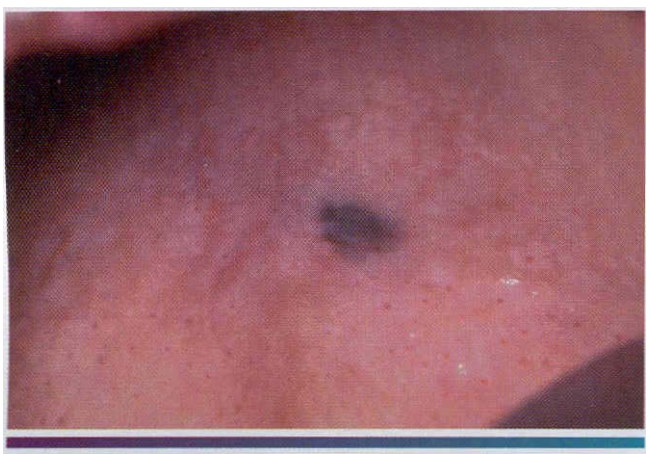

Figure 10-137 . Oral melanoma. This discrete area of pigmentation, measuring approximately 5 mm in diameter was discovered on the posterior hard palate of a middle-aged woman during a routine oral examination. Biopsy revealed melanoma *in* situ.

An oral lesion typically begins as a brown to black macule with irregular borders (Figures 10-137 and 10-138). The macule extends laterally. and a lobulated. **exophytic mass develops once the vertical growth is initiated** (Figure 10-139). Ulceration may develop early, but many lesions are dark, lobulated, exophytic masses without ulceration at the time of diagnosis. More than 20% of oral melanomas contain so little pigment that they **have an essentially normal mucosal tint. Pain is not a common feature except in ulcerated lesions, and** most lesions remain relatively soft to palpation. Underlying or adjacent bone may show radiographic evidence of irregular **or "moth-eaten" destruction.**

Histopathologic Features

With cutaneous and oral melanomas, atypical melanocytes **are initially 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 the early stages of the neoplasm. atypical melanocytes are seen either scattered singly among the basal epithelial cells or as nests within the basal cell layer. The atypical melanocytes are usually larger than normal melanocytes and have varying degrees of nuclear pleomorphism and hyperchromatism.

With superficial spreading melanoma, *pagetoid spread* often **is seen. Large melanoma cells infiltrate the surface** epithelium singly or in nests (Figure 10-140). The resulting **microscopic pattern is called pagetoid because it** resembles an intraepithelial adenocarcinoma known as Pagers disease of skin.

The spreading of the lesionai cells along the basal layer constitutes the radial growth phase of the neoplasm. Such lateral spread of cells within the epithelium, which occurs before invasion into the underlying con-

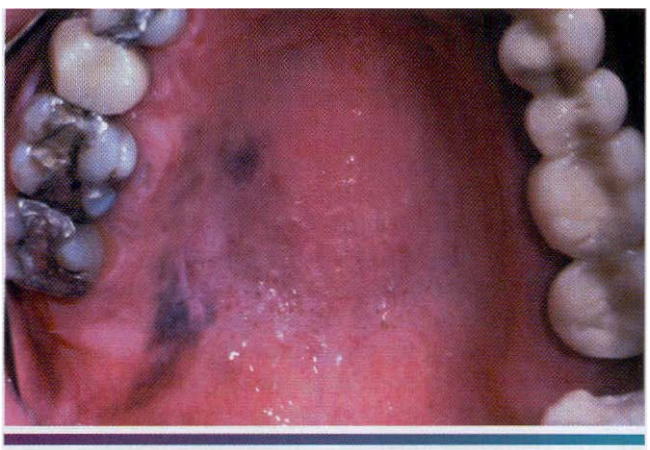

Figure 10-138 • Oral melanoma. Diffuse. splotchy area of pigmentation of the lateral hard palate. (Courtesy of Dr. Ien Morrow.)

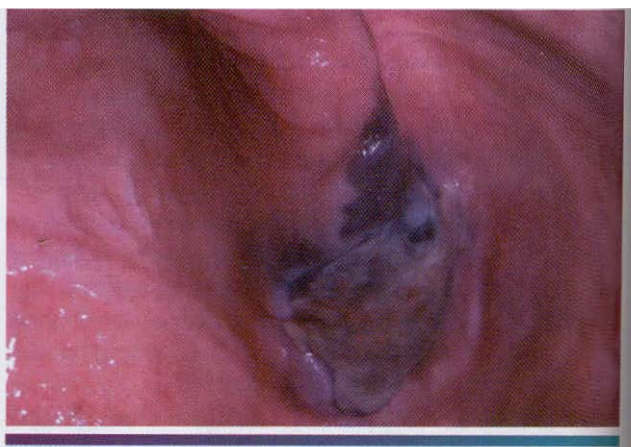

Figure 10-139 • Oral melanoma. Ulcerated pigmented mass of the posterior maxillary alveolar ridge.

nective tissue. is characteristically seen in superficial spreading melanoma, lentigo maligna melanoma, and acral Jentiginous melanoma. In acral lentiginous melanoma, many of the melanocytes have prominent dendritic processes (Figure 10-141).

When malignant melanocytes are observed invading the connective tissue, the vertical growth phase has taken place. In nodular melanoma, this vertical growth phase occurs early In the course of the tumor. No radial growth of cells can be observed in the overlying epithelium beyond the edge of the invasive tumor (Figure 10-142). The invasfve melanoma cells usually appear either spindle-shaped or epithelioid and Infiltrate the connective tissue as loosely aggregated cords or sheets of pleomorphic cells. Oral lesions tend to show invasion of lymphatic and blood vessels more readily 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, osteogenic sarcoma, and mesenchymal chondrosarcoma.

In most instances, the lesional cells of melanoma contain fine melanin granules, but they may demonstrate no melanin production (amelanotic melanoma). A lack of melanin production may cause diagnostic confusion at the light microscopic level because melanoma can mimic a variety of undifferentiated tumors. Immunohistochemical studies showing 5-100protein, MART-I, and HMB-45 reactivity of the lesional cells are beneficial in distinguishing such melanomas from other malignancies.

Treatment and Prognosis

Microscopic measurement of the depth of invasion is an important component of the histopathologic evaluation of melanoma because of its correlation with the prognosis. The Clark system of measurement assigns a "level" to the lesion that depends on the deepest anatomic cutaneous region that has been invaded by tumor cells. The more recent Breslow classification. however, appears to show a more accurate correlation with the prognosis and is based on the actual measurement of the distance from the top of the granular cell layer to the deepest identifiable point of tumor invasion (Table 10-4). Patients also are staged clinically in a fashion similar to patients with squamous cell carcinoma.

Surgical excision is the only curative treatment, although the extent of the excision is somewhat controversial. Older literature suggests that surgical margins of 3 to 5 cm around the tumor are necessary to achieve control, regardless of the site of the lesion. More recent studies indicate that a I em margin is adequate for small, early tumors. For larger, more deeply invasive tumors, wide surgical excision still is recommended. Surgical

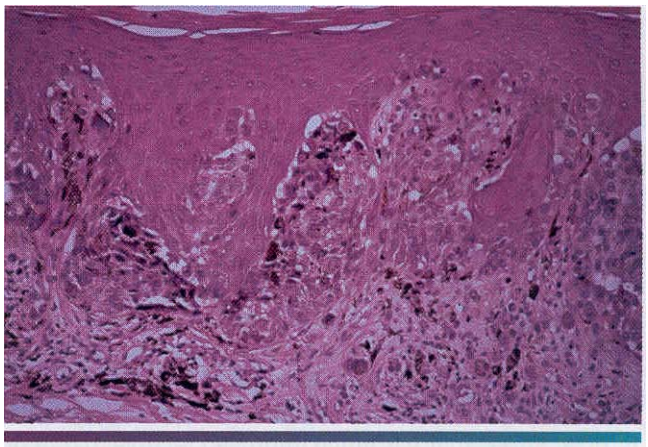

Figure 10-141 • Acrallentiginous melanoma. This palatal melanoma demonstrates numerous atypical melanocytes in the basilar portion of the epithelium with invasion into the superficial lamina propria. This represents the biopsy specimen from Figure 10-138.

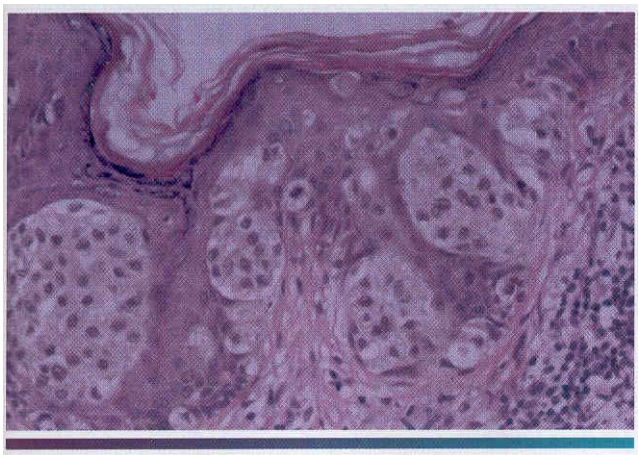

Figure 10-140 • Superficial spreading melanoma. The radial growth phase is characterized by the spread of atypical melanocytes along the basilar portion of the epidermis. Also note the presence of individual melanocytes invading the higher levels of the epithelium.

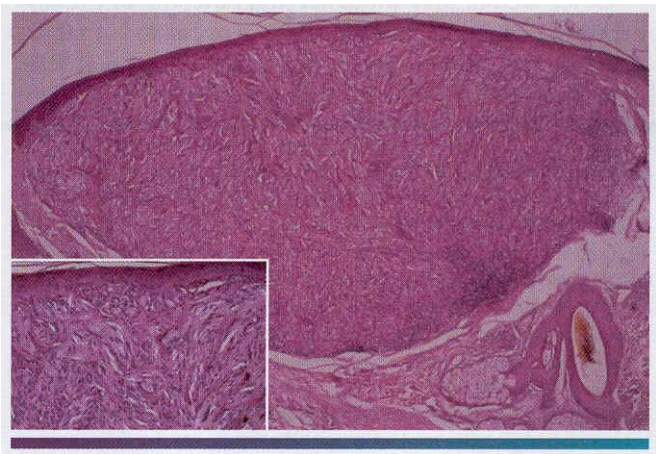

Figure 10-142 • Nodular melanoma. A nodular mass of spindle-shaped malignant melanocytes is seen invading into the dermis. Note the lack of radial growth in the adjacent overlying epidermis. The inset shows the tumor at higher power.

Table 10-4 *Two Classificalioll Systems! Used to Measure Depth of Invasion ;11 Cutaneous Melanoma*

Clark's Definition of Level of Tumor Invasion	Clark's Classification	Breslow's Depth of Invasion (mm)[2]	ESTIMATED IO-YEAR SURVIVAL RATE	
			Clark	Breslow
Cells confined to epithelium	level I	N/A	96%	N/A
Cells penetrating papillary dermis	Level I!	0.00 to 0.75 mm	96%	98%
Cells filling papillary dermis	Level III	0.76 to 1.69 mm	90%	89%
Cells extending into reticular dermis	Level IV	1.70 to 3.59 mm	67%	67%
Cells invading subcutaneous fat	level V	> 3.6 mm	26%	43%

'The Clark and Breslow classifications are the most widely used systems for prognostic purposes.
"srestcws depth is measured from the top of the granular cell layer.

removal of regional lymph nodes is recommended for lesions with a histopathologic depth of invasion that exceeds 1.24 mm. Radiation therapy has no significant impact on survival. although adjunct chemotherapy and immunotherapy are showing promise.

The cutaneous melanoma that is detected early and removed before metastasis has developed (stage I) is associated with an 89% 5-year survival rate and an 81 0/0 10-year survival rate. The melanoma that has metastasized to local lymph nodes at the time of diagnosis (stage II) is associated with a 61 % 5-year survival rate and a 47% IO-year survival rate. If disseminated disease is present at the time of diagnosis (stage III), the tumor is virtually always fatal. Overall. the 10-year survival rate is 79%. Survivability is much improved relative to that of past decades, primarily as a result of public education. Currently, the clinical features of cutaneous melanoma are so widely known that many lesions are discovered and treated at an early stage.

Other factors may influence the outcome of the disease besides the depth of invasion. For reasons that are unclear, melanomas affecting certain cutaneous sites seem to carry a worse prognosis than those at other sites with a similar depth of invasion. The areas with a worse prognosis are designated "BANS" (interscapular area of the Back. posterior upper Arm, posterior and lateral Neck. and Scalp). In addition. the prognosis is better for patients younger than 50 years of age and for women. Follow-up of patients treated for melanoma is important not only to monitor for metastatic disease but also because, in 3% to 5% of these patients. a second primary melanoma will eventually develop.

The prognosis for oral melanoma is extremely poor. Until recently, less than 20% of affected patients survived for 5 years or more. A large series from 1998, however. reported a 45% survival rate at 5 years, dropping to 28% at iOyears. The site of mucosal origin appears not to influence *survival*. but younger patients have a better survival than older ones. and patients with nonpigmented or amelanotic lesions appear to have a particularly poor prognosis. Patients usually die from distant metastasis rather than from the lack of local control. Radical surgical removal is the treatment of choice; hemimaxillectomy is done for lesions that invade the overlying maxillary bone.

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CHAPTER 11

Salivary Gland Pathology

CHAPTER OUTLINE

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 392), 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." 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 (Figures 11-1 to 11-3). 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 newborn infants and older people. 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.

The lower lip is the most common site for the mucocele, accounting for over 60% of all cases. Mucoceles usually are found lateral to the midline. Less common sites include the buccal mucosa, anterior ventral tongue, and floor of mouth (ranula). Mucoceles rarely develop on the upper lip. This is in contradistinction to salivary gland tumors, which are not unusual in the upper lip but are distinctly uncommon in the lower lip.

The soft palate and retromolar area are also 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 (Figure 11-4). 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. 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 avoid mistaking it microscopically for a vesiculobullous disorder, especially cicatricial (mucous membrane) pemphigoid.

Histopathologic Features

On microscopic examination, the mucocele shows an area of spilled mucin surrounded by a granulation tissue response (Figures 11-5 and 11-6). 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.

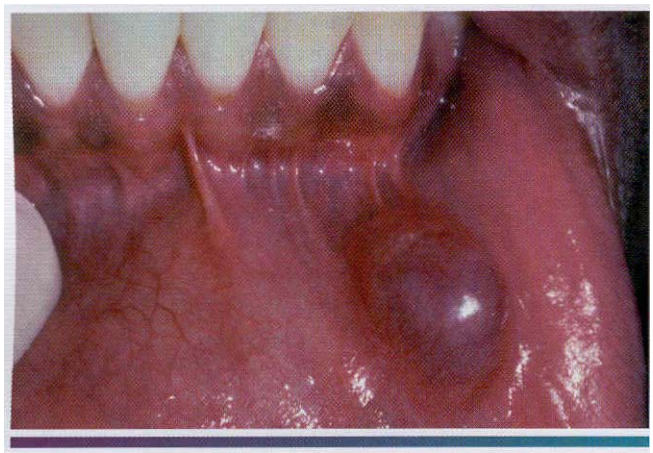

Figure 11-1 • Mucocele. Blue-pigmented nodule on the lower lip.

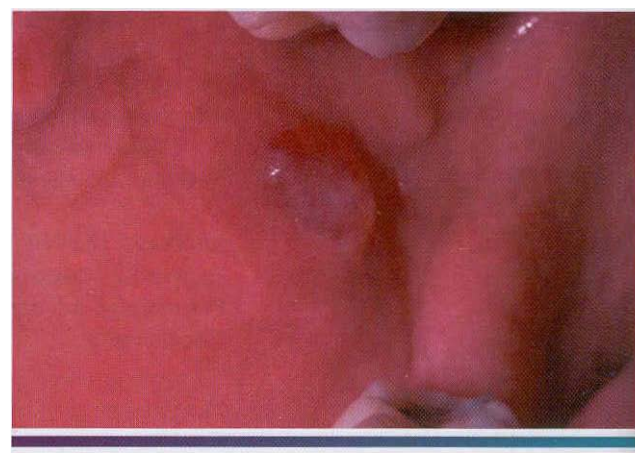

Figure 11-2 • Mucocele. Nodule on the posterior buccal mucosa.

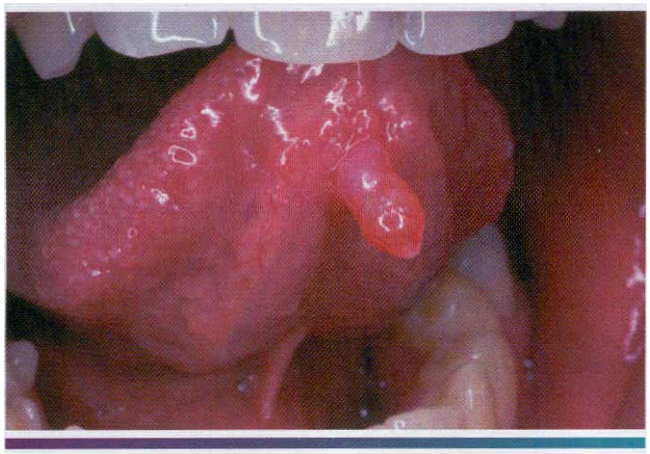

Figure 11-3 • Mucocele. Exophytic lesion on the anterior ventral tongue.

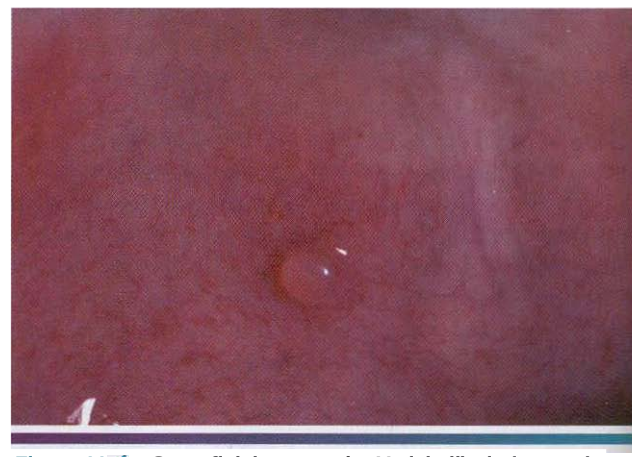

Figure 11-4 • Superficial mucocele. Vesicle-like lesion on the soft palate.

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, when the area is excised, the surgeon should remove any adjacent minor salivary glands that may be feeding into the lesion. 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.

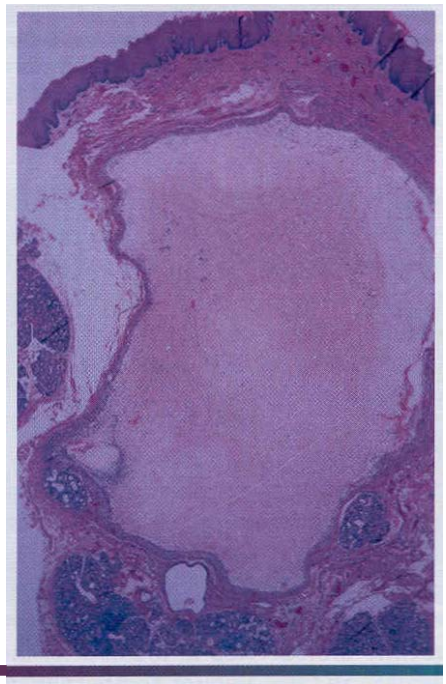

Figure 11-5 • Mucocele. Mucin-filled cystlike cavity beneath the mucosal surface. Minor salivary glands are present below and lateral to the spilled mucin.

RANULA

Ranula is a term used for mucoceles that occur in the floor of the mouth. 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 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). Although the source of mucin spillage is usually the sublingual gland, ranulas may arise from the submandibular duct or, possibly, from minor salivary glands in the *floor* of the mouth.

Clinical Features

The ranula appears as a blue, dome-shaped, fluctuant swelling in the floor of the mouth (Figure 11-7). Deeper lesions may be normal in color. Ranulas tend to be larger than mucoceles in other oral locations: they can develop into large masses that are many centimeters in diameter, 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 32). 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 (Figure 11-8). A concomitant swelling in the floor of the mouth may or may not be present. If no lesion is produced in the mouth, the clinical diagnosis of ranula may not be suspected.

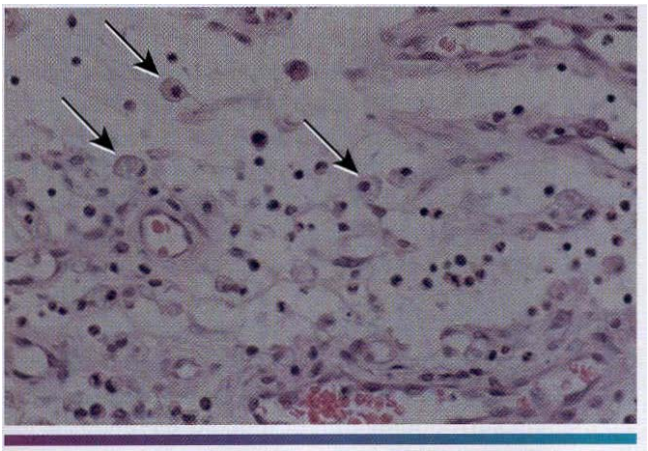

Figure 11-6 • Mucocele. High-power view showing spilled mucin that is associated with granulation tissue containing foamy histiocytes *(arrows)*.

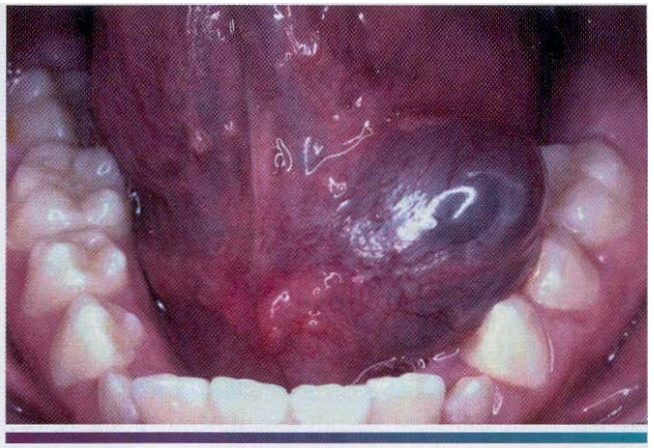

Figure 11-7 • Ranula. Blue-pigmented swelling in the left floor of the mouth.

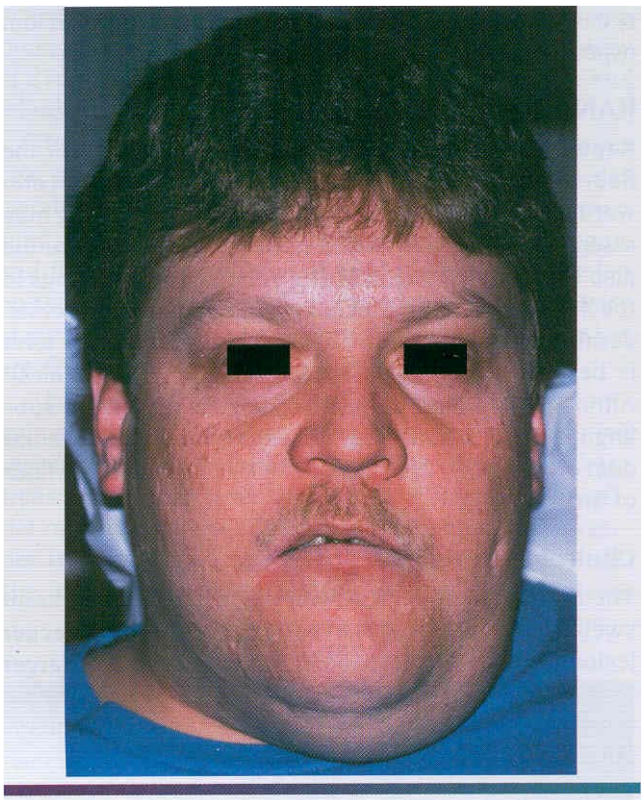

Figure 11-8 • Plunging ranula. Soft swelling in the neck.

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 subiingual gland and/or marsupialization. Marsupialization (exteriorization) entails removal of the roof of the intraoral lesion. potentially allowing the sublingual gland ducts to reestablish communication with the oral cavity. However. this procedure is often unsuccessful, and most authors emphasize that removal of the offending gland is the most important consideration in preventing a recurrence of the ranula. If the gland is removed. meticulous dissection of the lining of the lesion may not be necessary for the lesion to resolve, even for the plunging ranula.

SALIVARY DUCT CYST (MUCUS RETENTION CYST; MUCUS DUCT CYST; SIALOCYST)

The salivary duct cyst is an epithelium-iined cavity that arises from salivary gland tissue. Unlike the more common mucocele (see page 389), it is a true cyst because it is lined by epithelium. The cause of such cysts

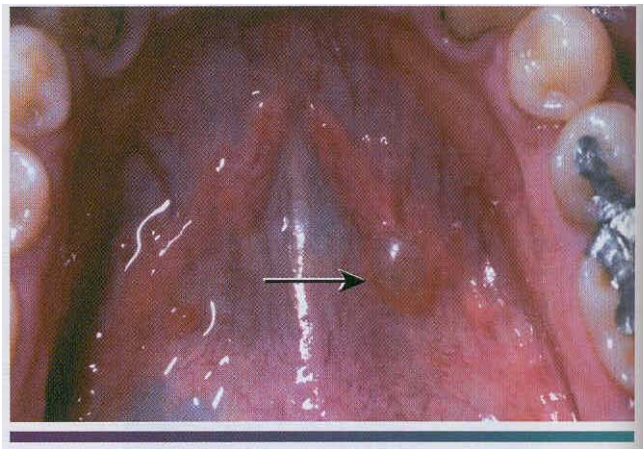

Figure 11-9 • Salivary duct cyst. Nodular swelling *(arrow)* overlying Wharton's duct.

is uncertain. Some cases may represent ductal dilatation secondary to ductal obstruction (e.g., mucus plug), which creates increased intraluminal pressure; some authors refer to such lesions as *mucus retention* cysts, Other cases appear to represent true developmental salivary duct cysts that are separate from the adjacent normal salivary ducts.

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 (Figure 11-9). 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 multiple mucus retention cysts that involve the excretory ducts of many of the minor salivary glands throughout the mouth. 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 (Figures II-iO and II-III. In some cases (especially those caused by ductal obstruction), the epithe-

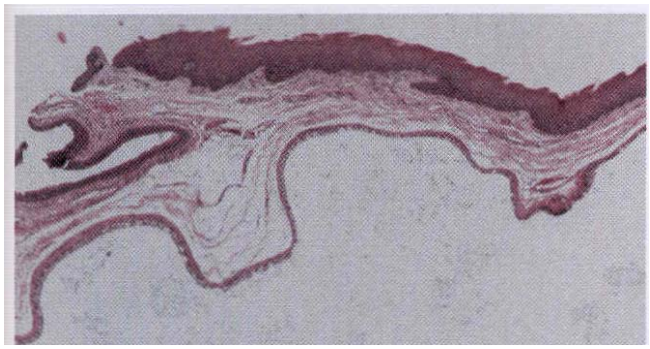

Figure 11-10 • **Salivary duct cyst.** Cystic cavity below the mucosal surface.

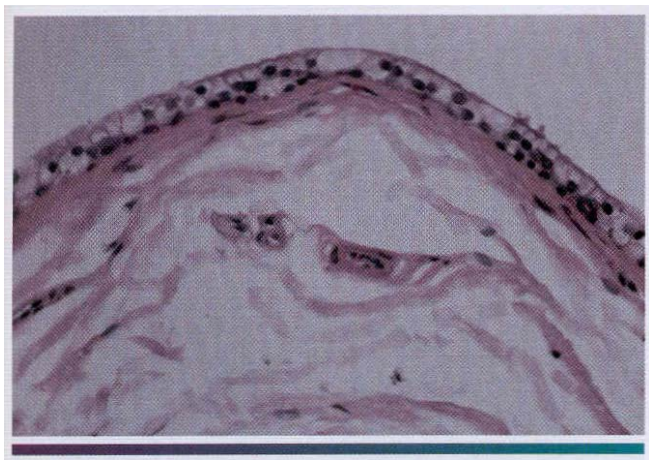

Figure 11-11 • **Salivary duct cyst.** High-power view of cystic lining demonstrating cuboidal to columnar epithelium with scattered mucin-producing cells.

lium may undergo oncocytic metaplasia. often demonstrating papillary folds into the cystic lumen, somewhat reminiscent of a small Warthin tumor (see page 415) but without the prominent lymphoid stroma. If this proliferation is extensive enough. these lesions are sometimes diagnosed as papillary cystadenoma, although it seems likely that most are not true neoplasms. The individual 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 multiple 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. Sialogogues 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. They are believed to 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 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: the formation of stones within the parotid gland system is distinctly less frequent. The long, tortuous, upward path of the submandibular (Wharton's) 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 back pressure produced within the gland. If the stone is located toward the terminal portion of the duct, a hard mass may be palpated beneath the mucosa (Figure 11-12).

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 aiong the length of the duct or within the gland itself. Stones in the terminal portion of the submandibular duct are best demonstrated with an occlusal radiograph (Figure 11-13). 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 (Figure 11-14). Multiple parotid stones radiographically can mimic calcified

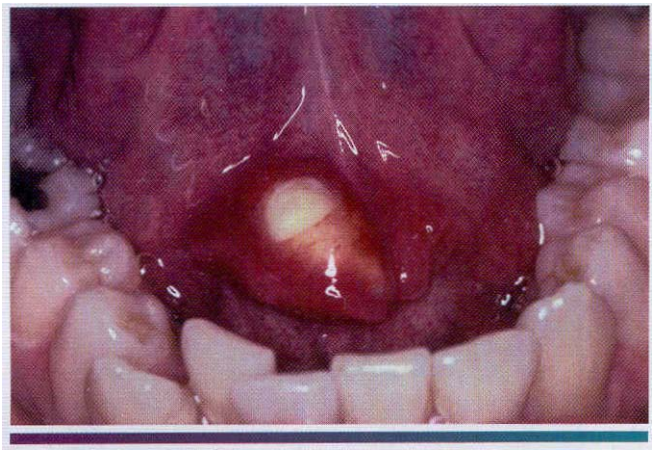

Figure 11-12 • Sialolithiasis. Hard mass at the orifice of Wharton's duct.

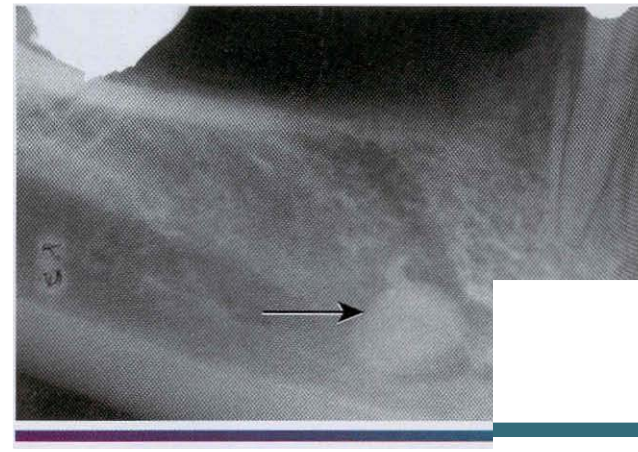

Figure 11-14 • Sialolithiasis. Periapical film of the same sialolith as depicted in Figure "-13. A radiopacity *(arrow)* is superimposed on the mandible. Care must be taken not to confuse such lesions with intrabony pathosis.

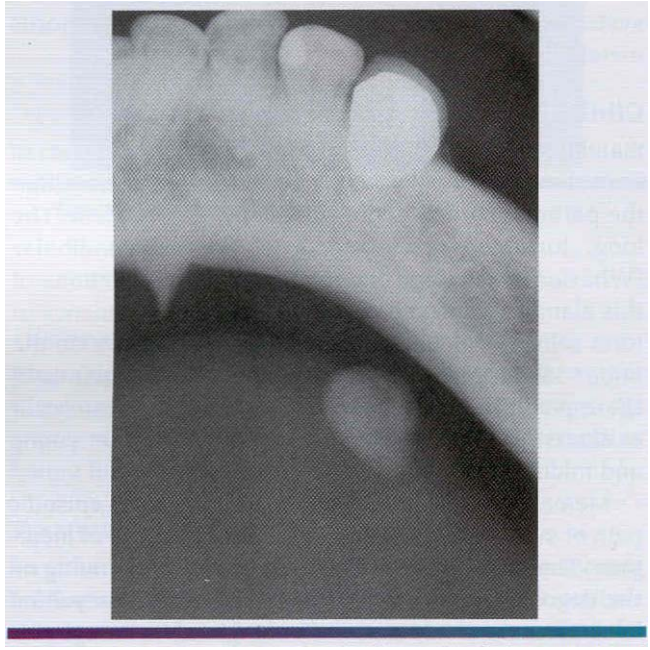

Figure 11-13 • Sialolithiasis. Occlusal radiograph demonstrating radiopaque stone in Wharton's duct.

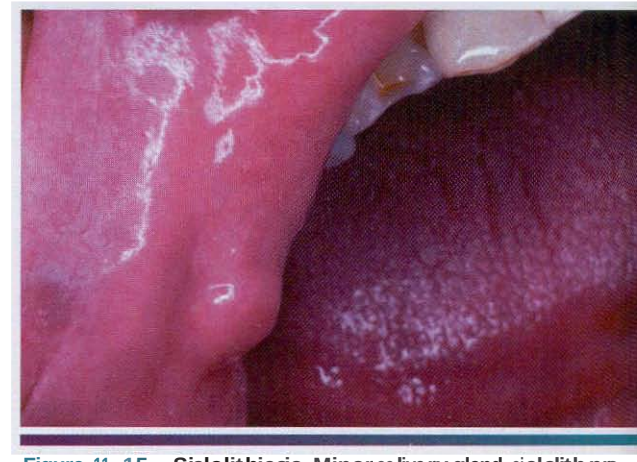

Figure 11-15 • Sialolithiasis. Minor salivary gland sialolith presenting as a hard nodule in the upper lip.

parotid lymph nodes. such as might occur in tuberculosis. Sialography. ultrasound. and computed tomography leT) scanning may be heipful additional imaging studies for sialoliths.

Minor gland staloliths often are asymptomatic but may produce local swelling or tenderness of the affected gland (Figure It-t5). A small radiopacity often can be demonstrated with a soft tissue radiograph (Figure 11-16).

Histopathologic Features

On gross examination, siaJoliths appear as hard masses that are round. oval. or cylindrical. They are typicaiiy yellow. although they may be white or yellowish-brown. 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 caicified mass exhibits concentric **lamination**s **that may surround a nidus of amorphous debri**s (Figure t1-t7). If the associated duct also is **removed, it often demonstrates squamous,** oncocync, **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.

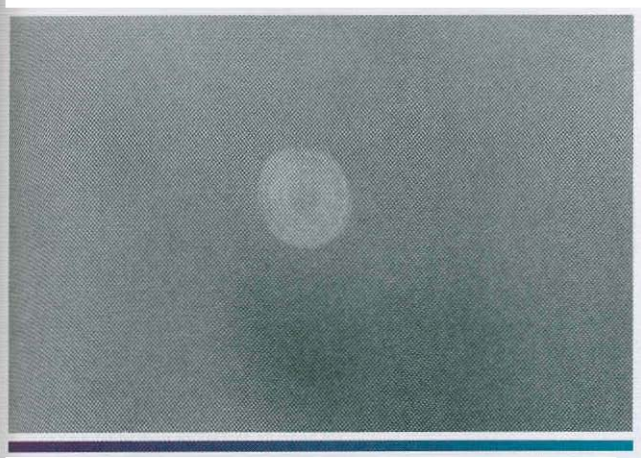

Figure 11-16 • Sialolithiasis. Soft tissue radiograph of the same lesion depicted in Figure 11-15. A laminated calcified mass is revealed.

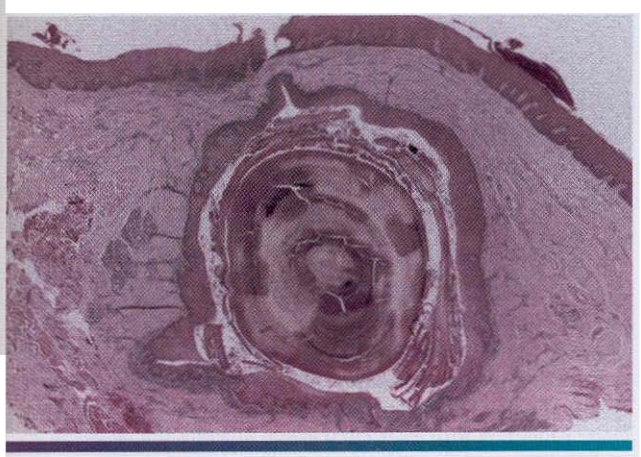

Figure 11-17. Sialolithiasis. Intraductal calcified mass showing concentric laminations. The duct exhibits squamous metaplasia.

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, the gland may need to be removed. Minor gland sialoliths are best treated by surgical removal, including the associated gland.

Salivary gland endoscopy is a newer method that has proven useful in the removal of some major gland sialoliths. This technique may be combined with intracorporeal lithotripsy to help fragment the stones. Extracorporeal shock wave lithotripsy also has been used successfully in Europe and Japan for the management of some patients.

SIALADENITIS

Inflammation of the salivary glands (sialadenitis) can arise from various infectious and noninfectious causes. The most common viral infection is mumps (see page 233), although a number of other viruses also can involve the salivary glands, including Coxsackie A, ECHO, choriomeningitis, parainfluenza, and cytomegalovirus (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 393), 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 cases of acute bacterial sialadenitis are due to *Staphylococcus aureus*, but they also may arise from streptococci or other organisms. Noninfectious causes of salivary inflammation include Sjögren syndrome (see page 401), sarcoidosis (see page 292), radiation therapy (see page 261), 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 erythematous (Figure 11-18). An associated low-grade fever may be present, as well as trismus. A purulent discharge often is observed from the duct orifice when the gland is massaged (Figure 11-19).

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 (Figure 11-20). In the submandibular gland, persistent enlargement may occur *(Karlna tumor),* which is difficult to distinguish from a true neoplasm. Chronic sialadenitis also can occur in the minor glands, possibly as a result of blockage of ductal flow or local trauma.

Subacute necrotizing sialadenitis is a recently recognized form of salivary inflammation that occurs most

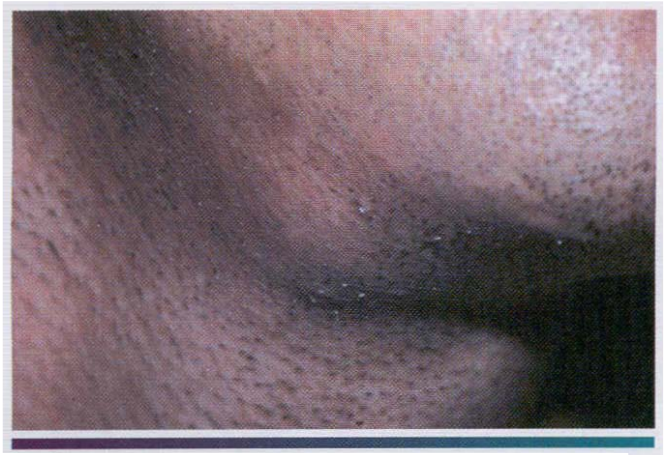

figure 11-18 • Sialadenitis. Tender swelling of the submandibular gland.

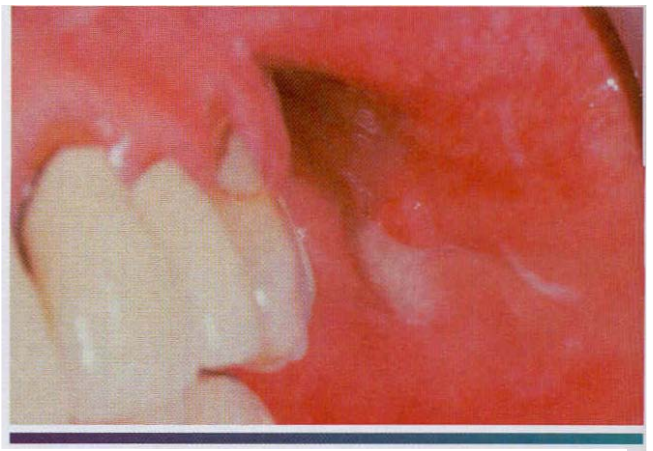

Figure 11-19 • Sialadenitis. A purulent exudate can be seen arising from Stensen's duct when the parotid gland is massaged.

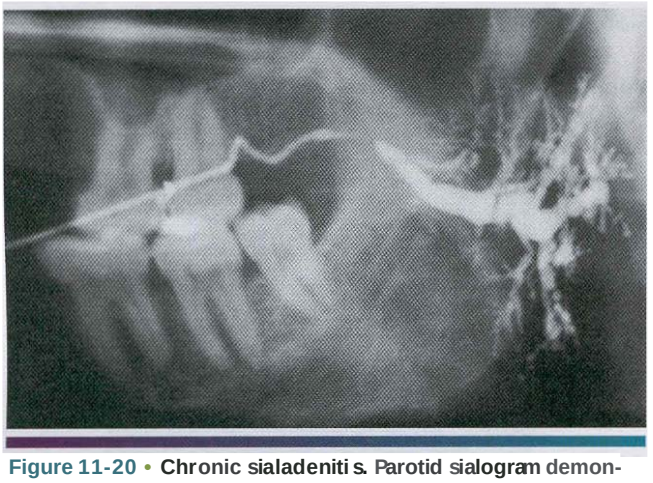

Figure 11-20 • Chronic sialadenitis. Parotid sialogram demonstrating ductal dilatation proximal to an area of obstruction. (Courtesy of Dr. George Blozis.]

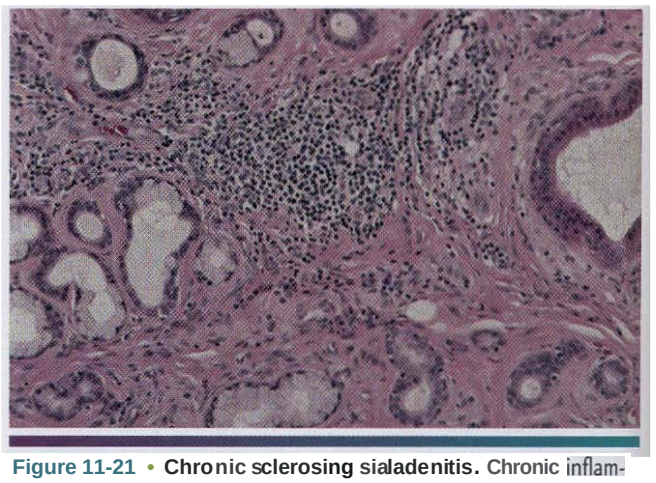

Figure 11-21 • Chronic sclerosing sialadenitis. Chronic inflammatory infiltrate with associated acinar atrophy, ductal dilatation, and fibrosis.

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 405), 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, the term chronic sclerosing sialadenitis is used (Figure 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

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 and duration of the condition. Early cases that develop secondary to ductal blockage may respond to *removal* of the sialolith or other obstruction. If sialectasia is present, the dilated ducts can lead to stasis of secretions and predispose the gland to further sialolith formation. If sufficient inflammatory destruction of the salivary tissue has occurred, surgical *removal* of the affected gland may be necessary.

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, syphilis, poor hygiene, and heredity.

Clinical Features

Cheilitis glandularis characteristically occurs on the lower lip, although there are also purported cases involving 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 (Figure 11-22). 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 266).

Historically, cheilitis glandularis has been classified into three types, based on the severity of the disease:

1. Simple
2. Superficial suppurative (Baelz's disease)
3. Deep suppurative (cheilitis glandularis aposternatosa)

The latter two types represent progressive stages of the disease with bacterial involvement and are characterized by increasing inflammation, suppuration, ulceration, and swelling of the lip.

Histopathologic Features

The microscopic findings of cheilitis glandularis are not specific and usually consist of chronic sialadenitis and ductal dilatation. Concomitant dysplastic changes may be observed in the overlying surface epithelium in some cases.

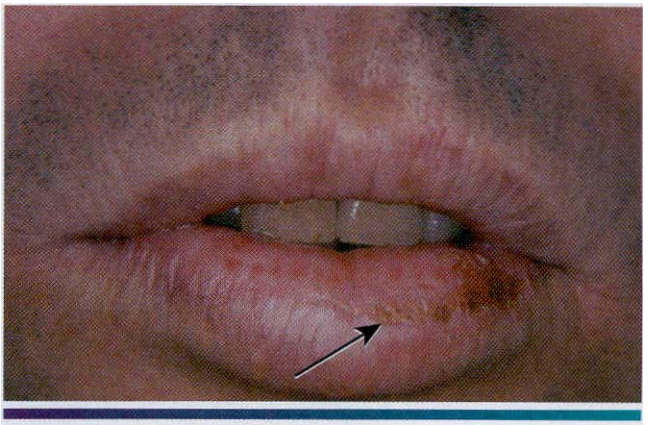

Figure 11-22 • Cheilitis glandularis. Prominent lower lip with inflamed openings of the minor salivary gland ducts. An early squamous cell carcinoma has developed on the patient's left side just lateral to the midline *(arrow)*. (Courtesy of Dr. George Blozis.)

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. A significant percentage of cases (18% to 35%) 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 272). It also may occur as a consequence of certain medications, such as lithium and cholinergic agonists.

Drooling can be a problem for patients who are mentally retarded, who *have* a neurologic disorder such as cerebral palsy, or who have undergone surgical resection of the mandible. In these instances, the drooling is probably not caused by overproduction of saliva but to poor neuromuscular control.

Clinical Features

The excess saliva production typically produces drooling and choking, which may cause social embarrassment. In children with mental retardation or cerebral palsy, the 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. 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. Speech therapy can be used to improve neuromuscular control. but patient cooperation is necessary.

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
- 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 also produces a loss of taste to the anterior two thirds of the tongue.

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 playa role in the cause of xerostomia, and these are listed in Box II-I. 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 accepted 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. *Over* 500 drugs have been reported to produce xerostomia as a side effect, including 63% of the 200 most frequently prescribed medicines in the L1nited States. A list of the most common and significant drugs associated with xerostomia is provided in Table ii-i. 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 01 whether the individual medications are xerogenlc or not.

Box 11-1 *Causes of Xerostomia*

DEVELOPMENTAL
Salivary gland aplasia

WATER/METABOLITE LOSS
Impaired fluid intake
Hemorrhage
Vomiting/diarrhea

IATROGENtC
Medications
Radiation therapy to the head and neck

SYSTEMIC DISEASES
Sjogren syndrome
Diabetes mellitus
Diabetes insipidus
Sarcoidosis
HIV infection
Graft-versus-host disease
Psychogenic disorders

LOCAL FACTORS
Decreased mastication
Smoking
Mouth breathing

Clinical Features

Examination of the patient typically demonstrates a reduction in salivary secretions, and the residual saliva

Table 11-1 *Medications that May Produce Xerostomia*

CLASS OF DRUG	EXAMPLE
Antihistamines	Diphenhydramine
	Chlorpheniramine
Decongestants	Pseudoephedrine
Antidepressants	Amitriptyline
Antipsychotics	Phenothiazine derivatives
	Haloperidol
Antihypertensives	Reserpine
	Methyldopa
	Chlorothiazide
	Furosemide
	Metoprolol
	Calcium channel blockers
Anticholinergics	Atropine
	Scopolamine

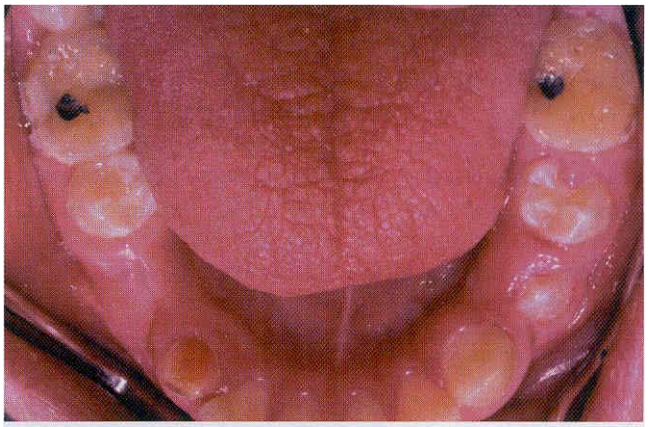

figure 11-23 • Xerostomia. Dry, leathery tongue in a patient with aplasia of the salivary glands.

appears either foamy or thick and "ropey." The mucosa appears dry 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 (Figure 11-23). The patient may complain of difficulty with mastication and swallowing and 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 262).

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 (Blctene toothpaste and mouth rinse; Oralbalance gel). if the dryness is secondary to the patient's medication, 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 has shown great promise as a sialogogue. 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, an acetylcholine derivative, also has recently been approved by the U.S. Food and Drug Administration for use as a sialogogue. Both pilocarpine and cevimeJine 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.

BENIGN IYMPHOEPITHELIAIIESION (MYOEPITHELIAL SIALADENITIS)

In the late 1800s, Johann von Mikulicz-Radecki described the case of a patient with an unusual bilateral painless swelling of the lacrimal glands and all of the salivary glands. Histopathologic examination of the *involved* glands showed an intense lymphocytic infiltrate, with features that today are recognized microscopically as the benign lymphoepitheliallesion. This clinical presenta-

tion became known as Mikulicz disease. and clinicians began using this term to describe a variety of cases of bilateral parotid and lacrimal enlargement. However, many of these cases were not examples of benign lymphoepithelial lesions microscopically; instead, they represented salivary and lacrimal involvement by other disease processes, such as tuberculosis. sarcoidosis. and lymphoma. These cases of parotid and lacrimal enlargement secondary to other diseases were later recognized as being different and termed Mikulicz syndrome, with the term Mikulicz disease reserved for cases associated with benign lymphoepithelial lesions. However. these two terms have become so confusing and ambiguous that they should no longer be used.

Many cases of so-called Mikulicz dlscase may be examples of what is now more commonly known as Sjogren syndrome (see page 401). Sjogren syndrome is an autoimmunc disease that may produce bilateral salivary and lacrimal enlargement, with microscopic features of benign lymphoepithelial lesion. However. not all benign lymphoepithelial lesions are necessarily associated with the clinical disease complex of Sjogren syndrome.

Clinical Features

Most benign lymphoepithelial lesions develop as a component of Sjogren syndrome. Those not associated with Sjogren syndrome are usually unilateral. although occasional bilateral examples are seen. On occasion, benign lymphoepitheliallesions occur in association with other salivary *gland* pathologic conditions, such as sialoliths and benign or malignant epithelial tumors.

The benign lymphoepithelial lesion most often develops in adults, with a mean age of 50 years. From 60% to 80% of cases occur in women. Eighty-five percent of cases occur in the parotid gland, with infrequent examples also reported in the submandibular gland and minor salivary glands. The lesion usually appears as a firm, diffuse swelling of the affected gland that sometimes is dramatic in size. It may be asymptomatic or associated with mild pain.

Histopathologic Features

Microscopic examination of the benign lymphoepithelial lesion shows a heavy lymphocytic infiltrate associated with the destruction of the salivary acini (Figure 11-24). Germinal centers may or may not be seen. 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 *epimyoepitheltal islands,* throughout the lymphoid proliferation. The presence of epimyoepithelial islands once was considered indicative of a benign process. but now it is recognized that these islands also can be found in low-grade salivary lymphomas of the mucosa-associated lymphoid tissue (MALT lymphomas).

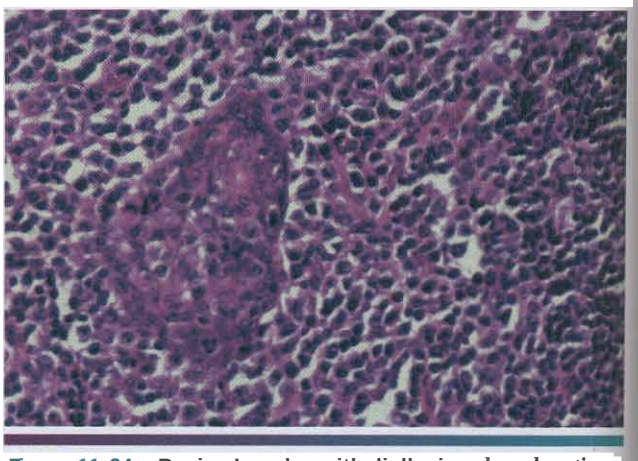

Figure 11-24 • Benign lymphoepitheliallesion. lymphocytic infiltrate ofthe parotid gland with an associated epimyoepithelial **island.**

Treatment and Prognosis

Although the benign lymphoepithelial lesion frequently necessitates surgical removal of the involved gland, the prognosis in most cases is good. However, individuals with benign lymphoepitheliallesions have an increased risk for lymphoma, either within the affected gland or in an extrasalivary site. Although the exact risk is uncertain. one study showed the risk in patients with Sjogren syndrome to be more than 40 times higher than expected in the general population. (The management of patients with Sjogren syndrome is discussed on page 403.)

With the development of modern molecular techniques to assess for gene rearrangements and monoclonality within lymphoid infiltrates. it is now recognized that some lesions originally believed to represent benign lymphoepithelial lesions are actually early-stage MALT lymphomas. Many experts now recognize a spectrum of salivary lymphoid proliferations, which range from benign lymphoepithelial lesions to borderline lesions to frank lymphomas. Because of this. some authors hsve dropped the term "benign" from this spectrum and refer to these proliferations only as *lymphoeptheiia! lesions*. Fortunately, most MALT lymphomas are low-grad, tumors that tend to remain localized with good survival rates. However, occasional tumors transform to higher-grade lymphomas with more aggressive behavior,

In addition, a rare malignant counterpart of this lesion, called a malignant lymphoepithelial lesion or lymphoepithelial carcinoma, represents a poorly differen-

tlated **salivary carcinoma with a prominent lymphoid stroma. Most of these lesions have occurred in Inuits** (Eskimos) and Asians and appear to have arisen *de novo* as **carcinomas; however, some cases (especially in non-**Inuits) have been reported to develop from a prior benign lymphoepithelial lesion. Because of the strong ethnic association of this tumor, attempts have been made to **determine a common causative agent. Most of this speculation** has centered on the Epstein-Barr virus, although delinite proof has not been established. The prognosis lor these carcinomas appears guarded, although Asian **patients have had a better survival rate.**

SJOGREN SYNDROME

Sjogren 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* = dry), and the clinical presentation of both xerostomia and xerophthalmia is also sometimes called the sicca syndrome. Two forms of the disease are recognized:

I. Primary Sjogren syndrome (sicca syndrome alone; **no other autoimmune disorder is present)**

2. Secondary Sjogren syndrome (the patient manifests sicca **syndrome in addition to another associated autoimmune disease)**

The cause of Sjogren syndrome is unknown. Although it is not a hereditary disease *per se,* there is evidence of a genetic influence. Relatives of affected patients have an **increased frequency of other autoimmune diseases. In** addition, certain histocompatibility antigens (HLAs) are lound with greater frequency in patients with Sjogren 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. It has been suggested that viruses, such as Epstein-Barr virus or human T cell lymphotropic virus, may playa pathogenetic role in Sjogren syndrome, but evidence for this is still speculative.

Clinical and Radiographic Features

Sjogren syndrome is not a rare condition. Although the **exact prevalence is unknown. estimates have ranged** from 0.2% to 3.0%, depending on the population studied and the clinical criteria used. Application of the stricter San Diego criteria (Box 11-2) results in a lower prevalence rate than the European Economic Community criteria. Between 80% and 90% of cases of Sjogren syn**drome occur in females. It is seen predominantly in** middle-aged adults, but rare examples have been described in children.

Box 11-2 *Sail Diego Criteria for Sjogrell Syndrome*

I. Primary Sjogren syndrome
- **A. Symptoms and objective signs of ocular dryness**
  1. **Schirmer's test less than 8 mm wetting per 5 minutes, AND**
  2. **Positive Rose Bengal staining of cornea or conjunctiva to demonstrate keratoconjunctivitis sicca.**
- **B. Symptoms and objective signs of dry mouth**
  1. **Decreased parotid flow rate using Lashley cups or other methods, AND**
  2. **Abnormal findings from biopsy of minor salivary gland (focus score of ≧ 2 based on average of four evaluable lobules).**
- **C. Serologic evidence of a systemic autoimmunity**
  1. **Elevated rheumatoid factor > 1:320, OR**
  2. Elevated antinuclear antibody (ANA) > 1:320, OR
  3. Presence of anti-SS-A (Ro) or anti-SS-B (La) **antibodies**

II. Secondary Sjogren syndrome
Characteristic signs and symptoms of Sjogren syndrome (as previously described), PLUS clinical features sufficient to allow a diagnosis of rheumatoid arthritis, systemic lupus erythematosus, polymyositis, scleroderma, or biliary cirrhosis.
Exclusions: sarcoidosis, preexisting lymphoma, human immunodeficiency virus (HIV), hepatitis B or C, primary fibromyalgia, and other known causes of autonomic neuropathy, keratitis sicca. or salivary gland enlargement.

From Fox RI: Sjogren's syndrome. In Klippel/H, Weyand eM. Wortmann RL: *Primeron the rheumatic diseases.* ed II, pp 283-288. Atlanta. 1997, Arthritis Foundation.

When the condition is associated with another connective tissue disease, it is called secondary Sjogren 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 Sjogren syndrome. In addition, secondary Sjogren syndrome may develop in 30% of patients with systemic lupus erythematosus (see page 689).

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 (Figure 11-25). The oral mucosa may be red and tender,

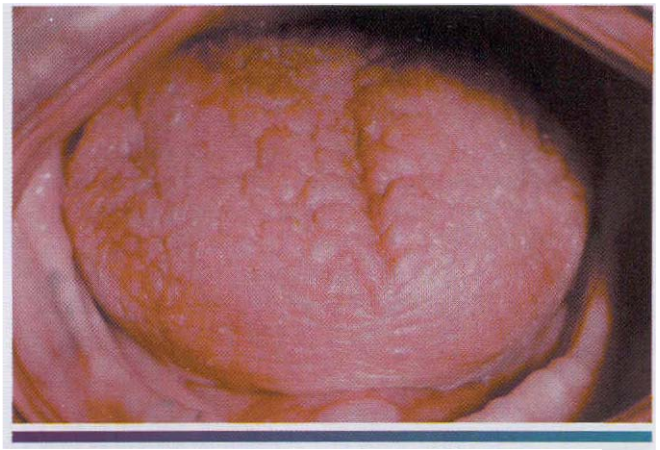

Figure 11-25 • Sjogren syndrome. Dry and fissured tongue. (Courtesy of Dr. David Schaffner.)

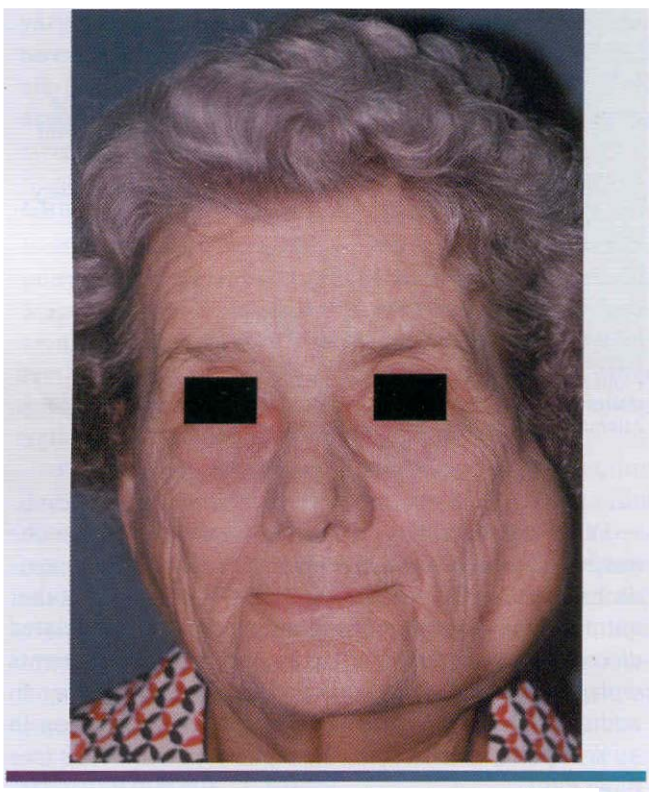

Figure 11-26 • Sjogren syndrome. Benign lymphoepithelial lesion of the parotid gland. (Courtesy of Dr. David Schaffner.)

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 (Figure 11-26). 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.

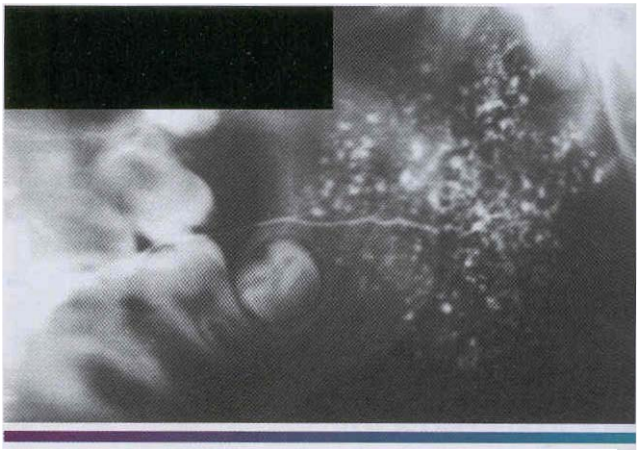

Figure 11-27 • Sjogren syndrome. Parotid sialogram demonstrating atrophy and punctate sialectasia (fruit-laden, branchless tree). (Courtesy of Dr. George Blozis.)

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 (Figure 11-27). 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 and can be demonstrated with rose bengal dye. Vision may become blurred, and sometimes there is an aching pain. The ocular manifestations are least severe in the morning on wakening and become more pronounced as the day progresses.

A simple means to confirm the decreased tear secretion is the Schirmer test. Standardized strips of sterile filter paper are placed over the margins of the lower lids so that their tabbed ends rest just inside the lower lid. By measuring the length of wetting of the filter paper, tear production can be assessed. Values below 5 mm (after a

s-mlnute period) are highly suggestive of keratoconjunctivitis slcca, and values from a to 2 mm strongly confirm a dry-eye state.

Sjogren 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. Fatigue is fairly common, and depression somelimes can occur. Other possible associated problems include lymphadenopathy. primary biliary cirrhosis. Raynaud's **phenomenon, interstitial nephritis, interstitial** lung fibrosis. vasculitis. and peripheral neuropathies.

Laboratory Values

In patients with Sjogren syndrome. the erythrocyte sedimentatlon rate is high and serum immunoglobulin 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 rheumalOid factor (RF) is found in 75% of cases. regardless of whether the patient has rheumatoid arthritis. Antinuclear antibodies (ANA) are also present in most patients. Two particular nuclear autoantibodies-anti-SS-A (anti-Ro) and anti-SS-B (anti-La)-frequently are found. especially in patients with primary Sjogren syndrome. 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). Several studies have suggested that salivary protein electrophoresis is a potentially useful test for the diagnosis of Sjogren syndrome.

Histopathologic Features

The basic microscopic finding in Sjogren syndrome is a lymphocytic infiltration of the salivary glands. with destruction of the acinar units. if the major glands are **enlarged. microscopic examination usually shows pro**gression to a lymphocpithelial lesion (see page 399), with characteristic epimyoepithelial islands in a background lymphoid stroma. 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 has become a useful test in the diagnosis of Sjogren syndrome. A 1.5 to 2.0 em 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 acces**sory glands. These glands then are examined histopathologically for the presence of focal chronic inflammatory aggregates (50 or more lymphocytes and plasma cells). These aggregates should be adjacent to normal-appearing

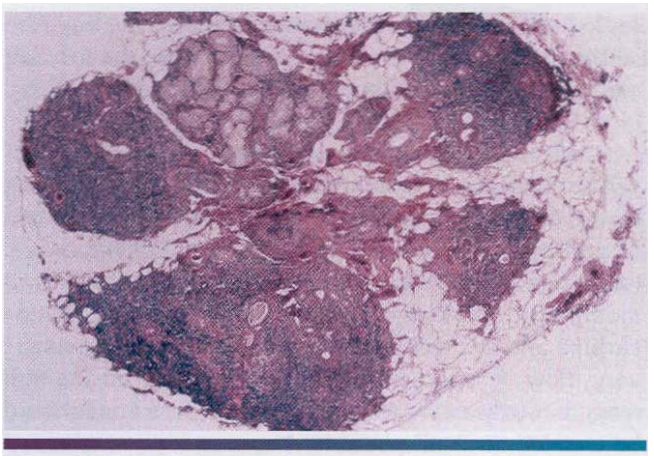

Figure 11-28 • Sjogren syndrome. labial gland biopsy showing multiple lymphocytic foci.

acini and should be found consistently in most of the glands in the specimen. The finding of more than one focus of 50 or more cells within a 4-mm' area of glandular tissue is considered supportive of the diagnosis of Sjogren syndrome (Figure 11-28). The greater the number of foci (up to 10 or confluent foci), the greater 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 Sjogren syndrome. Although labial salivary gland biopsy has become a widely used test in the diagnosis of Sjogren syndrome, it is not 100% reliable. Some patients diagnosed with Sjogren syndrome will show no significant labial gland inflammation; conversely. examination of labial glands removed incidentally from non-Sjogren patients sometimes will show focal lymphocytic infiltrates.

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 demon**strating Inflammatory changes that support the diagnosis of Sjogren 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 Sjogren 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 of 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; Oralbalance gel). Sialagogues, such as pilocarpine and cevimeJine, 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 Sjogren syndrome have an increased risk for lymphoma. up to 40 times higher than the normal popuiation. 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 (c.g.. *in situ* hybridization. polymerase chain reaction [peR]), 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's B-cell lymphomas of the mucosa-associated lymphoid tissue (MALT lymphomas). aithough occasionally. high-grade MALT lymphomas can develop which demonstrate more aggressive behavior. 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 11-3). The best known of these conditions include diabetes mellitus. general malnutrition, alcoholism. and bulimia.

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.

Clinical and Radiographic Features

Sialadenosis usually appears as a slowly evolving swelling of the parotid glands. which may or may not be painful (Figure 11-29). The condition is usually bilateral, but it also can be unilateral. In some patients. the submandibular glands can be involved. 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.

Box 11-3 *Conditions* ***Associated With*** *Sialadenosts*

A. ENDOCRINE
- Diabetes mellitus
- Diabetes insipidus
- Acromegaly
- Hypothyroidism
- Pregnancy

B. NUTRITIONAL
- General malnutrition
- Alcoholism
- Anorexia nervosa
- Bulimia

C. NEUROGENIC MEDICATIONS
- Antihypertensive drugs
- Psychotropic drugs
- Sympathomimetic drugs used for treating asthma

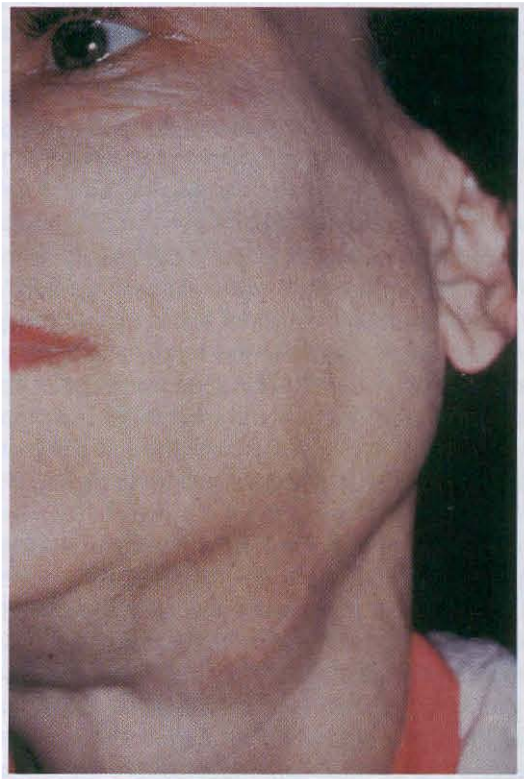

Figure 11-29 • Sialadenosis. Enlargement of the parotid and submandibular glands secondary to alcoholism. (Courtesy of D. George Blozis.)

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 longstanding 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, partial parotidectomy can be performed. Pilocarpine recently has been reported to be beneficial in the treatment of bulimic patients with sialadenosis.

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 playa 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.

f1istopathologic 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 in nature.

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,

NECROTIZING SIAIOMETAPLASIA

Necrotizing sialomctaplasia 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

It has been suggested that these factors may playa 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 (Figure It-30>. Within 2 to 3 weeks, necrotic tissue sloughs out, leaving a craterlike ulcer that can range from less than

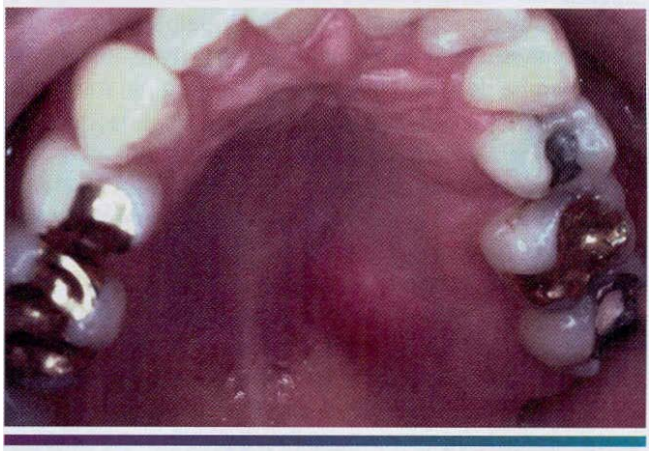

Figure 11-30 • Necrotizing sialometaplasia. Early lesion demonstrating swelling of the posterior lateral hard palate. (From Allen CM, Camisa C: Diseases of the mouth and lips. In Sams WM, Lynch P, editors: *Principles of dermatology.* New York, 1990, Churchill Livingstone.)

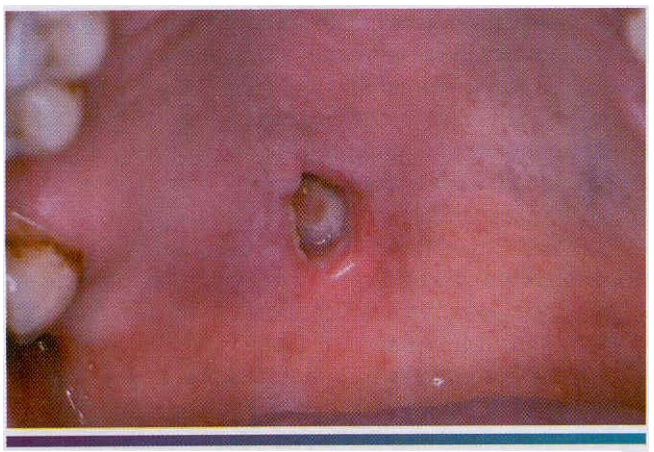

Figure 11-31 • Necrotizing sialometaplasia. Later-stage lesion showing crater-like defect of the posterior palate.

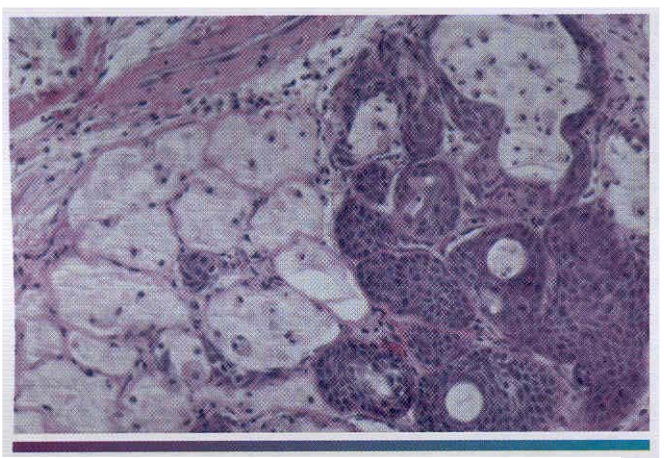

Figure 11-32 • Necrotizing sialometaplasia. Necrotic mucous acini *(left)* and adjacent ductal squamous metaplasia *(right)*.

I em to more than 5 ern in diameter (Figure 11-31). 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 sialorneta-plas!a is characterized by acinar necrosis in early lesions, followed by associated squamous metaplasia of the salivary ducts (Figure 11-32). Although the mucous acinar cells are necrotic, the overall lobular architecture of the involved glands is still preserved-a helpfui 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. This mistaken impression may be further compounded by the frequent association of pseudoepitheliomatous hyperplasia of the overlying epithelium. In most cases, however. the squamous proliferation has a bland cytologic appearance.

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 I 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 different salivary tumors have been identified and categorized. In addition. the classification scheme is a dynamic one that changes as clinicians [earn more about these lesions. Box 11-4 includes most of the currently recognized tumors. Some of the tumors on this iist are not specifically discussed because their rarity places them outside the scope of this book.

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 we try to compare them with more recent analyses. (For example, the polymorphous low-grade adenocarcinoma was first identified in 1983, but clinicians now recognize that it is one of the more common malignancies In the minor glands.) Notwithstanding these difficulties, it is stiii 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.

Box 11-4 *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
- Sialoblastoma

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
- 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
- Adenocarcinoma, not otherwise specified (NOS)

Tables 11-2 and 11-3 summarize four 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 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 64% 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, and two thirds to three quarters of these parotid tumors are benign.

Table 11-4 summarizes five large, well-known series of parotid neoplasms. The pleomorphic adenoma is overwhelmingly the most common tumor (53% to 77% of all cases in the parotid gland). Warthin tumors are also fairly common; they account for 6% to 14% of cases. A variety of malignant tumors occur, with the mucoepidermoid carcinoma appearing to be the most frequent overall. However, two studies from Great Britain show a significantly lower prevalence of this tumor, possibly indicative of a geographic difference, especially compared with reports of cases from the United States.

From 8% to 11% of all salivary tumors occur in the submandibular gland, but the frequency of malignancy in this gland is almost double that of the parotid gland, ranging from 37% to 45%. However, as shown in Table 11-5, the pleomorphic adenoma is still the most common tumor and makes up 44% to 68% 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 12% to 27% of all cases.

Tumors of the sublingual gland are rare, comprising no more than 1% of all salivary neoplasms. However, 70% to 90% of sublingual tumors are malignant.

Tumors of the various smaller minor salivary glands make up 9% to 23% of all tumors, which makes this group the second most common site for salivary neoplasia. Table 11-6 summarizes the findings of three large surveys of minor gland tumors. Unfortunately, a relatively high proportion (almost 50%) of these have been malignant in most studies. Excluding rare sublingual tumors, it can be stated that the smaller the gland, the greater 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. The mucoepidermoid carcinoma and adenoid cystic carcinoma generally have been considered the two most common malignancies, although the recently delineated polymorphous low-grade adenocarcinoma also is becoming recognized as one of the more common minor gland tumors.

The palate is the most frequent site for minor salivary gland tumors, with 42% to 54% of all cases found there (Table 11-7). Most of these occur on the posterior lateral hard or soft palate, which have the greatest concentration of glands. Table 11-8 shows the relative prevalence of various tumors on the palate. The lips are the second most

Table 11-2 *Sites of Occurrence of Primary Epitheliul Salivary Gland TItmors*

		SITE OF OCCURRENCE (%)			
Author (year)	*Number of cases*	*Parotid*	*Submandibular*	*Sublinglml*	*Minor*
Eveson and Cawson (1985)	2.410	73%	11%	0.3%	14%
Seifert et 01. (1986)	2.579	80%	10%	1.0%	9%
Spiro (1986)	2.807	70%	8%	(included with minorgland tumors)	22%
Ellis et 01. (1991)	13.749	64%	10%	0.3%	23%

Table 11-3 *Frequency of Malignancy for Salivary TIm/ors at Different Sites*

		PERCENTAGE OF CASES THAT ARE MALIGNANT			
Author (year)	*Number of cases*	*Parotid*	*Submandibular*	*Sublingual*	*Minor*
Eveson and Cawsan (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%

Table 11-4 ***Parotid n,mors***

	ELLIS ET AL. (United States, 1991)	EVESON & CAWSON (Great Britain. 1985)	THACKRAY & LUCAS (Great Britain, 1974)	ENEROTH (Sweden. 1971)	FOOTE & rRAZELL (United States, 1953)
Total number of cases	8222	1756	651	2158	764
Benign Tumors					
Pleomorphic adenoma	53.0%	63.3%	72.0%	76.8%	58.5%
Warthin tumor	7.7%	14.0%	9.0%	4.7%	6.5%
Oncocytoma	1.9%	0.9%	0.6%	1.0%	0.1%
Basal cell adenoma	1.4%				
Other benign tumors	3.7%	7.1% (includes all "other monomorphic adenomas")	1.8%		0.7%
Total	67.7%	85.3%	83.4%	82.5%	65.8%
Malignant n""ors					
Mucoepidermoid carcinoma	9.6%	1.5%	2.3%	4.1%	11.8%
Acinic cell adenocarcinoma	8.6%	2.5%	1.2%	3.1%	2.7%
Adenoid cystic carcinoma	2.0%	2.0%	3.3%	2.3%	2.1%
Malignant mixed tumor	2.5%	3.2%	4.1%	1.5%	6.0%
Squamous cellcarcinoma	2.1%	1.1%	1.0%	0.3%	3.4%
Other malignant tumors	7.5%	4.4%	4.7%	6.3%	8.1%
Total	32.3%	14.7%	16.6%	17.5%	34.2%

Table 11-5 *Submandibular Tl,tllors*

	ELLIS [T AL. (United States, 1991)	EVESON & CAWSON (Great Britain, 1985)	THACKRAY & LUCAS (Great Brttatn, 1974)	ENEROTH (Sweden, 1971)	FOOTE 8: FRAZELL (United States, 1953)
Total number of cases	1235	257	60	170	107
Benign Tl,mors					
Pleomorphic adeno ma	53.3%	59.5%	68.0%	60.0%	43.9%
Warthin tumor	1.3%	0.8%	1.7%	2.4%	0.0%
Oncocyto ma	1.5%	0.4%	0.0%	0.6%	0.0%
Basal cell adenoma	1.0%				
Other benign tumors	1.7%	1.9% (includes all "other monomorphic adenomas")	0.0%		0.0%
Total	58.8%	62.6%	69.7%	62.9%	43.9%
Malignant Tl,moTs					
Mucoepidermoid carcinoma	9.1%	1.6%	0.0%	3.5%	7.5%
Acinic cell adenocarcinoma	2.7%	0.4%	0.0%	0.6%	0.0%
Adenoid cystic carcinoma	11.7%	16.8%	17.0%	15.3%	15.9%
Malignant mixed tumor	3.5%	7.8%	1.7%	1.8%	10.3%
Squamouscell carcinoma	3.4%	1.9%	3.3%	7.1%	12.1%
Other malignant tumors	10.8%	8.9%	8.3%	8.8%	10.3%
Total	41.2%	37.4%	30.3%	37.1%	56.1%

Table 11-6 *Minor Salivary Gland TI'nlors*

	ELLIS ET AL. (1991)	WALDRON ET AL. (1988)	EVESON 8: CAWSO N (1985)
Total number of cases	3355	426	336
Benign Tumors			
Pleomorphic adenoma	38.1%	40.8%	42.6%
'Monomorphic" adenoma (canalicular and basal cell adenoma)	4.5%	10.8%	11.0%
Other benign tumors	8.8%	5.9%	
Total	51.3%	57.5%	53.6%
Malignant Tllmors			
Mucoepidermoid carcinoma	21.5%	15.3%	8.9%
Acinic cell adenocarcinoma	3.5%	3.5%	1.8%
Adenoid cystic carcinoma	7.7%	9.4%	13.1%
Malignant mixed tumor	1.7%	1.4%	7 1%
Polymorphous low-grade adenocarcinoma	2.2%	11.0%	
Other malignant tumors	12.1%	1.9%	15.2%
Total	48.7%	42.5%	46.4%

Table 11-7 *Location of Minor Salivary Gland TIllllOrs*

XUrUOU (YEAR)	NUMBER OF CASES	PALATE	LIPS	BUCCAL	RETRO,\IOLAR	FLOOR OF MOUTH	TONGUE	OTIIER
Eveson & Cawson (1985)	336	54%	21%	11%	1%		4%	8%
Waldron et al. (1988)	426	42%	22%	15%	5%	5%	1%	9%
Ellis et al. (1991)	3355	44%	21%	12%	2%	3%	5%	12%

Table 11-8 *Pillatill Salivury Gland TlmlOrs*

	ELLIS ET AL. (1991)	WALDRON ET AL (1988)	EVESON & CAWSON (1985)
Total number of cases	1478	181	183
Benign Tumors			
Pleomorphic adenoma	48.2%	51.9%	47.0%
Other benign tumors	5.0%	6.0%	6.0%
Total	53.2%	58.0%	53.0%
Malignant TlmlOfs			
Mucoepidermoid carcinoma	20.7%	9.9%	9.3%
Acinic cell adenocarcinoma	1.4%	1.7%	1.1%
Adenoid cystic carcinoma	8.3%	10.5%	15.3%
Malignant mixed tumor	2.4%	2.2%	8.2%
Polymorphous low-grade adenocarcinoma	3.0%	16.0%	
Other malignant tumors	11.0%	1.7%	13.1%
Total	46.8%	42.0%	47.0%

Table 11-9 *LOCI/IIOII of Labial Salivary Gland Tumors*

AUTHOR (YEAR)	NUI\IBER OF CASES	UPPER LIP	LOWER LIP
Eveson & Cawson (1985)	71	89%	11%
Waldron et al. (1988)	93	85%	15%
Neville et al. (1988)	103	84%	16%
Ellis et al. (1991)	536	77%	23%

Table 11-10 ***Intraoral** Minor **Salivary** Gland **TUIIIors:** Percentage Malignant **by Site***

AUTtIOR (YE,\R)	PALATE	UPPER LIP	LOWER LIP	BUCCAL	RETROMOLAR	fIOOR OF XiOuru	TONGUE
Evescn & 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%

common location for minor gland tumors (21% to 22% **of** cases), followed by the buccal mucosa (11% to 15% of cases). Labial tumors are significantly more common in the upper lip. which accounts for 77% to 89% of all lip tumors (Table 11-9). Although rnucoceles 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 11-10. 42% to 50% of tumors of the palate and **buccal mucosa sites are malignant. similar to the** overall prevalence of malignancy in all minor salivary gland sites combined. In the upper lip. however. only 14% 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, 50% to 86% are malignant (mostly mucoepi**dermoid carcinomas). Up to 91% of retromolar** tumors are malignant. also because of a predominance of mucoepi**dermoid carcinomas. Unfortunately. most tumors in** the floor of the mouth and tongue are also malignant.

PLEOMORPHIC ADENOMA (BENIGN MIXED TUMOR)

The pleomorphic adenoma, or benign mixed tumor. is easily the most common salivary neoplasm. It accounts for 53% to 77% of parotid tumors, 44% to 68% of submandibular tumors. and 38% to 43% of minor gland **tumors.**

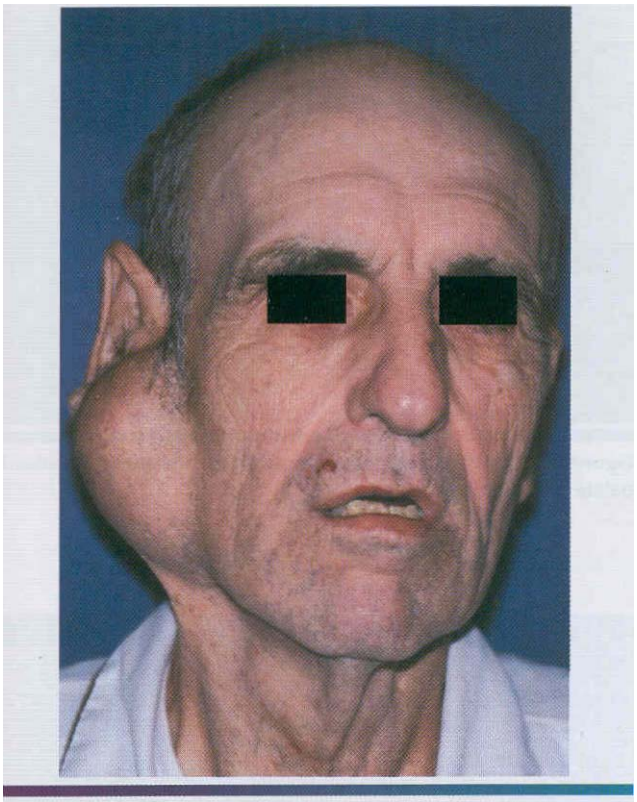

Figure 11-33 • Pleomorphic adenoma. Slowly growing tumor of the parotid gland.

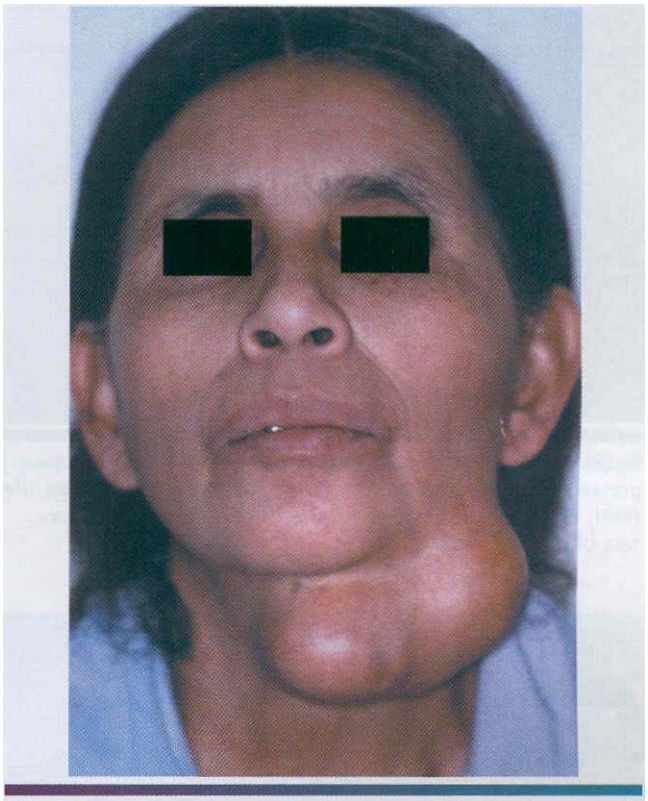

Figure 11-34 • Pleomorphic adenoma. Tumor of the submandibular gland. (Courtesy of Dr. Román Carlos.)

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.

Clinical and Radiographic Features

Regardless of the site of origin, the pleomorphic adenoma typically appears as a painless, slowly growing, firm mass (Figures 11-33 and 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 adults between the ages of 30 and 50. 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, 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 (Figure 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.

The palate is the most common site for minor gland mixed tumors, accounting for approximately 60% of intraoral examples. This is followed by the upper lip (20%) and buccal mucosa (10%). Palatal tumors almost always are found on the posterior lateral aspect of the palate, presenting as smooth-surfaced, dome-shaped masses (Figures 11-36 and 11-37). If the tumor is traumatized, 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 (Figure 11-38). However, the capsule may be incomplete or show infiltration by tumor cells. This lack of complete encapsulation is more

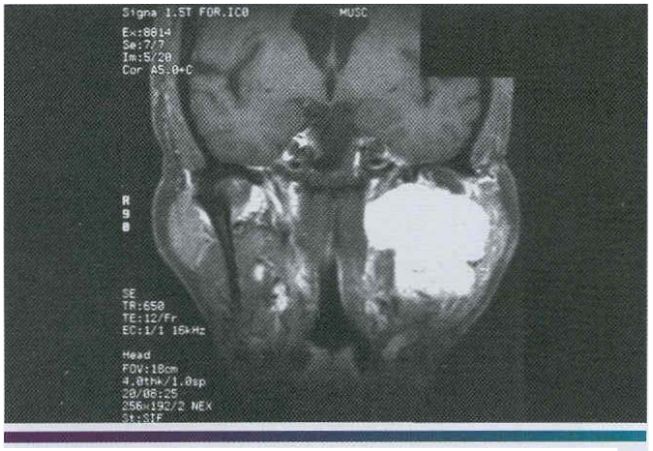

Figure 11-35 • Pleomorphic adenoma. T1-weighted, fat-suppressed, contrast-enhanced coronal magnetic resonance image (MRI) of a tumor of the deep lobe of the parotid gland. (Courtesy of Dr. Joel Cure.]

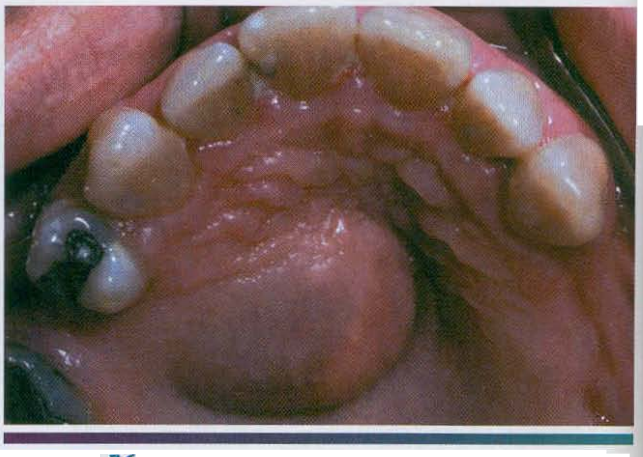

Figure 11-36 • Pleomorphic adenoma. Firm mass of the hard palate lateral to the midline.

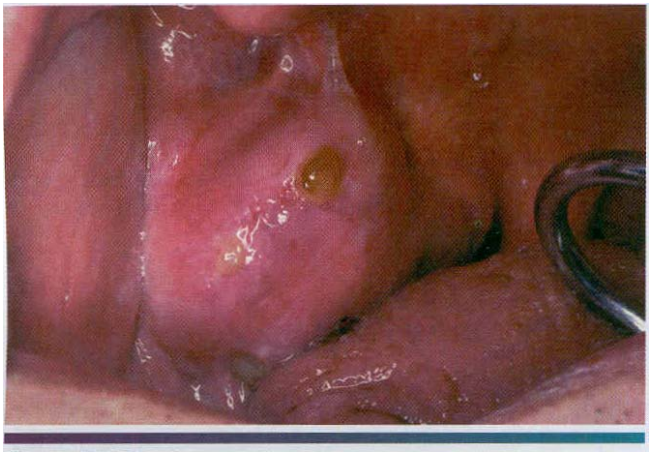

Figure 11-37 . Pleomorphic adenoma. Tumor of the pterygomandibular area.

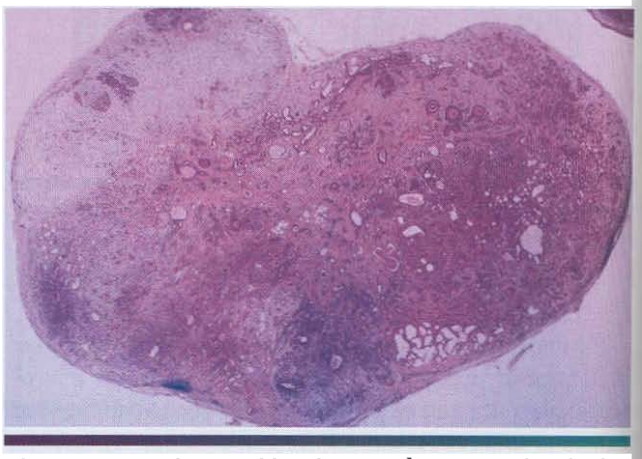

Figure 11-38 • Pleomorphic adenoma. low-power view showing a well-circumscribed, encapsulated tumor mass. Even at this power, the variable microscopic pattern of the tumor is evident.

common for minor gland tumors, especially along the superficial aspect of palatal tumors beneath the epithelial surface.

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 (Figure 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 (Figure 11-40). Vacuolar degeneration of cells in these areas can produce a chondroid appearance (Figure 11-41). In many tumors, the stroma exhibits areas of an eosinophilic, hyalinized change (Figure 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

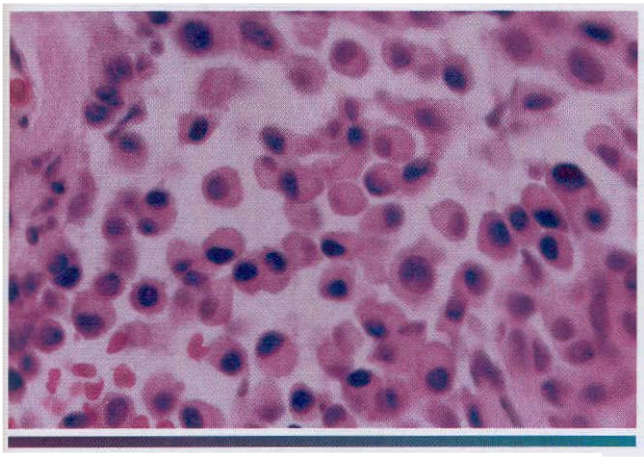

Figure 11-39 • Pleomorphic adenoma. Plasmacytoid myoepithelial cells.

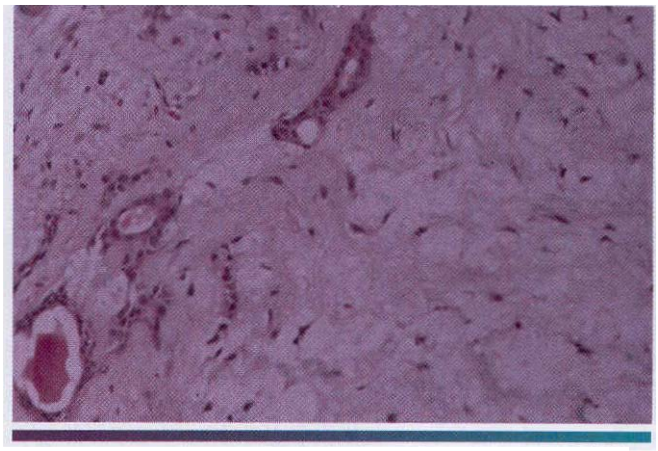

Figure 11-40 • Pleomorphic adenoma. Ductal structures *(left)* with associated myxomatous background *(right)*.

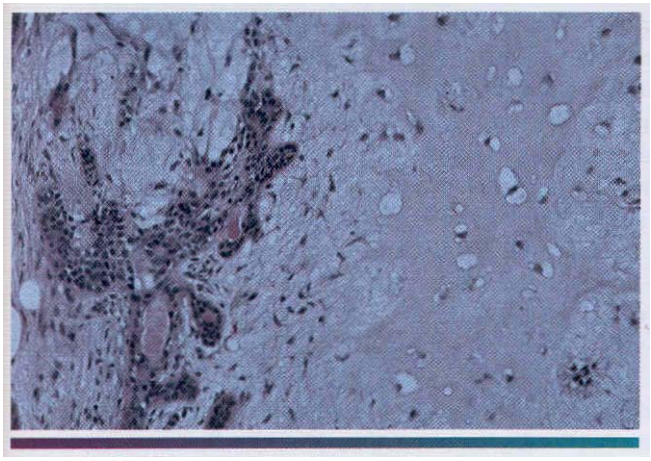

Figure 11-41 • Pleomorphic adenoma. Chondroid material *(right)* with adjacent ductal epithelium and myoepithelial cells.

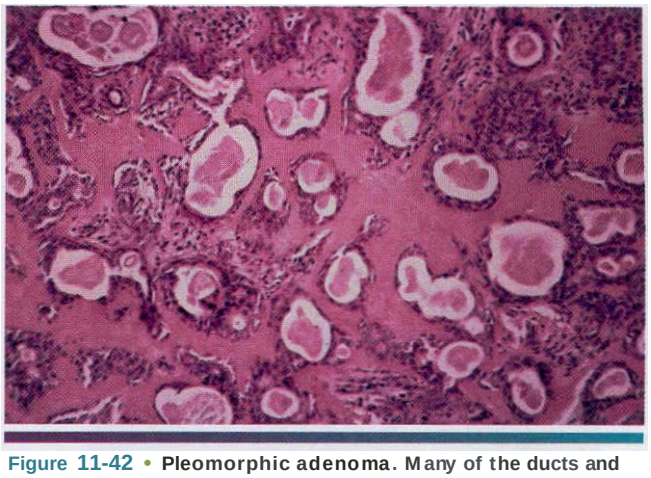

Figure 11-42 • Pleomorphic adenoma. Many of the ducts and myoepithelial cells are surrounded by a hyallnized, eosinophilic background alteration.

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 enucleation of parotid tumors often results in recurrence, with management of these cases made difficult as a result of multlfocal seeding of the primary tumor bed. In such cases, multiple recurrences are not** unusual. Malignant degeneration is a potential complication, resulting in a carcinoma ex pleomorphic adenoma (see page 424). The risk of malignant transformation is probably small. but it may occur in as many as 5% of all cases.

ONCOCYTOMA (OXYPHILIC ADENOMA)

The oncocytoma is a benign salivary gland tumor composed of large epithelial cells known as oncocytes. It is a rare neoplasm, representing approximately 1% of all salivary tumors.

Clinical Features

The oncocytoma is predominantly a tumor of older adults, with a peak prevalence in the eighth decade of life. A slight female predilection has been observed but may not be significant. 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 multinodular oncocytic hyperplasia (oncocytosis).

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 (Figure 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.

The granularity of the cells is created by 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 other clear cell salivary gland tumors that have a low-grade malignant potential.

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.

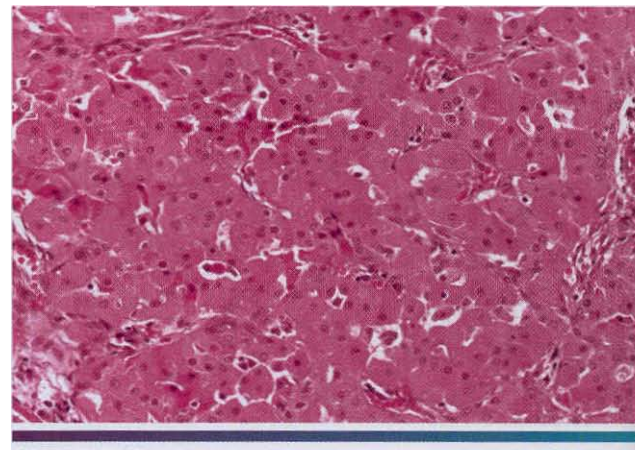

figure 11-43 • Oncocytoma. Sheet of large, eosinophilic oncocytes.

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 (NODULAR 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 a common finding in the salivary glands. Focal oncocytic metaplasia also may be a feature of other salivary gland tumors. Oncocytosis refers to both the proliferation and 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. 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 granuiar, eosinophilic cytoplasm as a result of the proliferation of mitochondria. On occasion, these cells may have a clear cytoplasm from the accumulation of glycogen (Figure 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.

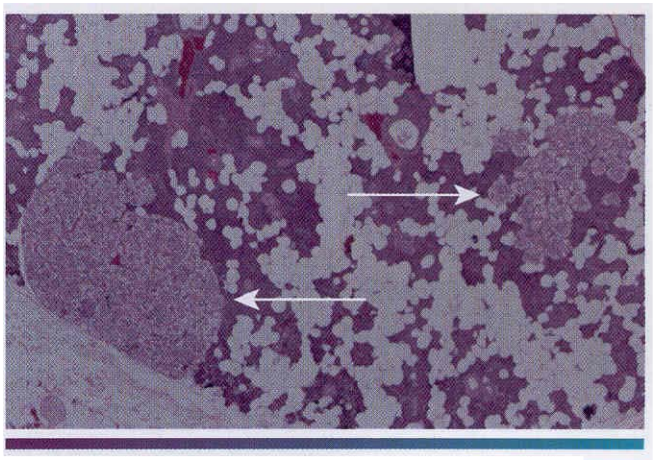

Figure 11-44 • Oncocytosis. Multifocal collections of dear oncocytes *(arrows)* in the parotid gland.

WARTHIN TUMOR (PAPILLARY CYSTADENOMA LYMPHOMATOSUM)

Warth!" 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 14% of all parotid neoplasms. The nameadenolymphoma 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.

The pathogenesis of these tumors is uncertain. The traditional hypothesis suggests that they arise from heterotopic salivary gland tissue found within parotid lymph nodes. However, it also has been suggested that these tumors may develop from a proliferation of salivary gland ductal epithelium that is associated with secondary formation of lymphoid tissue. Several recent papers have supported this latter theory, including studies that have found cytogenetic abnormalities in the epithelial component. 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. Epstein-Barr virus also has been implicated in the pathogenesis of Warthin tumor.

Clinical Features

The Warthin tumor usually appears as a slowly growing, painless, nodular mass of the parotid gland (Figure 11-45). It may be firm orfluctuant 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 14% of cases. Most

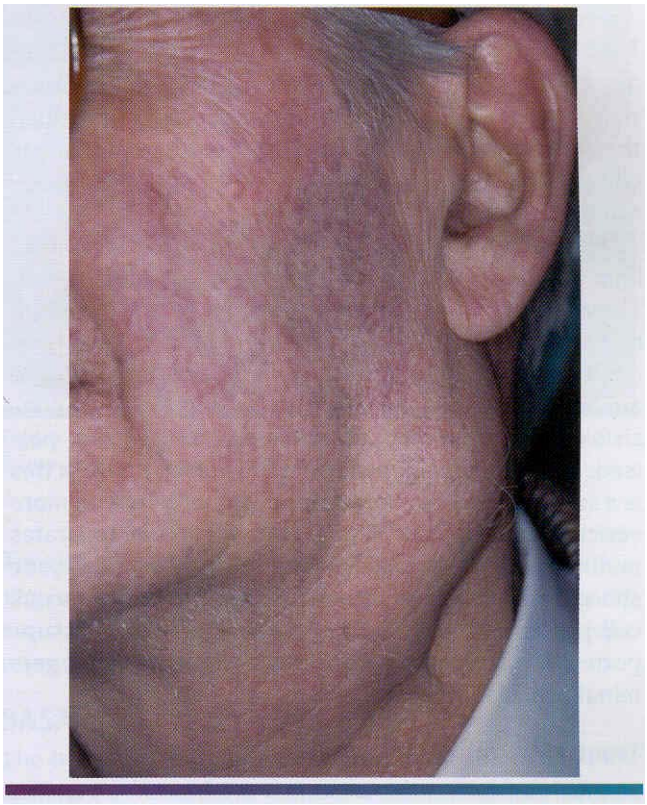

Figure 11-45 • Warthin tumor. Mass in the tail of the parotid gland. (Courtesy of Dr. George Blozis.)

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 salivary duct cyst with oncocytic ductal metaplasia.

Warthin tumor most often occurs in older adults, with a peak prevalence in the sixth and seventh decades of life. The observed frequency of this tumor is much lower in blacks than in whites. Most studies show a decided male predilection. with some early studies demonstrating a male-to-female ratio up to 10 to 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 the increased prevalence of smoking in females 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 might 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 (Figures 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 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 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. A 6% to 12% recurrence rate has been reported. 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.

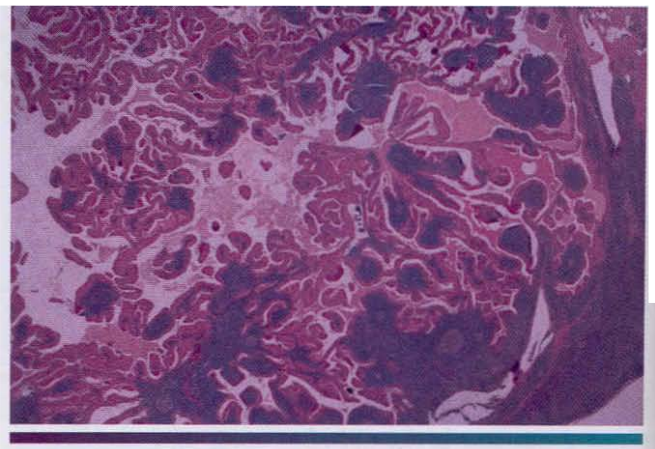

Figure 11-46 • Warthin tumor. low-power view showing a papillary cystic tumor with a lymphoid stroma.

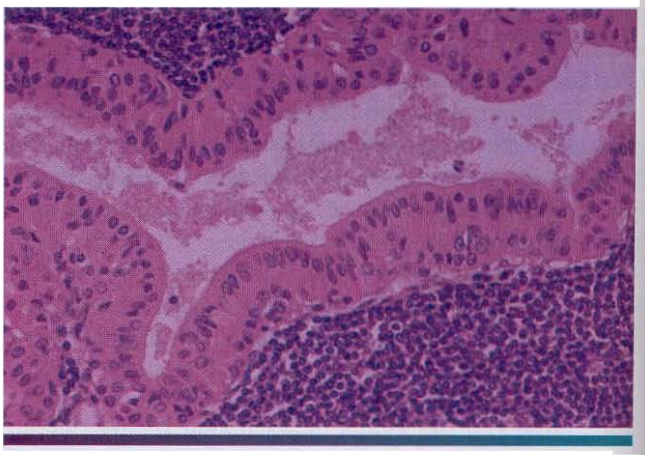

Figure 11-47 • Warthin tumor. High-power view of epithelial lining showing double row of oncocytes with adjacent lymphoid stroma.

MONOMORPHIC ADENOMA

The term monomorphic adenoma was originally 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 iorthe 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 a peak prevalence in the seventh decade of life. There is a definite female predominance, ranging from 1.2 to i.8 females for each male.

The canalicular adenoma appears as a slowly growing, painless mass that usually ranges from several millimeters to 2 em (Figure li-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.

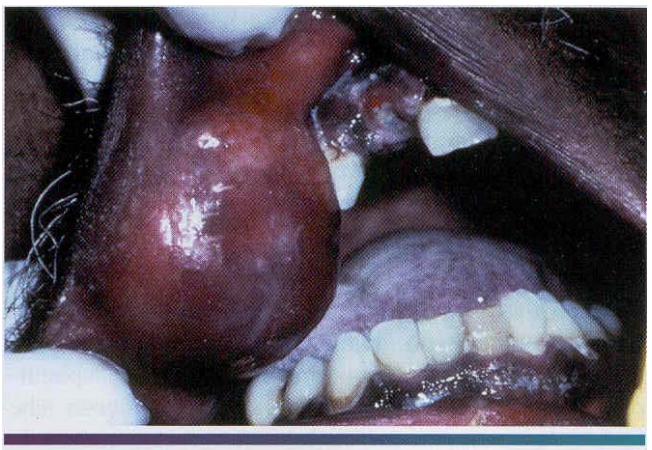

Figure 11-48 • Canalicular adenoma. Mass in the upper lip. (Courtesy of Dr. John Fantasia.)

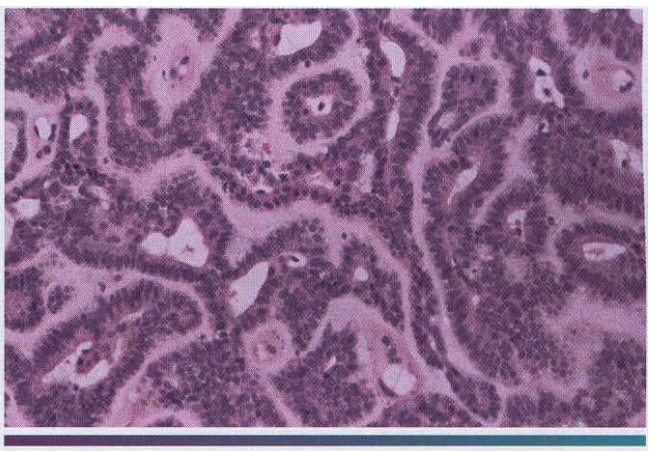

Figure 11-49 • Canalicular adenoma. Uniform columnar cells forming canal-like ductal structures.

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 (Figure 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 epitheliu m may demonstrate papillary projections into the cystic lumina. The tumor cells arc 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 incipient foci of additional tumors sometimes are observed in the surrounding salivary gland tissue.

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 I% to 2% 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. Also. 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 epithe-

lium 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 can be noted that 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 a peak prevalence in the seventh decade of life. The tumor appears to be more common in females. with some studies showing as high as a 2:I 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 em in diameter. Parotid tumors usually are located within the superlicial 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 hyperchromalic; 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 (Figure II-50). The tubular subtype is characterized by the formatlon of small, round, ductllke structures. Frequently, a mixture of histopathologic subtypes is seen.

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 materiai, 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% 10 37% recurrence rate, possibly related to its multtfocal 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 PAPILUFERUM; 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 316) of the oral mucosa will arise at the site where a minor salivary gland duel merges with the surface epithelium. Because of this location, such squamous papillomas also contain scattered mucous cells within the exophytic papillary growth, and these lesions have sometimes been called "ductal

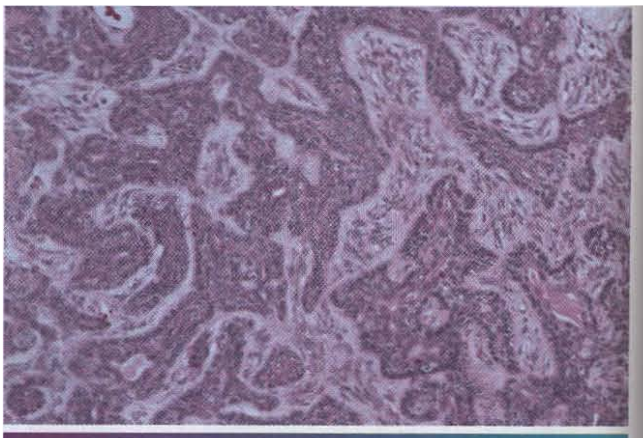

Figure 11-50. Basal cell adenoma. Parotid tumor showing cords of basaloid cells arranged in a trabecular pattern.

papillomas." However, it should be emphasized that these lesions are viral (human papillomavirus [HPV]) 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 male-to-female ratio. The tumor appears as an exophytic, papillary surface growth that is clinically similar to the common squamous papilloma.

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 submucosal nodule, which sometimes may show a pit or indentation in the overlying surface mucosa.

Histopathologic Features

At low power, 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 (Figure 11-51). 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 (Figure 11-52). These ductal cells often have an oncocytic appearance. An inflammatory infiltrate of plasma cells, lymphocytes, 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 (Figure 11-53).

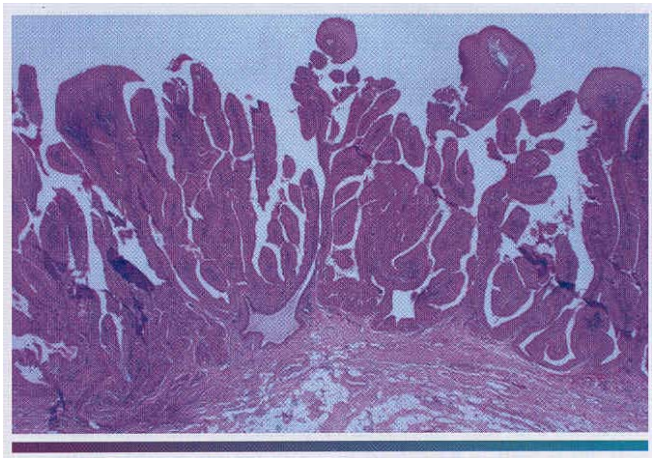

Figure 11-51 • Sialadenoma **papilliferum. Low-power view showing a papillary surface tumor with associated ductal structures in the** superficial lamina **propria.**

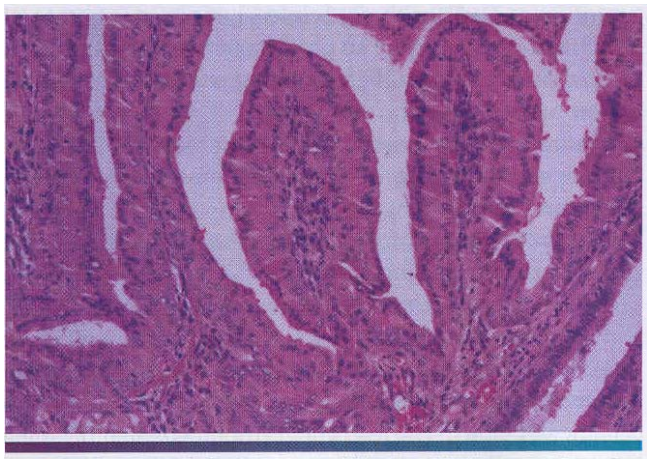

Figure 11-52 • **Sialadenoma papilliferum. High-power view of cystic areas lined by papillary, oncocytic epithelium.**

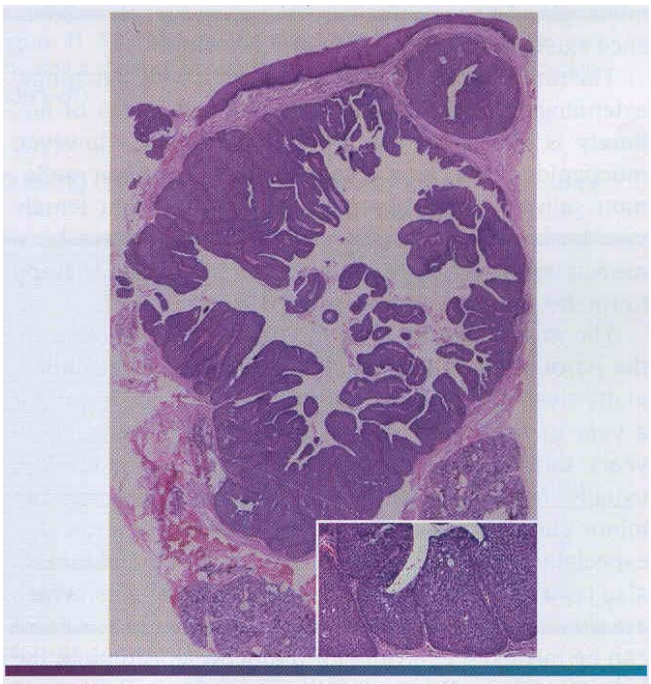

Figure 11-53 • **Inverted ductal papilla. Papillary intraductal proliferation located beneath the mucosal surface. Higher-power view shows both squamous cells and mucous cells *(inset).* (Courtesy of Dr. Dean K. White.)**

This epithelium may be contiguous with the overlying mucosal epithelium, communicating with the surface through a small pcrelike 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.

Treatment and Prognosis

All three forms of ductal papilloma are best treated by conservative surgical excision. Recurrence is rare.

MUCOEPIDERMOID CARCINOMA

The mucoepidermoid carcinoma is one of the most common salivary gland malignancies. Because of its highly variable biologic 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, it was later recognized that even low-grade tumors occasionally could exhibit malignant behavior; therefore. the term mucoepidermoid carcinoma is the preferred designation.

Clinical Features

Most studies show that the mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm. in the United States, it makes up 10% of all major gland tumors and 15% to 2\% of minor gland tumors. However, British studies have shown a much lower relative frequency, with mucoepidermoid carcinoma accounting for only I% to 2% of major gland neoplasms and 9% of minor gland tumors. Perhaps a true geographic difference exists in the prevalence of this lesion.

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. A slight female predilection has been noted. Some tumors have been associated with a previous history of radiation therapy to the head and neck region.

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 a 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 (Figure II-54). 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

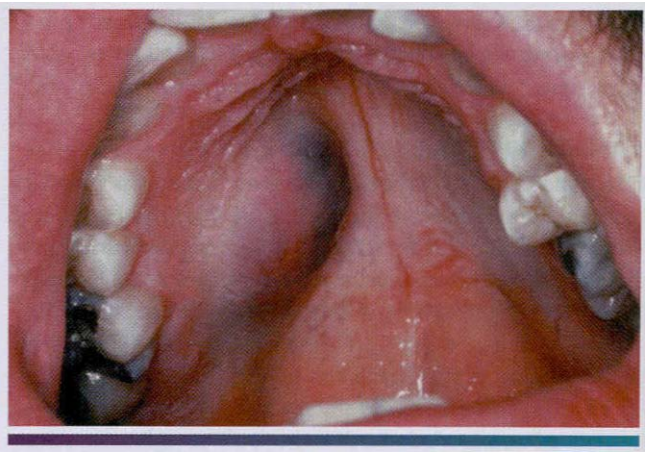

figure 11-54 • Mucoepidermoid carcinoma. Blue-pigmented mass of the posterior lateral hard palate. (Courtesy of Dr. James F. Drummond.)

areas are uncommon locations for salivary gland neoplasia. the mucoepidermoid carcinoma is the most common salivary tumor in each of these sites (Figure I1-551. Intraosseous tumors (discussed next) also may develop in the jaws.

Histopathologic Features

As its name implies. the mucoepidermoid carcinoma is composed of a mixture of mucus-producing cells and squamous (epidermoid) cells (Figures II-56 to u-ss). 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 is typically present-the intermediate cell. This cell is basaloid in appearance and is believed to be a progenitor of the mucous and epidermoid cells. Some tumors also show variable numbers of clear cells. which sometimes can predominate the microscopic picture (Figure II-59). 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.

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

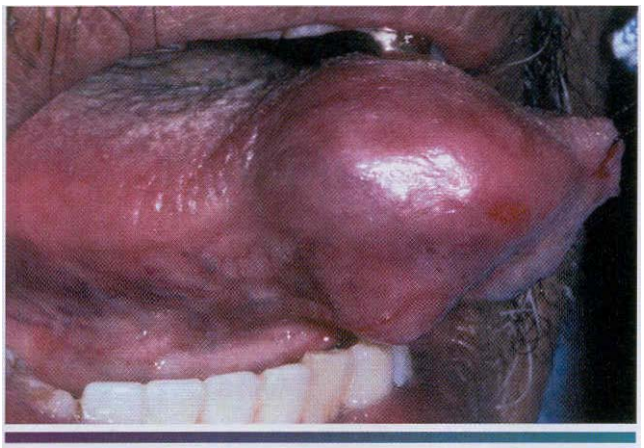

Figure 11-55 • **Mucoepidermoid carcinoma.** Mass of the tongue.

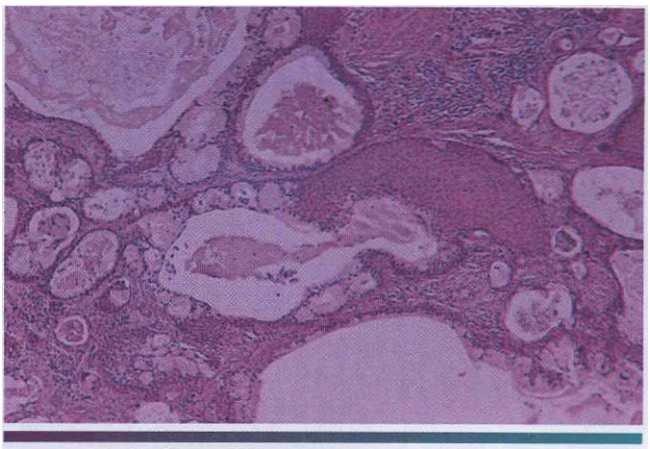

Figure 11-56. **Mucoepidermoid carcinoma.** Low-power view of a moderately well-differentiated tumor showing ductal and cystic spaces surrounded by mucous and squamous cells.

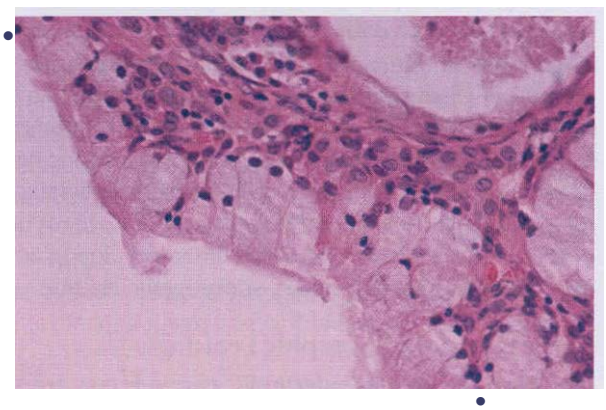

Figure 11-57 • **Mucoepidermoid carcinoma.** This low-grade tumor shows numerous large mucous cells surrounding a cystic space.

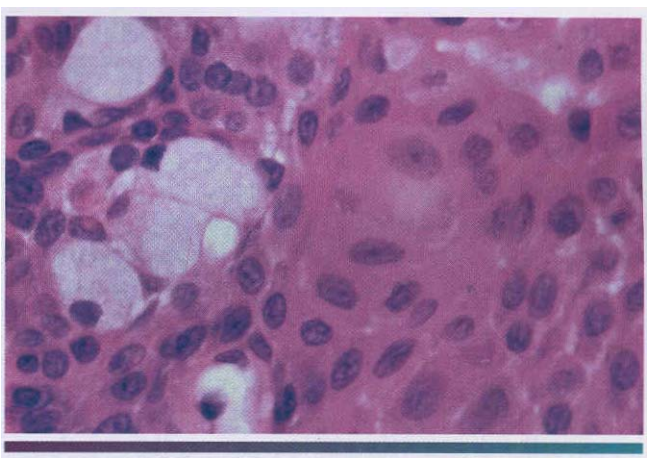

Figure 11-58 • **Mucoepidermoid carcinoma.** High-power view showing a sheet of squamous cells with focal mucus-producing cells *(left)*.

demonstrate considerable pleomorphism and mitotic activity. 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 experts have found that the relative proportion of the three different cell types does not correlate with prognosis. Instead, they have identified five significant microscopic parameters, to which relative point values have been assigned to determine the grade of the tumor (Table 11-11).

Table 11-11 *Mucoepidermoid Carcinoma: Grading Parameters and Point values*

PARAMETER	POINT VALUE
Intracystic component < 20%	+2
Neural invasion present	+2
Necrosis present	+3
Four or more mitoses per 10 HPF	+3
Anaplasia present	+4
GRADE	**TOTAL POINT SCORE**
Low	0-4
Intermediate	5-6
High	7-14

HPF. High power fields.

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.

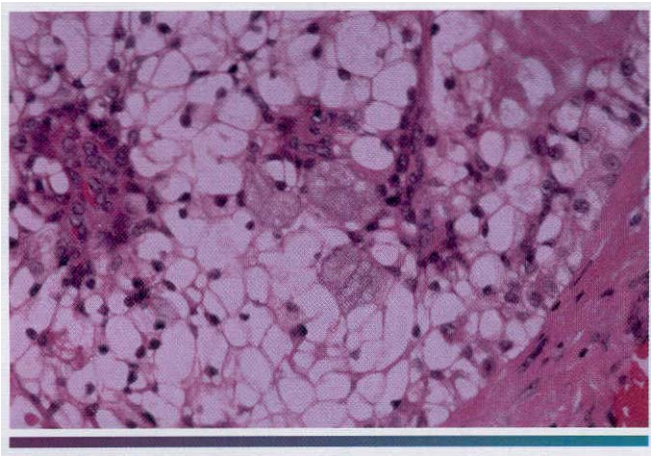

Figure 11-59. Mucoepidermoid carcinoma. Clear cell mucoepidermoid carcinoma.

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 giand, with sacrifice of the facial nerve, Submandibular gland turners are treated by total removal of the gland, Mucoepidermoid carcinomas of the minor glands usually are treated by **assured surgical** cxclslon. **For low-grade neoplasms.** only a modest margin of surrounding normal tissue may need to be removed, but high-grade or large tumors war**rant wider resection, similar to that required for squa**mous cell carcinomas. **If** there is underlying bone **destruction, the involved bone must be excised.**

Radical 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 95% 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 guarded. with only 30% to 54% of **patients surviving.**

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 mucoepi-dermoid 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,** 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 and, there**fore. this seems an unlikely source for most intrabony sali**vary 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 590). in addition, many intra**osseous mucoepidermoid carcinomas develop in** association with impacted teeth or odontogenic cysts.

Clinical and Radiographic Features

tntraosseous **mucoepidermoid carcinomas are most** common in middle-aged adults and demonstrate a slight **female predilection. They are three times 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.

Radiographs usually reveal either a unilocular or multilocular radiolucency with well-defined borders (Figure 11-601. However, some examples are characterized bya 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.**

Ilistopathologic Features

The microscopic appearance of intraosseous rnucoepi**dermoid carcinoma is similar to that of its soft tissue counterpart. Most tumors arc 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;**

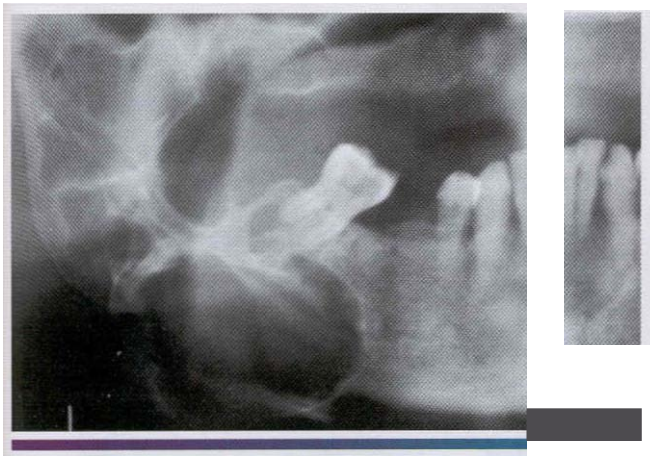

Figure 11-60 • Intraosseous mucoepidermoid carcinoma. Multilocular lesion of the posterior mandible. (Courtesy of Dr. Joseph F. Finelli.)

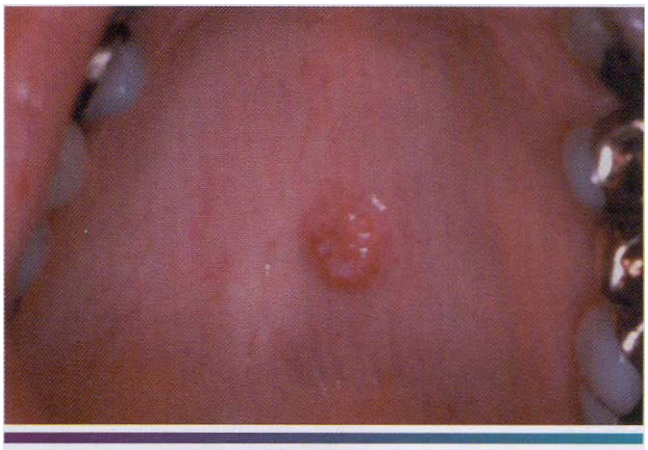

Figure 11-61 • Acinic cell adenocarcinoma. Small, nodular mass of the hard palate. (Courtesy of Dr. Rick Canaan.)

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 CEII ADENOCARCINOMA

The acinic cell adenocarcinoma 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 adenocarcinoma should be considered a low-grade malignancy.

Clinical Features

Around 85% of all acinic cell adenocarcinomas occur in the parotid gland. a logical finding because this is the largest gland and one that is composed entirely of serous elements. Most surveys have shown that this neoplasm makes up 1% 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 4% of these tumors. About 9% of all acinic cell adenocarcinomas develop in the oral minor salivary glands, with the buccal mucosa, lips. and palate being the most common sites (Figure 11-61). Overall, around 2% to 6.5% of all minor salivary gland tumors are acinic cell adenocarcinomas.

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. Approximately 60% of cases occur in women. The tumor usually appears as a slowly growing mass. and the lesion often is appears for many months or years before a diagnosis is made. The tumor may be otherwise asymptomatic, although associated pain or tenderness sometimes are reported. Facial nerve paralysis is an infrequent but ominous sign for parotid tumors.

Histopathologic Features

Acinic cell adenocarcinomas 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.

Several growth patterns may be seen. The solid variety consists of numerous well-differentiated acinar cells arranged in a pattern that resembles normal parotid gland tissue (Figures 11-62 and 11-63). 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

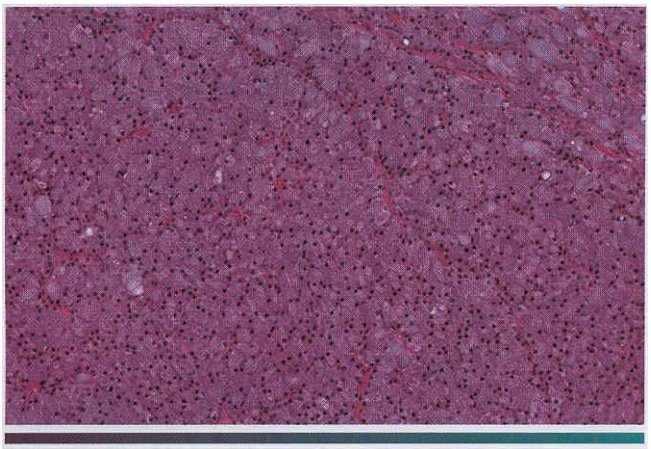

Figure 11-62 • Acinic cell adenocarcinoma. Parotid tumor demonstrating sheet of granular, basophilic serous acinar cells.

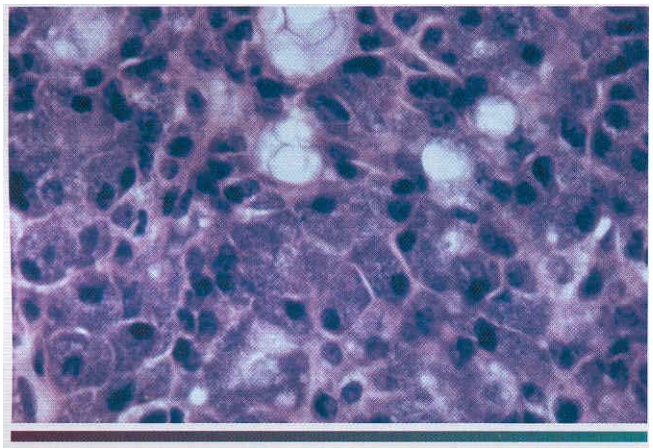

Figure 11-63 • Acinic cell adenocarcinoma. High-power view of serous cells with basophilic, granular cytoplasm.

(Figure 11-64). The follicular variety has an appearance similar to that of thyroid tissue. A lymphoid infiltrate is not unusual, sometimes with germinal center formation.

Treatment and Prognosis

Acinic cell adenocarcinomas 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 indicated unless there is clinical evidence of metastatic disease. Adjunctive radiation therapy may be considered for uncontrolled local disease.

The acinic cell adenocarcinoma is associated with one of the better prognoses of any of the malignant salivary

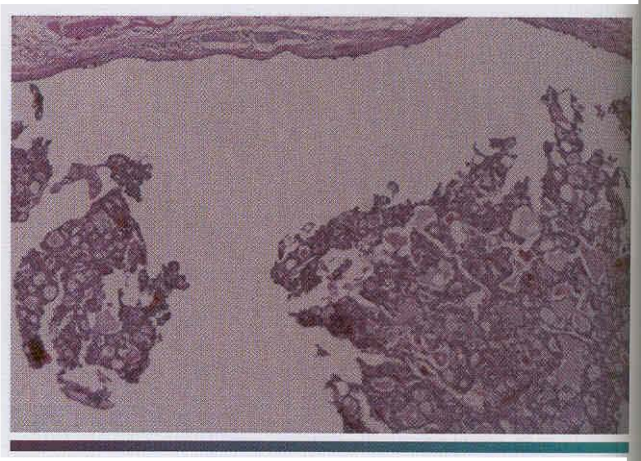

Figure 11-64 • Acinic cell adenocarcinoma. Papillary-cystic variant showing proliferation of tumor cells into a large cystic space.

gland tumors. Approximately one third of patients have recurrences locally, and metastases develop in 10% to 15% of patients. From 6% to 26% of patients die of their disease. The prognosis for minor gland tumors is better than that for tumors arising in the major glands.

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 6% 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

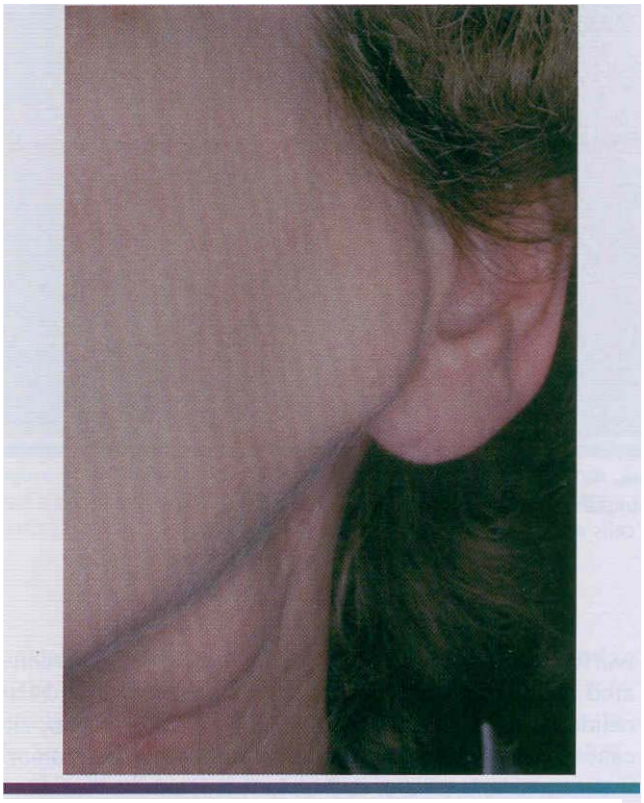

Figure 11·65 • Carcinoma ex pleomorphic adenoma. Mass of the parotid gland.

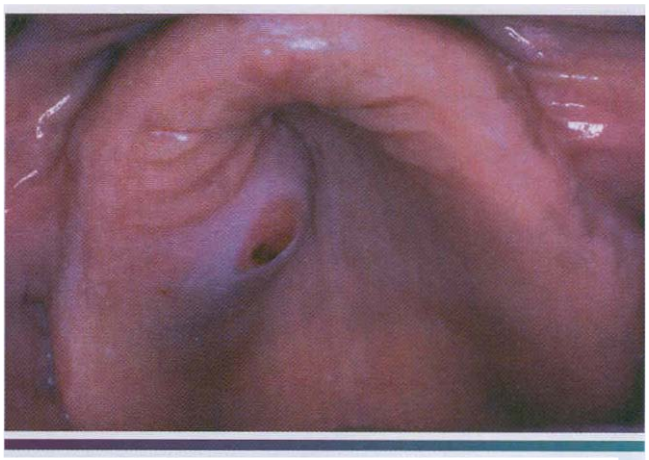

Figure 11·66 • Carcinoma ex pleomorphic adenoma. Painful, ulcerated mass of the palate.

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 t5 years older than that for the benign pleomorphic adenoma. It is most common in middle-aged and older adults. with a 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. How**ever, some tumors may have a short duration. The histo**pathologic 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.

Over 80% of cases of carcinoma ex pleomorphic adenoma are seen within the major glands, primarily the parotid gland (Figure 11-65). Nearly two thirds of minor salivary gland cases occur on the palate (Figure tJ-66). There is a slight female predilection. 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.

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 car**cinoma 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 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. Within the tumor are areas of malignant degeneration of the epithelial component. characterized by cellular pleomorphism and abnormal mitotic activity (Figure t1-67). This change is most often in the form of a poorly differentiated adenocarcinoma, but other patterns also can develop. including polymorphous low-grade adenocarcinoma, **mucoepidermoid carcinoma, and adenoid** cystic **carci**noma. The malignant component often has an aggressive growth pattern. with capsular invasion and infiltra-

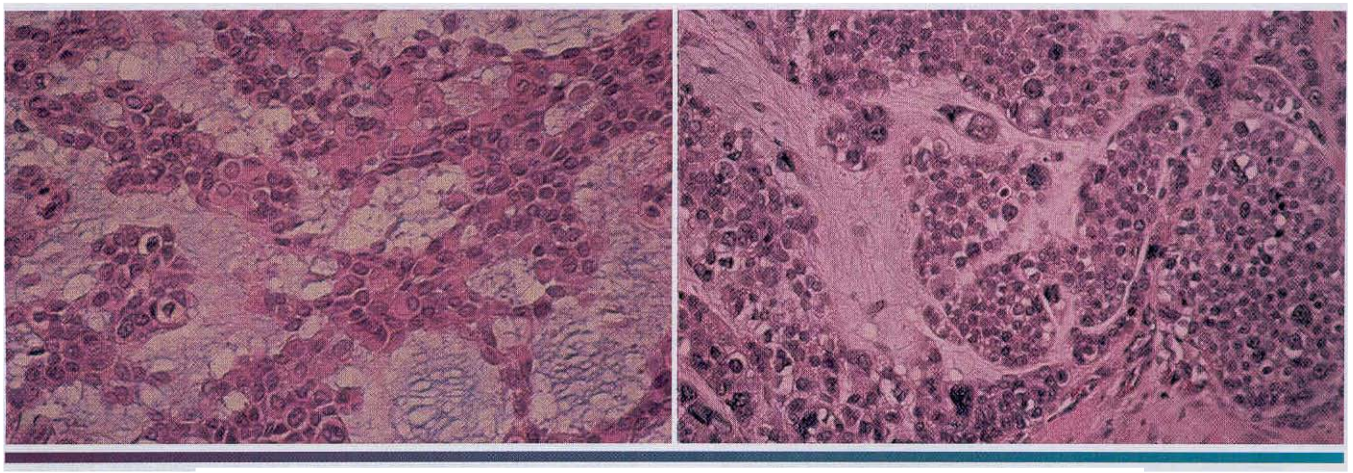

Figure 11-67 • Carcinoma ex pleomorphic adenoma. A. Medium-power view of the benign portion of the tumor showing sheets of plasmacytoid myoepithelial cells within a myxoid background. B, Malignant portion of the tumor showing epithelial cells with pleomorphic nuclei.

tion into surrounding tissues. However, in rare instances it is discovered as a small focus within the center of an encapsulated mixed tumor. Because such tumors have a markedly better prognosis than invasive tumors, they have been designated as noninvasive carcinoma ex mixed tumor or carcinoma *in situ* ex mixed tumor.

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, 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 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 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. In contrast, 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. However, for cases of *in situ* (noninvasive) carcinoma ex mixed tumor, the prognosis is similar to that for benign mixed tumor.

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 suffering from 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 metastatic sites. A mortality rate of 22% 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 used sometimes as a synonym for this neoplasm. However, use of the term cylindroma probably should be avoided today because the 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 50% develop within the minor salivary glands. The palate is the most common site for minor gland tumors (Figure 11-68). 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

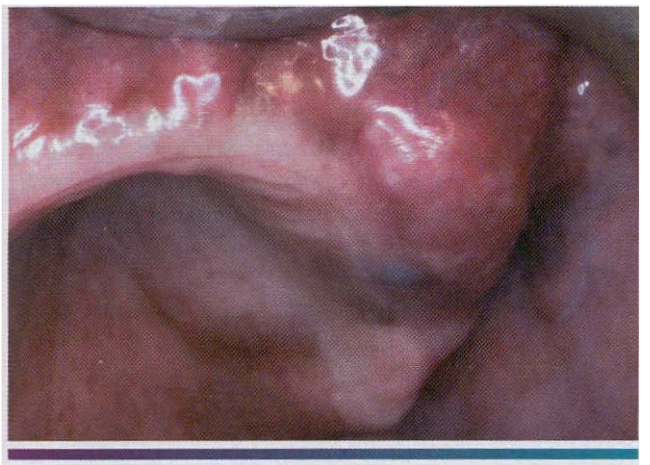

Figure 11-68 • Adenoid cystic carcinoma. Painful mass of the hard palate and maxillary alveolar ridge. (Courtesy of Dr. George Blozis.)

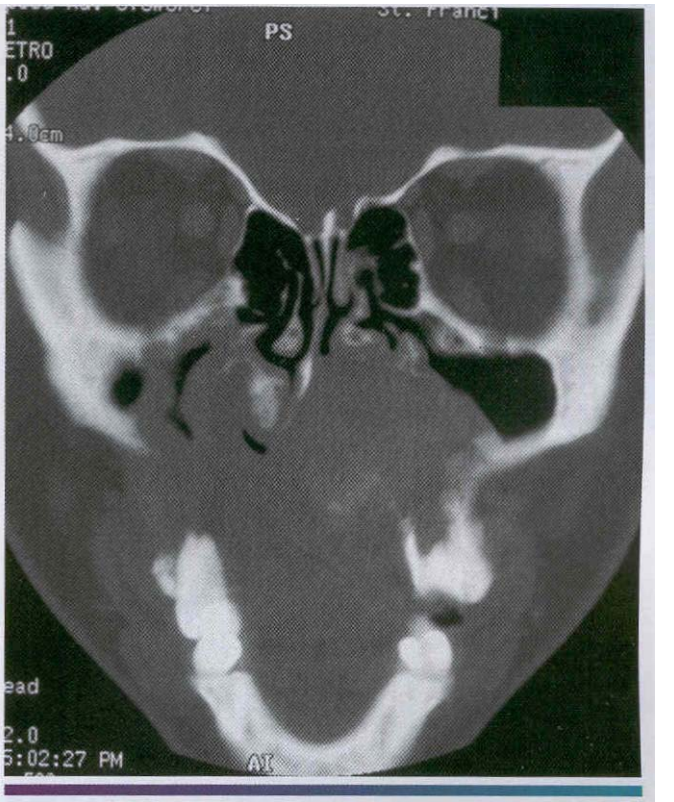

Figure 11-69 • Adenoid cystic carcinoma. Computed tomography scan of this massive palatal tumor shows extensive destruction of the hard palate with extension of the tumor into the nasal cavity and both maxillary sinuses. (Courtesy of Dr. Kevin Riker.)

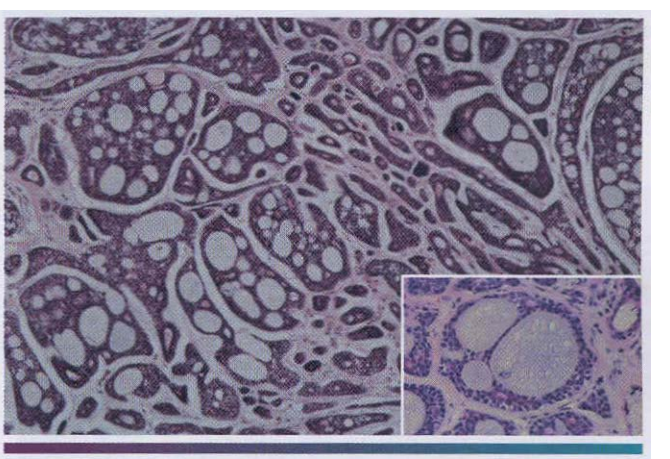

Figure 11-70 • Adenoid cystic carcinoma. Islands of hyperchromatic cells forming cribriform and tubular structures. Inset shows a high-power view of a small cribriform island.

striking difference can be seen among the various glands. In the parotid gland, the adenoid cystic carcinoma is relatively rare, constituting only 2% to 3% *at* all tumors. In the submandibular gland, this tumor accounts for 12% 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. There is a fairly equal sex distribution, although some studies have shown a slight female predilection.

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 may show radiographic evidence of bone destruction (Figure 11-69).

Histopathologic Features

The adenoid cystic carcinoma is composed of a mixture of myoepithelial cells and ductal cells that can have a varied arrangement (Figure 11-70). Three major patterns are recognized; (1) cribriform, (2) tubular, and (3) solid. Usually a combination *at* 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 cylindric, 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 (Figure 11-71), or small strands of tumor are found embedded

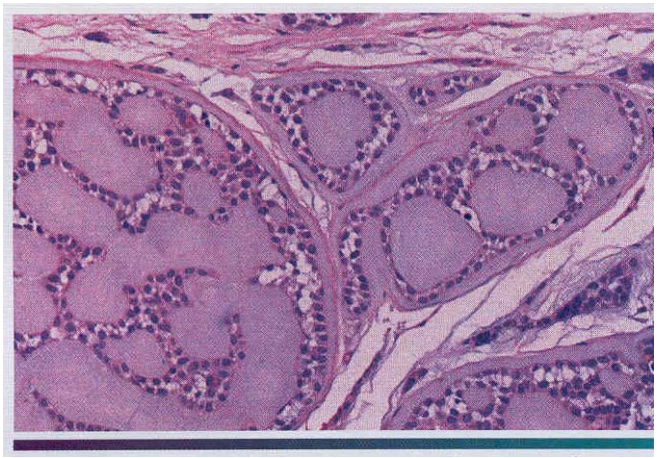

Figure 11-71 • Adenoid cystic carcinoma. The tumor cells are surrounded by hyalinized material.

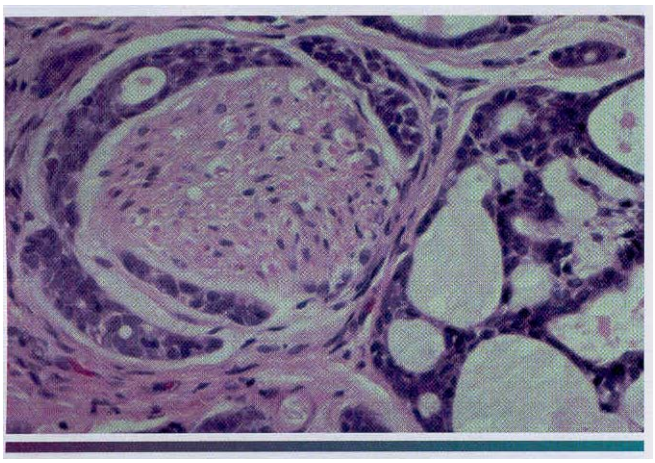

Figure 11-72 • Adenoid cystic carcinoma. Perineural invasion.

within this hyaiinized "stroma." The tumor ceils are smail and cuboidal. exhibiting deeply basophilic nuclei and little cytoplasm. These ceils are fairly uniform in **appearance, and mitotic activity is rarely seen.**

In the tubular pattern, the tumor ceils are similar but occur as multiple smail ducts or tubules within a hyalinlzed stroma. The tubular lumina can be lined by one to several layers of cells, 'and sometimes both a layer of ductal ceils and myoepitheiial ceils can be discerned.

The solid variant consists of larger islands or sheets of tumor ceils that demonstrate little tendency toward duct or cyst formation. Unlike the cribriform and tubular patterns, ceilular pieomorphism 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** (Figure 11-72), which probably corresponds to the common clinical finding of pain in these patients. Sometimes the ceils appear to *have* a swirling arrangement around **nerve bundles. However, perineural invasion is not pathognomonic for adenoid cystic carcinoma; italso may** be seen in other *salivary* malignancies. especiaily polymorphous low-grade adenocarcinomas.

Treatment and Prognosis

Adenoid cystic **carcinoma is a relentless tumor that is prone to local recurrence and eventual distant metas**tasis. Surgical excision is usually the treatment of choice, and adjunct radiation therapy may slightly *improve* **patient survival in some cases. Because metastasis to** regional lymph nodes is uncommon, radical neck dissection typically is not indicated. Because of the poor **overall prognosis, regardless of treatment, clinicians** shouid be cautioned against needlessly aggressive and mutilating surgical procedures for large tumors or cases already showing metastases.

Because the tumor is prone to late recurrence and metastasis, the S-year *survival* rate has little significance **and does not equate to a cure. The 5-year survival rate** may be as high as 70%. but this rate continues to decrease over time. By 20 years, only 20% 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 maxil**lary sinus and submandibular gland. Most studies *have* **shown that microscopic identification of perineural inva**sion has little effect on the prognosis.

Death usually results from local recurrence or distant metastases. Tumors of the palate or rnaxllary sinus eventualiy may *invade* upward to the base of the brain. Metastatic spread most commonly occurs to the lungs **and bones.**

POLYMORPHOUS LOW-GRADE ADENOCARCINOMA (LOBULAR CARCINOMA; TERMINAL DUCT CARCINOMA)

The polymorphous low-grade adenocarcinoma is a recently recognized type of *salivary* malignancy that was first described in i983. Before its identification as a distinct entity. examples of this tumor were categorized as pleomorphic adenoma. an unspecified form of adeno**carcinoma, or sometimes adenoid cystic carcinoma. Once recognized as** a specific **entity, however. it was real**ized 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 (Figure 11-73), with the upper lip and buccal mucosa **being the next most common locations. It is most** common in older adults, having a 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.

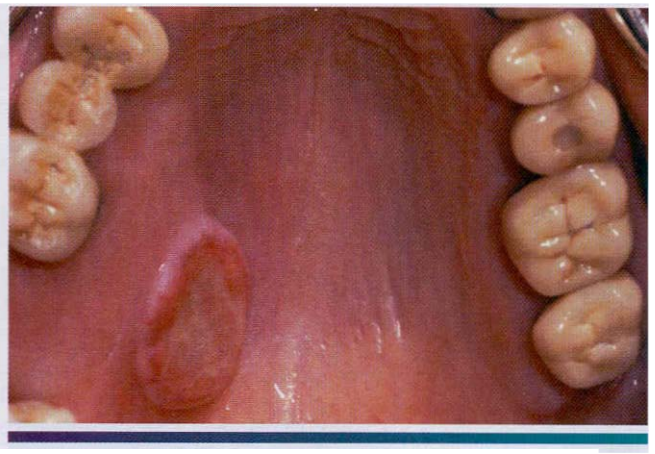

Figure 11-73 • Polymorphous low-grade adenocarcinoma. Ulcerated mass of the posterior lateral hard palate.

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 (Figure 11-74). **Mitotic figures are uncommon.**

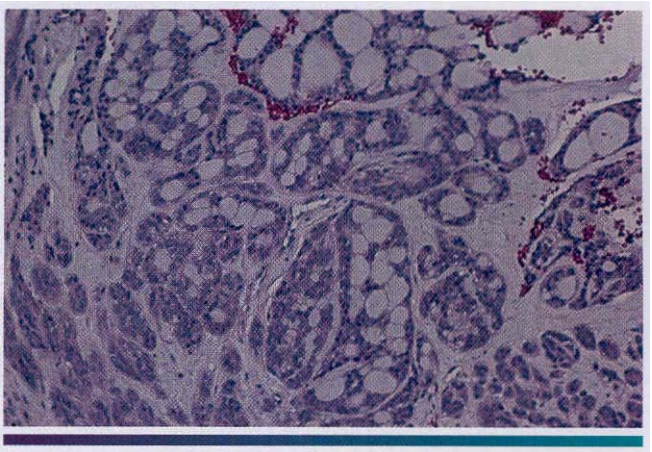

Figure 11-74 • Polymorphous low-grade adenocarcinoma. This medium-power view shows a cribriform arrangement of uniform tumor cells with pale-staining nuclei.

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 (Figure 11-75). 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 common- another feature that** may cause the tumor to be mistaken for adenoid cystic carcinoma (Figure 11-76). However, a distinction between these two tumors is important because of their vastly dif**ferent prognoses.**

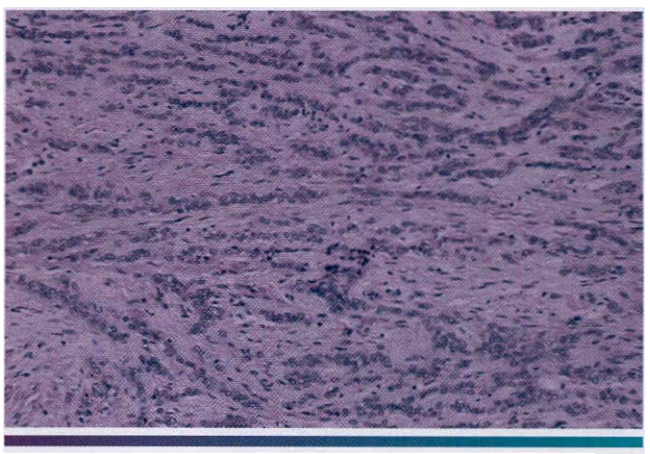

Figure 11-75 • Polymorphous low-grade adenocarcinoma. Pale-staining cells which infiltrate as single-file cords.

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 just** under 10% of patients. Therefore, radical neck dissec**tion seems unwarranted unless there is clinical evidence of cervical metastases. Distant metastasis is rare.**

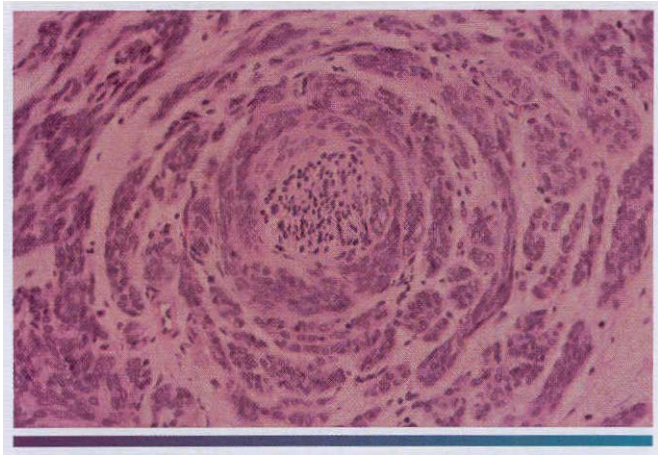

Figure 11-76 • Polymorphous low-grade adenocarcinoma. Perineural invasion.

The overall prognosis is relatively good. Recurrent disease has been reported in 9% to 17% 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.

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 (Figures 11-77 and 11-78). 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.

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.

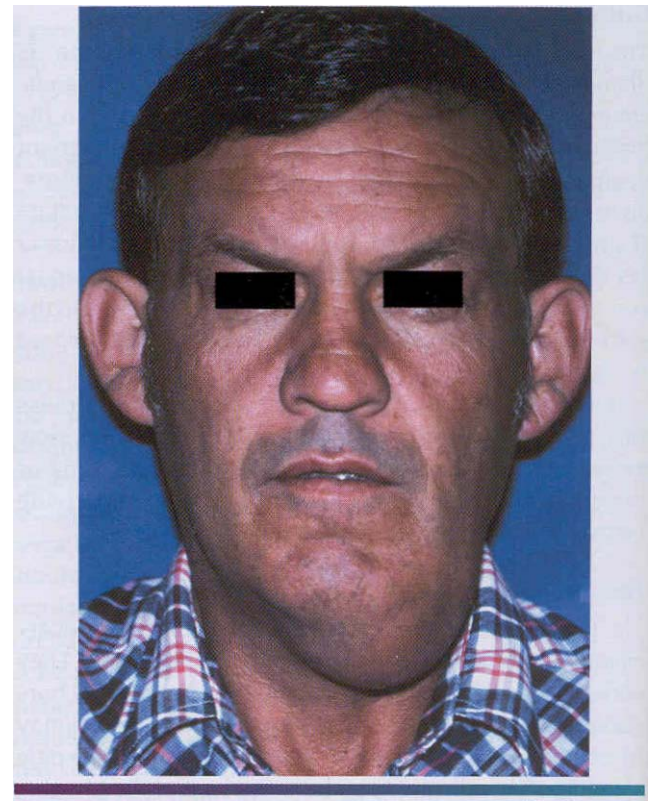

Figure 11-77 • Salivary adenocarcinoma. "Clear cell" adenocarcinoma of the submandibular gland.

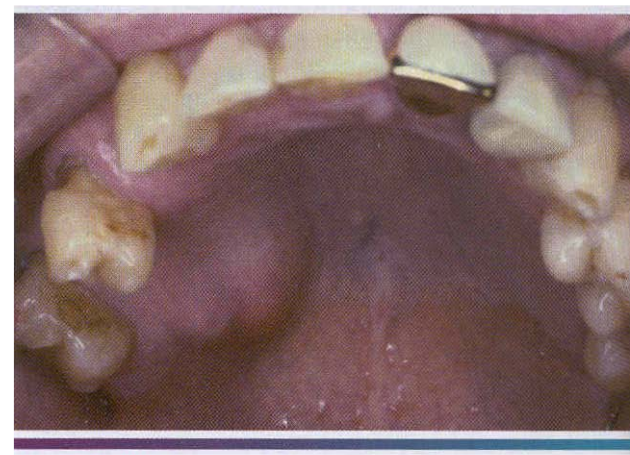

Figure 11-78 • Salivary adenocarcinoma. Mass of the posterior lateral hard palate.

Treatment and Prognosis

The prognosis for salivary adenocarcinoma (NOS) is guarded, 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.

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CHAPTER 12

Soft Tissue Tumors

CHAPTER OUTLINE

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 hyper-**plasia 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 (Figures 12-1 and 12-21. The labial mucosa. tongue. and gingiva also are common sites (Figures 12-3 and 12-4). tt is likely that many gin-**gival fibromas represent fibrous maturation of a preex-**isting 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 grayish brown pigmentation. In some** cases, the surface may appear white as a result of hyper-**keratosis from continued irritation. Most fibromas are** sessile. although some are pedunculated. They range in size from tiny lesions that are only a couple of millime-**ters in diameter to large masses that are several cen-**timeters **across; however. most fibromas are 1.5 cm or** less in diameter. The lesion usually produces no symp-**toms, unless secondary traumatic ulceration of the sur-face 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.

Histopathologic Features

Microscopic examination of the irritation fibroma shows a nodular mass of fibrous connective tissue covered by

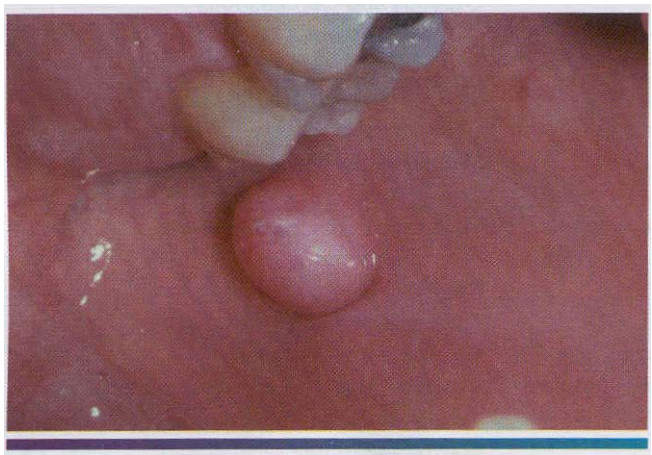


Figure 12-1 • Fibroma. Pink nodule of the posterior buccal mucosa near the level of the occlusal plane.

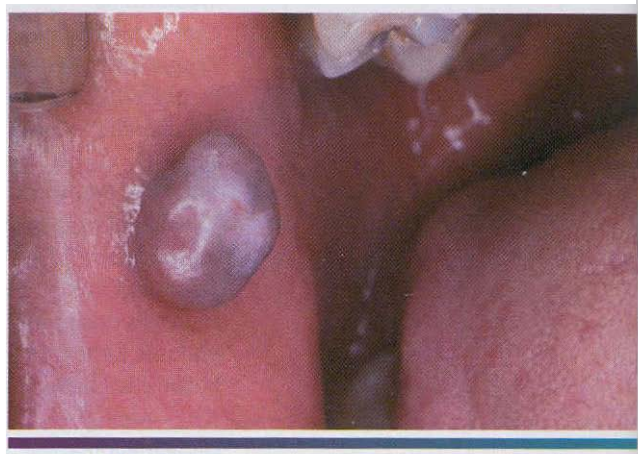


Figure 12-2 • Fibroma. Black patient with a smooth-surfaced pigmented nodule on the buccal mucosa near the commissure.

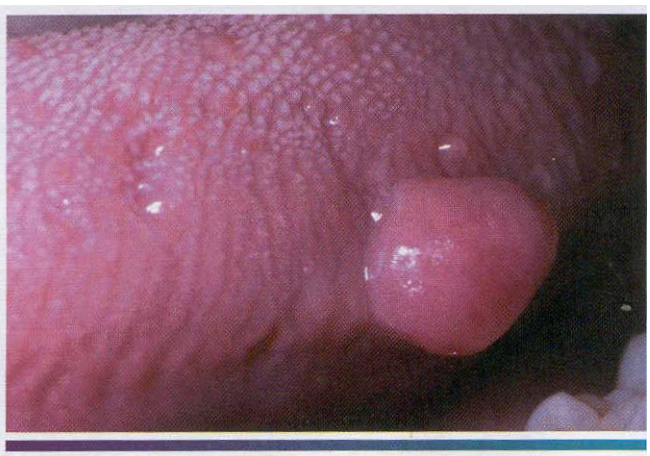


Figure 12-3 • Fibroma. lesion on the lateral border of the tongue.

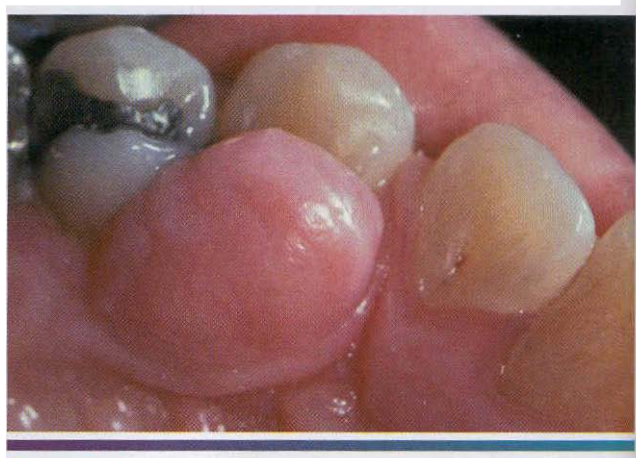


Figure 12-4 . Fibroma. Smooth-surfaced. pink nodular mass of the palatal gingiva between the cuspid and first bicuspid.

stratified squamous epithelium (Figures 12-5 and 12-6). **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.

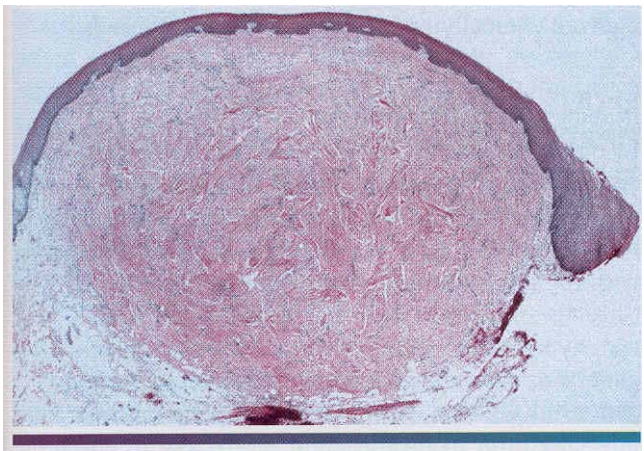


Figure 12-5 • **Fibroma. Low-power view showing an exophytic nodular mass of dense fibrous connective tissue.**

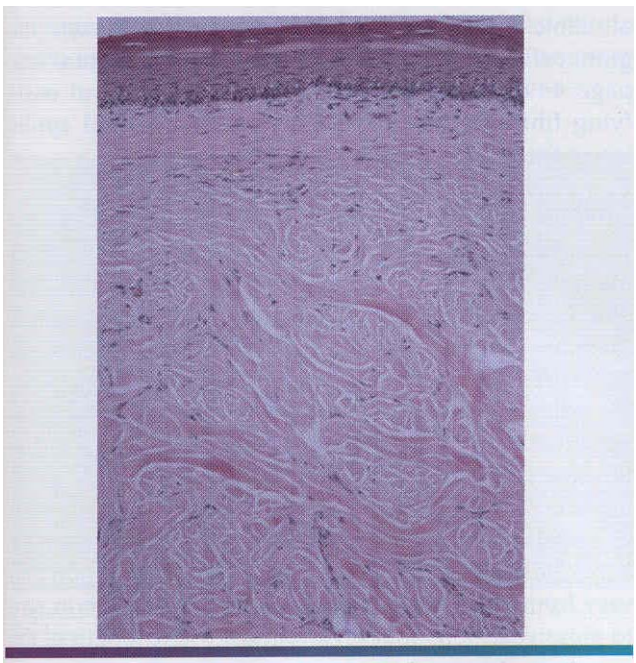


Figure 12-6 • **Fibroma. Higher-power view demonstrating dense collagen beneath the epithelial surface.**

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.

GIANT CEII 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 asymptornanc sessile or pedunculated nodule, usually less than I em in size (Figure 12-7), The surface of the mass often appears papillary; therefore, the lesion may be clinically mistaken for a papilloma, 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 3 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 the mandibular cuspid. It is frequently bilateral and typically appears as a small, pink papule that measures less than 5 mm in diameter (Figure 12-8), Retrocuspid papillae are quite common, having been reported in 25% to 99% of children and young adults. The prevalence **in** adults and the elderly drops to 6% to 19%, suggesting that the retrocuspid papilla represents a normal anatomic variation that disappears with age.

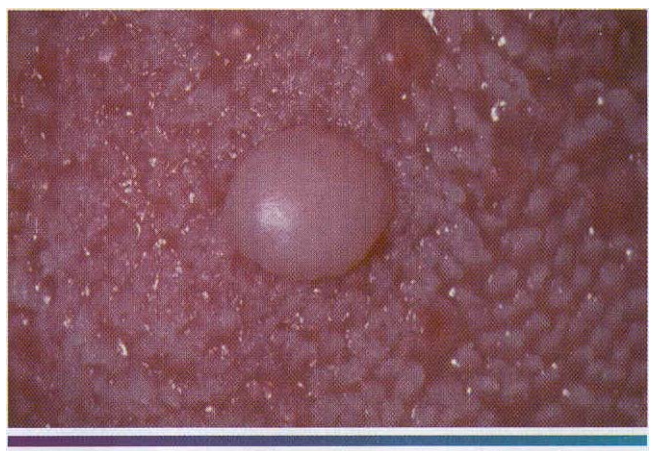


Figure 12-7 • **Giant cell fibroma. Exophytic nodule on the dorsum of the tongue.**

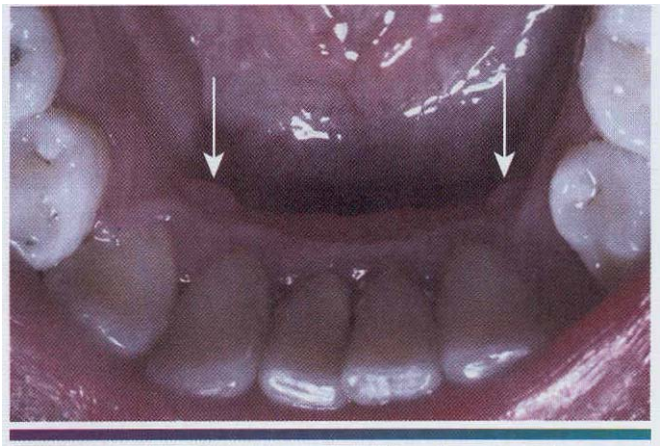


Figure 12-8 • Retrocuspid papilla. Bilateral papular lesions on the gingiva lingual to the mandibular canines *(arrows)*.

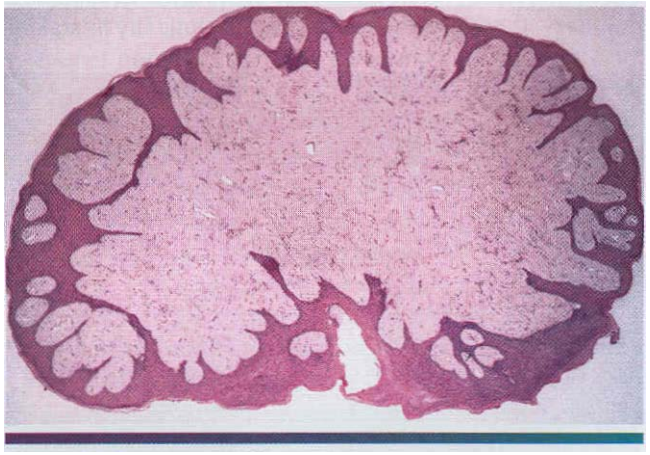


Figure 12-9 • Giant cell fibroma. Low-power view showing a nodular mass of fibrous connective tissue covered by stratified squamous epithelium. Note the elongation of the rete ridges.

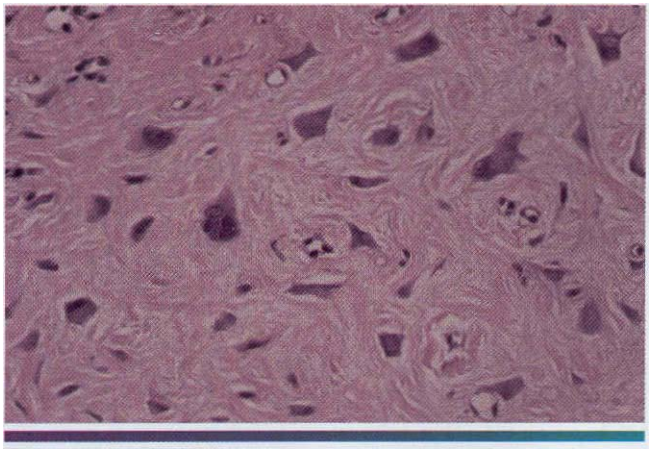


Figure 12-10 • Giant cell fibroma. High-power view showing multiple large stellate-shaped and multinucleated fibroblasts.

Histopathologic Features

Microscopic examination of the giant cell fibroma reveals a mass of vascular fibrous connective tissue, which is usually loosely arranged (Figure 12-9). The hallmark is the presence of numerous large, stellate fibroblasts within the superficial connective tissue (Figure 12-10). 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, usually retrocuspid papillae can be recognized clinically and do not need to be excised.

EPULIS FISSURATUM (INFLAMMATORY FIBROUS HYPERPLASIA; DENTURE INJURY TUMOR; DENTURE EPULIS)

The epulis fissuralum 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 fissuraturn, 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, preferring to call these lesions *inflammatory fibrous hyperplasia* or other descriptive names. However. epulis fissuratum is still widely used today, and this term is well understood by virtually all clinicians. Other examples of epulides include the giant cell epulis (peripheral giant cell granuloma) (see page 449), ossifying fibroid epulis (peripheral ossifying fibroma) (see page 451), and congenital epulis (see page 466),

Clinical Features

The epulis fissuratum typically appears as a single or multiple fold or folds of hyperplastic tissue in the alveolar vestibule (Figures 12-11 and 12-12). 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 442). 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

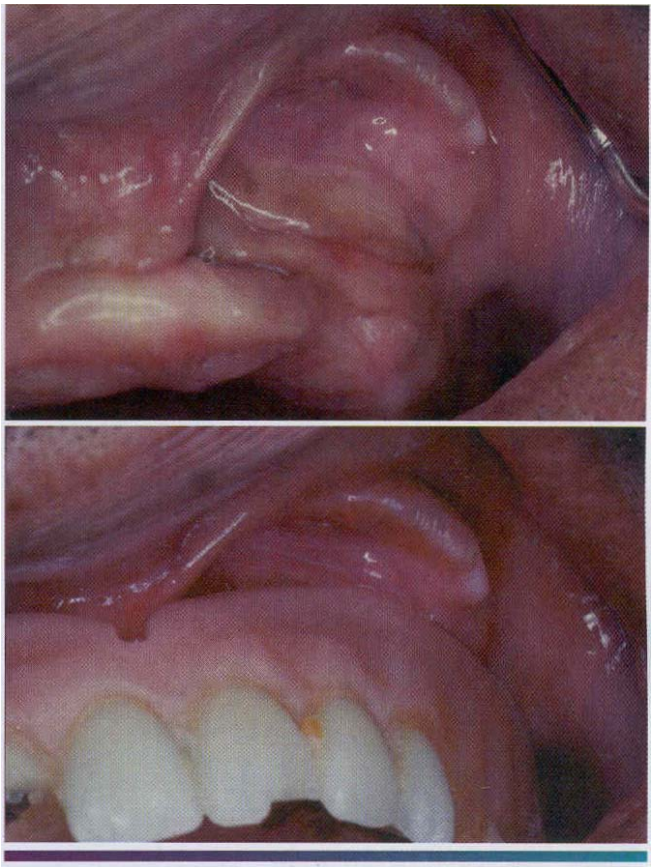
vestibule. The epulis fissuratum usually develops on the facial aspect of the alveolar ridge, although occasional lesions are seen lingual to the mandibular alveolar ridge lFigure 12-13).

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 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 Icaflike 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 (Figure 12-14). 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.

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 (Figure 12-15). The overlying epithelium is frequently hyperparakeratotic and demonstrates irregular hyperplasia of the rete ridges. In some instances, the epithelium shows inffammatory papillary hyperplasia (see page 442) or pseudoepitheliomatous (pseudocarcInornatous) 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



A

B

Figure 12-12 • 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.]

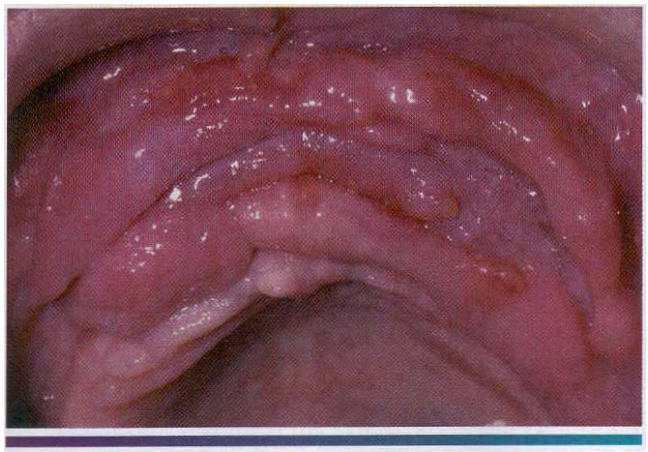


Figure 12-11 • Epulis fissuratum. Hyperplastic folds of tissue in the anterior maxillary vestibule.

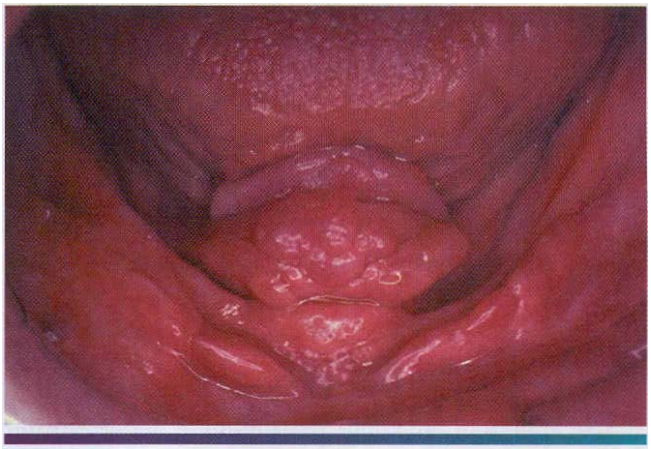


Figure 12-13 • Epulis fissuratum. Redundant folds of tissue arising in the floor of the mouth in association with a mandibular denture.

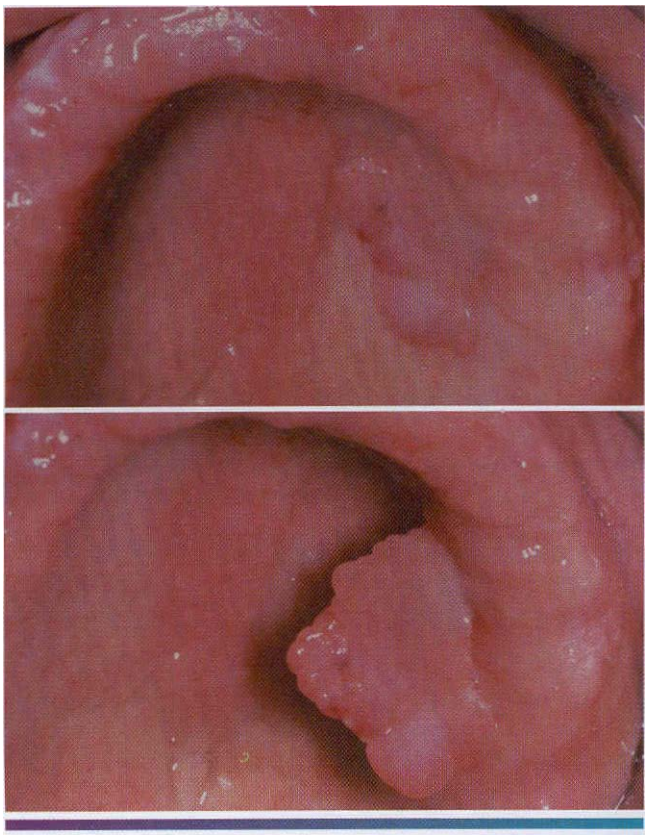


Figure 12-14 . Fibroepithelial polyp. Flattened mass of tissue arising on the hard palate beneath a maxillary denture; note its pedunculated nature. Because of its serrated edge. this lesion also is known as a leaflike denture fibroma. Associated inflammatory papillary hyperplasia is visible in the palatal midline.

cosinophtls or show lymphoid follicles. If minor salivary glands are included in the specimen, they usually show chronic staladerntts.

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 276). 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 fibroeplthehal polyp has a narrow core of dense fibrous connective tissue covered by stratified squamous epithelium. Like the epulis fissuraturn, the overlying epithelium may be hyperplastic.

Treatment and Prognosis

The treatment of the epulis fissura tum or fibrocplthellal polyp consists of surgical removal. with microscopic examination of the excised tissue. The ill-fitting denture should be remade or relined to prevent a recurrence of the lesion.

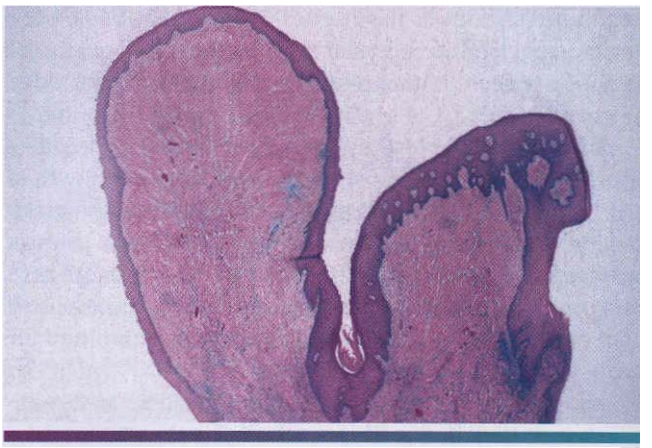


Figure 12-15 • Epulis fissuratum. Low-power photomicrograph demonstrating folds of hyperplastic fibrovascular connective tissue covered by stratified squamous epithelium.

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 192). 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* also has 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 (Figures 12-16 and 12-i7). 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 papillary surface. Many cases are associated with denture stomatitis.

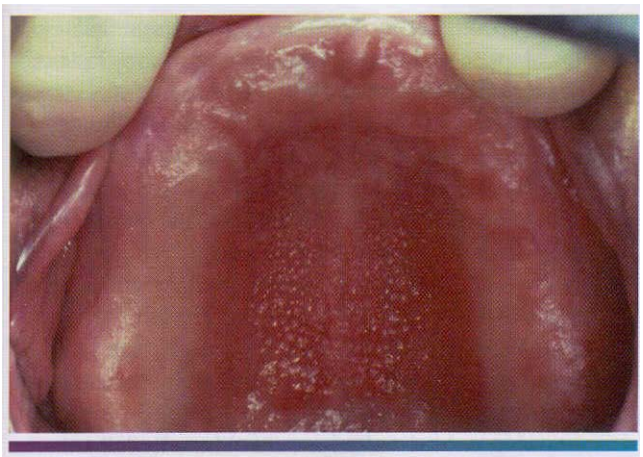


Figure 12-16 • **Inflammatory papillary hyperplasia.** Erythematous, pebbly appearance of the palatal vault.

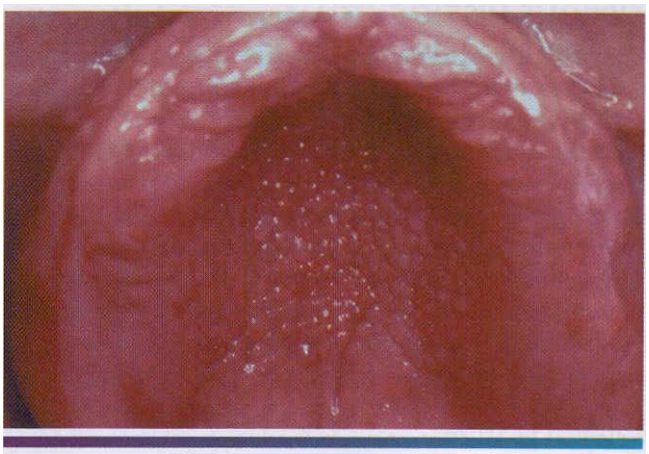


Figure 12-17 • **Inflammatory papillary hyperplasia.** An advanced case exhibiting more pronounced papular lesions of the hard palate.

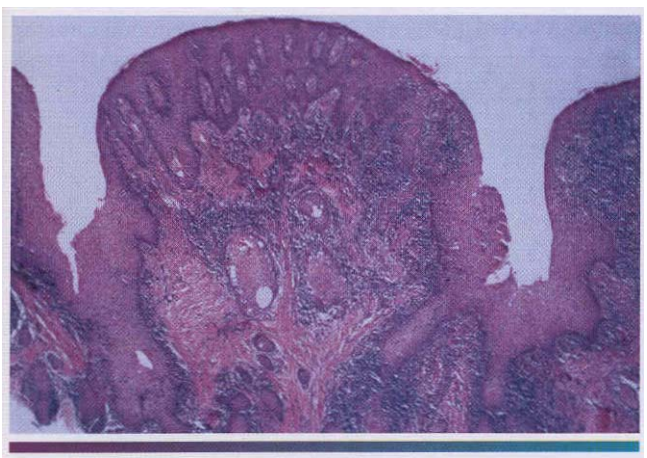


Figure 12-18 • **Inflammatory papillary hyperplasia.** Medium-power view showing fibrous and epithelial hyperplasia resulting in papillary surface projections. Heavy chronic inflammation is present.

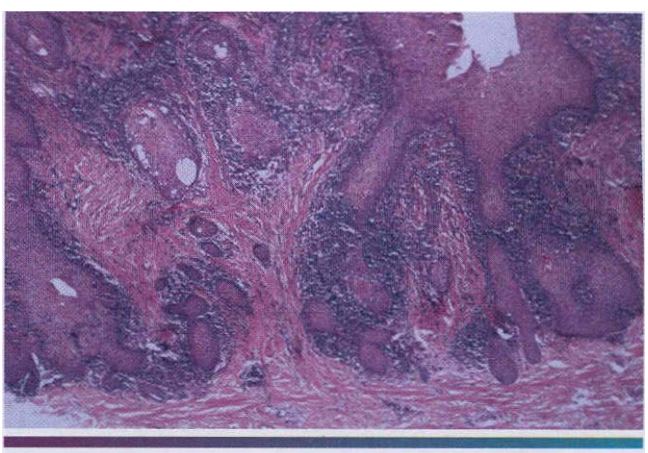


Figure 12-19 • **Inflammatory papillary hyperplasia.** Higher-power view showing pseudoepitheliomatous hyperplasia of the epithelium. This epithelium has a bland appearance that should not be mistaken for carcinoma.

Histopathologic Features

The mucosa in inflammatory papillary hyperplasia exhibits numerous papillary growths on the surface that are covered by hyperplastic stratified squamous epithelium (Figure 12-18). In advanced cases, this hyperplasia Is pscudoepitheliornatous in appearance, and the pathologist should not mistake it for carcino ma (Figure 12-19). The **connective tissue can vary from loose and edematous** to densely collagcnlzcd. 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, they often show sclerosing sialadenitis.

Treatment and Prognosis

For very early lesions of inflammatory papiilary hyperplasia, removal of the denture may allow the erythema and edema 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

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 both fibroblastic and histiocytic differentiation. Although the cell of origin is still uncertain. it may arise from the tissue histiocyte, which then assumes fibroblastic properties. Because of their variable nature, an array of terms has been used for these lesions, 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 uncommon. Although oral **tumors can occur at any site. the most frequent location** is the buccal mucosa and vestibule. Rare intrabony lesions of the jaws have also 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 (Figure** 12-20). Deeper tumors tend to be larger.

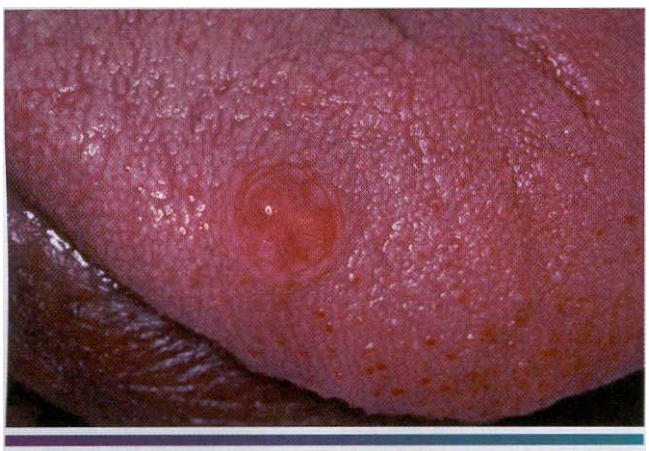


Figure 12-20 • Fibrous histiocytoma. Nodular mass on the dorsum of the tongue.

Histopathologic Features

Microscopically, the fibrous histiocytoma is characterized by a cellular proliferation of spindle-shaped fibroblastic cells with vesicular nuclei (Figures 12-21 and 12-22). 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.

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.**

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 partie-

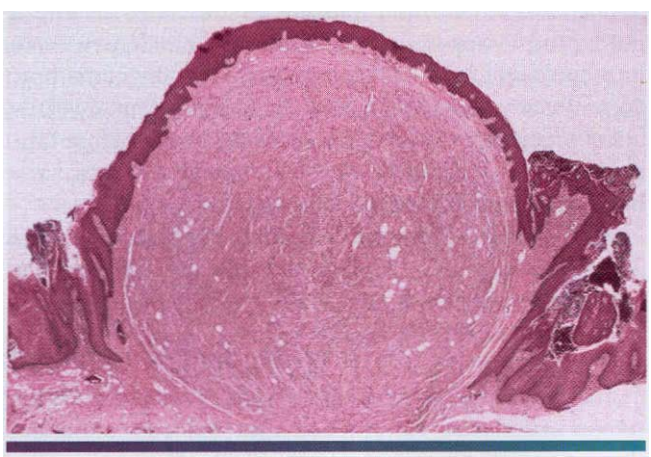


Figure 12-21 • Fibrous histiocytoma. low-power view showing a moderately cellular nodular tumor of the tongue.

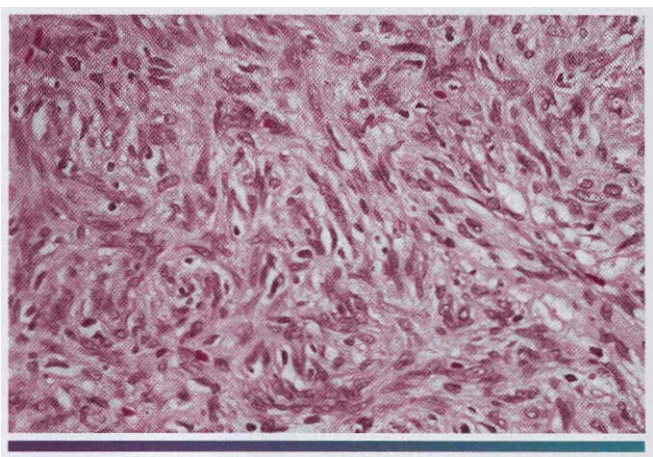


Figure 12-22 • Fibrous histiocytoma. High-power view demonstrating stcrifcrm **arrangement of spindle-shaped cells with** vesicular nuclei.

ular 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 573).

Clinical and Radiographic Features

Soft tissue fibromatosis of the head and neck is a firm, painless mass. which may exhibit rapid or insidious growth (Figure 12-23). 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 con-**siderable size. resulting in significant facial disfigurement. Destruction of adjacent bone may be observed on radiographs and other imaging studies.

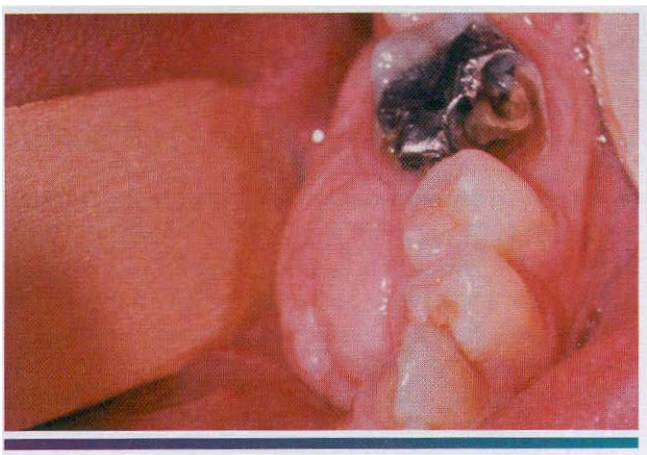


Figure 12-23 • **Fibromatosis. Locally aggressive proliferation of fibrous connective tissue of the lingual mandibular gingival mucosa.**

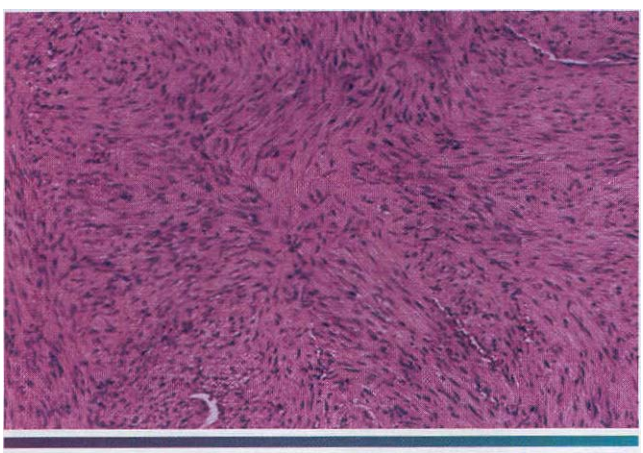


Figure 12-24 . **Fibromatosis. Streaming fascicles of fibroblastic cells that demonstrate little pleomorphism.**

Histopathologic Features

Soft tissue fibromatosis is characterized by a cellular proliferation of spindle-shaped cells that are arranged in **streaming fascicles and arc associated with a variable** amount of collagen (Figure 12-24). 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, A 23% recurrence rate has been reported for oral and para-**oral fibromatosis, but a higher recurrence rate has been noted for other head and neck sites. Metastasis does not occur.**

MYOFIBROMA (MYOFIBROMATOSIS)

Myofibroma is a rare spindle cell neoplasm that consists of myofibroblasts (i.c.. 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, Although it was originally **described as a multicentric tumor process affecting** infants and young children (myofibrornatosts), it is now recognized that most cases of the tumor are solitary and **that it can occur at any age.**

Clinical and Radiographic Features

Although myofibromas are rare neoplasms, they demonstrate a predilection for the head and neck region. The tumor occurs most frequently in the first four decades of life. with a mean age of 27 years. The most common oral location is the mandible. followed by the lips. cheek. and tongue. 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 (Figure 12-25). Multicentric myofibromatosis primarily affects neonates and infants who may have tumors of **the skin, subcutaneous tissue. muscle, bone. and viscera.**

Histopathologic Features

Myofibromas are composed of interlacing bundles of spindle cells with tapered or blunt-ended nuclei and eosinophilic cytoplasm (Figure 12-26). 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 hemangioperlcytoma-like appearance. The **tumor cells are positive for smooth muscle actin and** muscle-specific actin with immunohistochemistry. but they are negative for desrnin.

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 excision. 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.

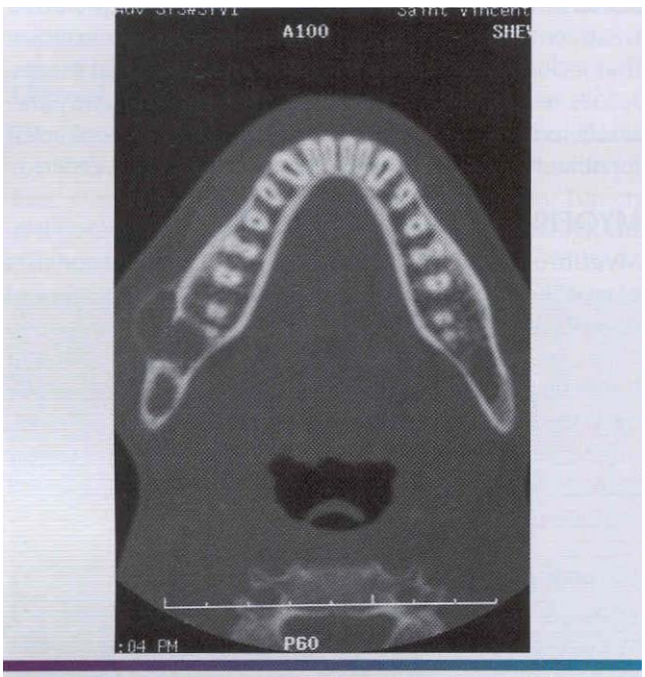


Figure 12-25 • Myofibroma. Computed tomography (CT) scan showing an expansile lytic mass of the posterior mandible on the left side of the illustration. (Courtesy of Dr. Timothy Armanini.)

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 is usually a sessile, painless **nodular mass that is the same color as the surrounding** mucosa (Figure 12-27). The surface Is typically smooth and nonulcerated. although occasional cases exhibit a lobulated appearance. The size varies from a few millimeters up to 2 em 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 (Figures 12-28 and t2-29). 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 sig-

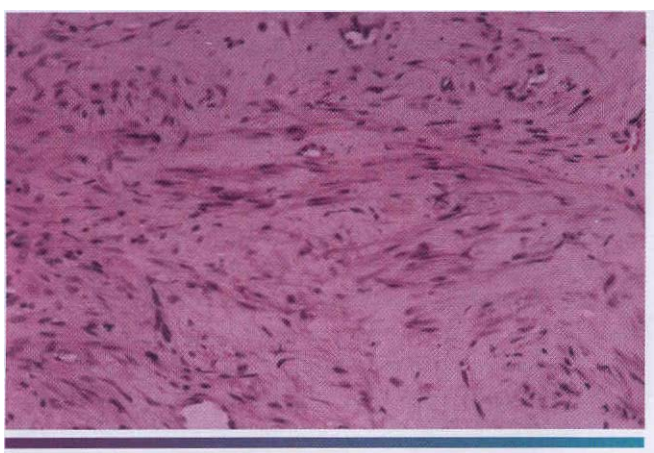


Figure 12-26 • Myofibromatosis. Proliferation of spindle-shaped cells with both fibroblastic and smooth muscle features.

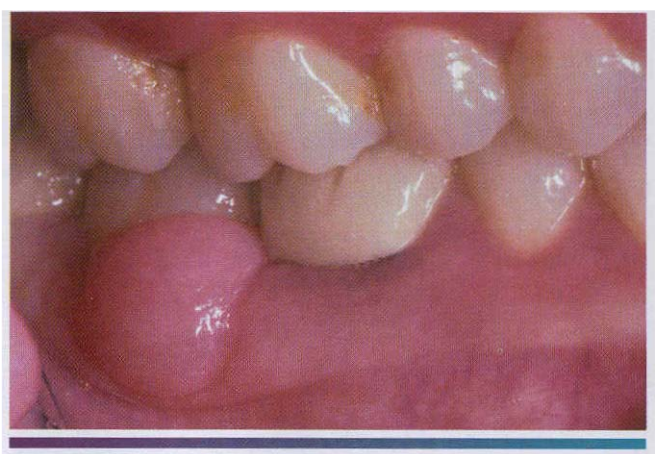


Figure 12·27. Oral focal mucinosis. Nodular mass arising from the gingiva between the mandibular first and second molars.

nificant 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.

Treatment and Prognosis

Oral focal mucinosis is treated by surgical excision and does not tend to recur.

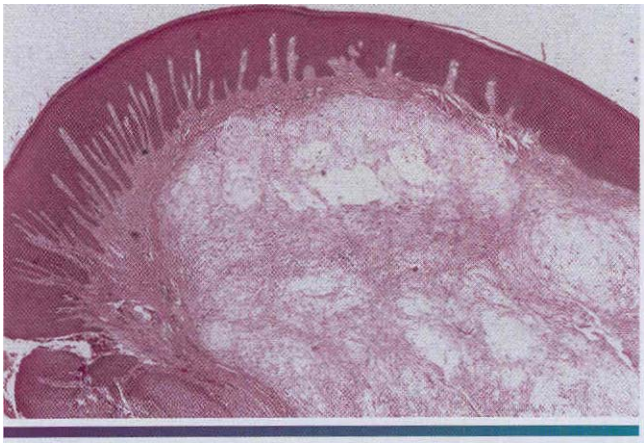


figure 12-28 • Oral focal mucinosis. Low-power view showing a nodular mass of loose, myxomatous connective tissue.

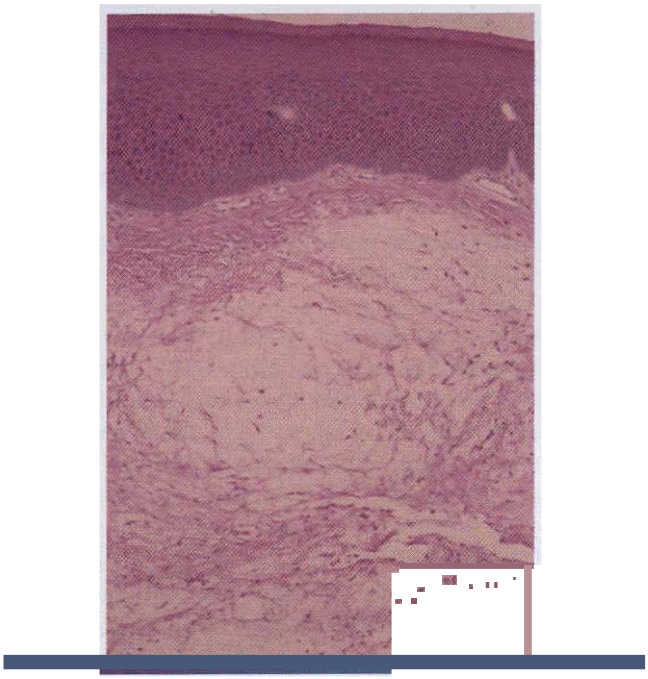


Figure 12-29 • Oral focal mucinosis. Higher-power view demonstrating the myxomatous change to the connective tissue.

PYOGENIC GRANULOMA

The pyogenic granuloma is a common tumorlike growth of the oral cavity that Is 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 (Figures 12-30 to 12-32). 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;

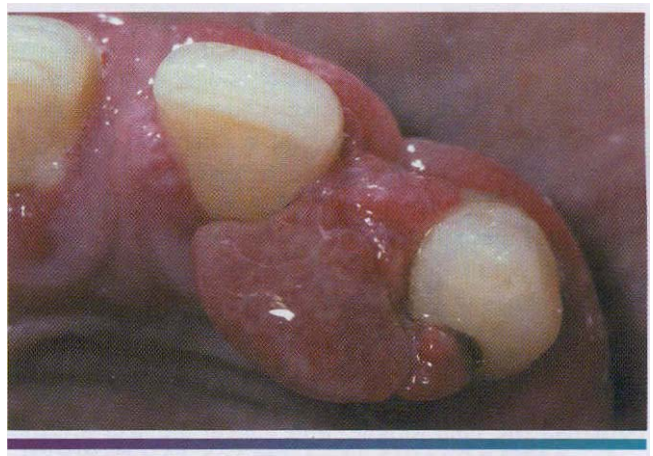


Figure 12-30 • Pyogenic granuloma. Erythematous, hemorrhagic mass arising from the maxillary anterior gingiva.

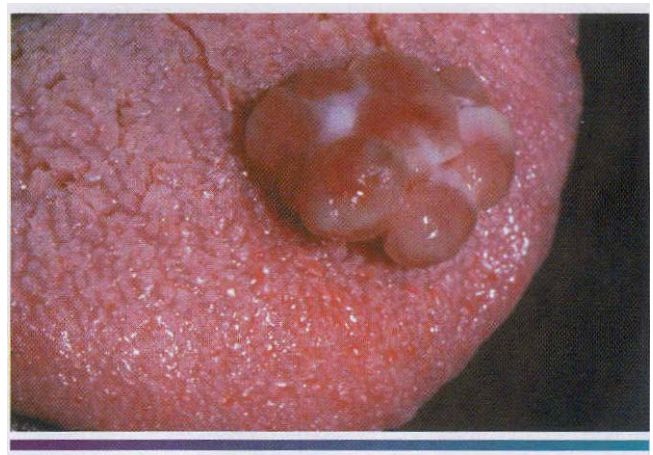


Figure 12-31 • Pyogenic granuloma. Ulcerated and lobulated mass on the dorsum of the tongue.

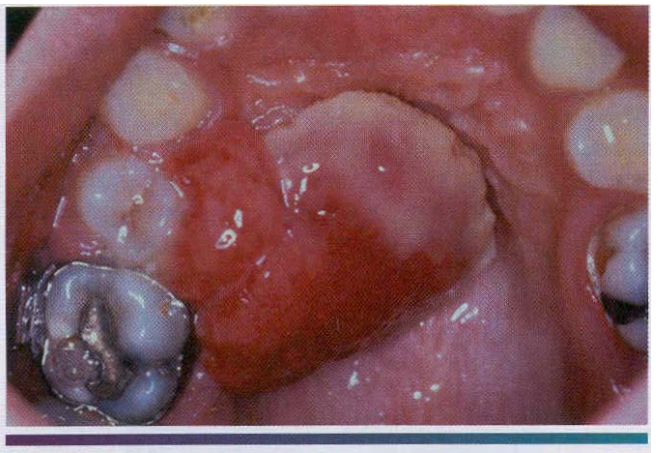
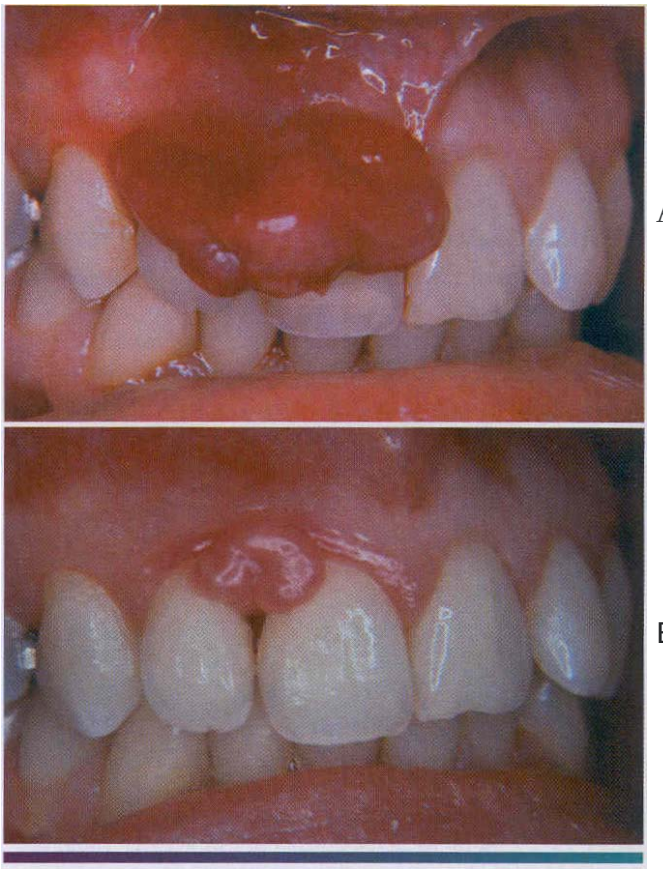


Figure 12-32 • **Pyogenic granuloma. Unusually large lesion arising from the palatal gingiva in association with an orthodontic band. The patient was pregnant.**



A

B

Figure 12-33 • **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.]

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 clinician, who may fear that the lesion might be malignant.

Oral pyogenic granulomas show a striking predilection for the gingiva. which accounts for 75% 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 extragingival pyogenic granulomas. Lesions are slightly more common on the maxillary gingiva than the mandibular gingiva; anlerior 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 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 iesions may begin to develop during the first trimester. and their incidence 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 (Figure 12-33).

Epulis granulomatosa is a term used to describe hyperplastic growths of granulation tissue that sometimes arise in healing extraction sockets (Figure 12-34). These lesions resemble pyogenic granulomas and usually represent a granulation tissue reaction to bony sequestra in the socket.

HistopathoJogk Features

Microscopic examination of pyogenic granulomas shows a highly vascular proliferation that resembles granulation tissue (Figures 12-35 and 12-36). Numerous small and larger endothelium-lined channels are formed that are engorged with red blood cells. These vessels some-

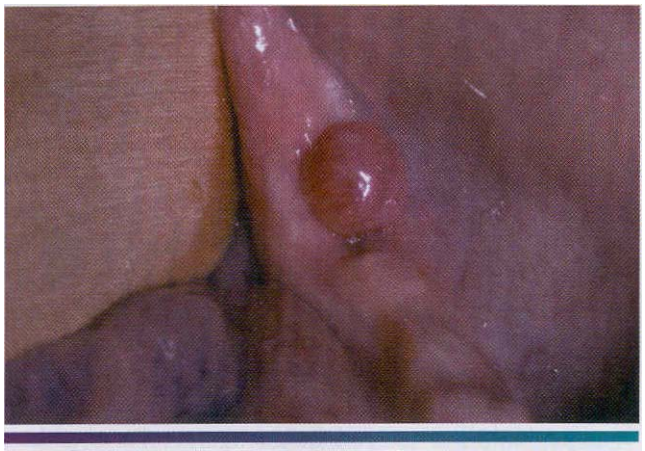


Figure 12-34 • Epulis granulomatosa. Nodular mass of granulation tissue that developed in a recent extraction site.

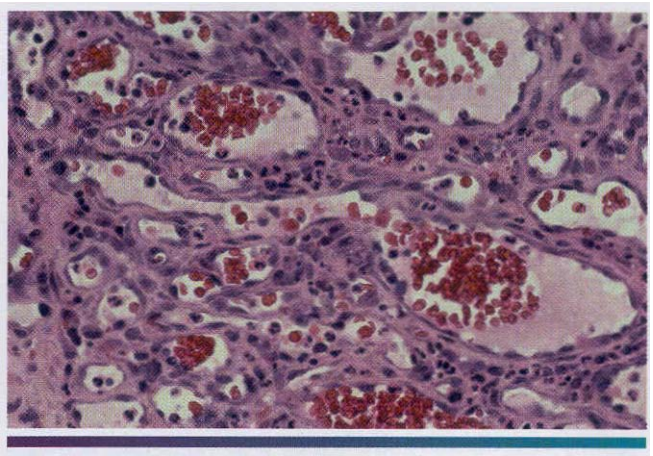


Figure 12-36 • Pyogenic granuloma. Higher-power view showing capillary blood vessels and scattered inflammation.

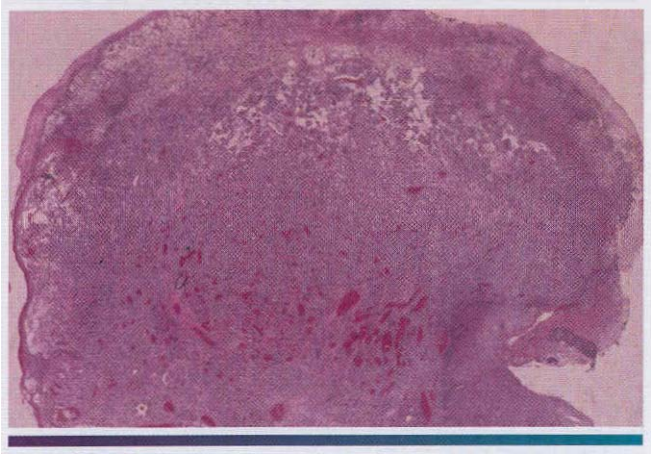


Figure 12-35 • Pyogen ic granuloma. I ow-power view showing an exophytic mass of granulation-like tissue with an ulcerated surface.

times are organized in lobular aggregates. and some pathologists require this lobular arrangement for the diagnosis *(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.

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. Occasionally. the lesion recurs and reexcision is necessary, 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 544), and some pathologists believe that it may represent a soft tissue counterpart of this central bony lesion.

Clinical and Radiographic Features

The peripheral giant cell granuloma occurs exclusively on the gingiva or edentulous alveolar ridge, presenting

as a red or reddish-blue nodular mass (Figures 12-37 and 12-38). Most 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 447), although the peripheral giant cell granuloma often is more bluish-purple compared with the bright red of a typical pyogenic granuloma.

Peripheral giant cell granulomas can develop at almost any age but show peak prevalence in the fifth and sixth decades of life. Approximately 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 (Figures 12-39 and 12-40). 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.

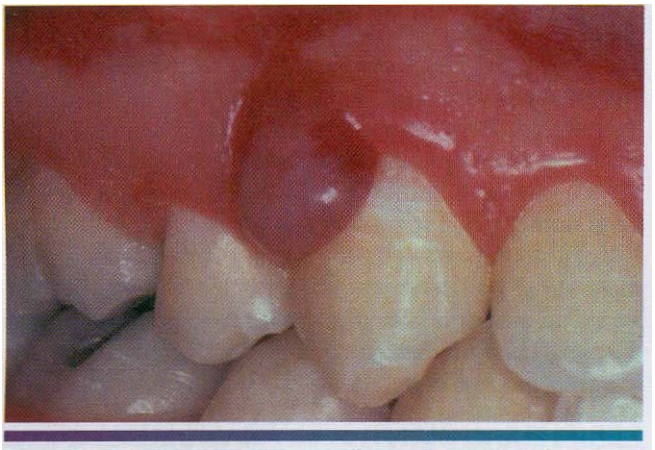


Figure 12-37 • Peripheral giant cell granuloma. Nodular reddish-purple mass of the maxillary gingiva. (Courtesy of Dr. Lewis Claman.)

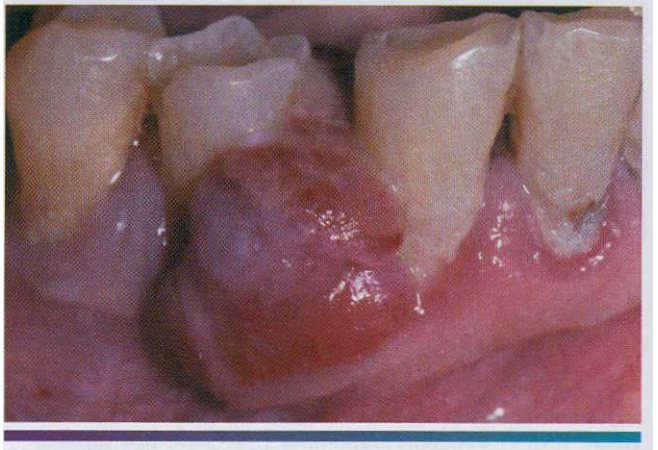


Figure 12-38 . Peripheral giant cell granuloma. Ulcerated mass of the mandibular gingiva.

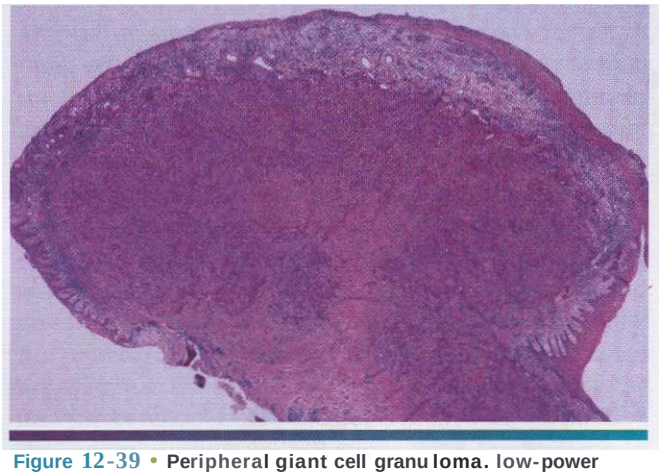


Figure 12-39 • Peripheral giant cell granuloma. Low-power view showing a nodular proliferation of multinucleated giant cells within the gingiva.

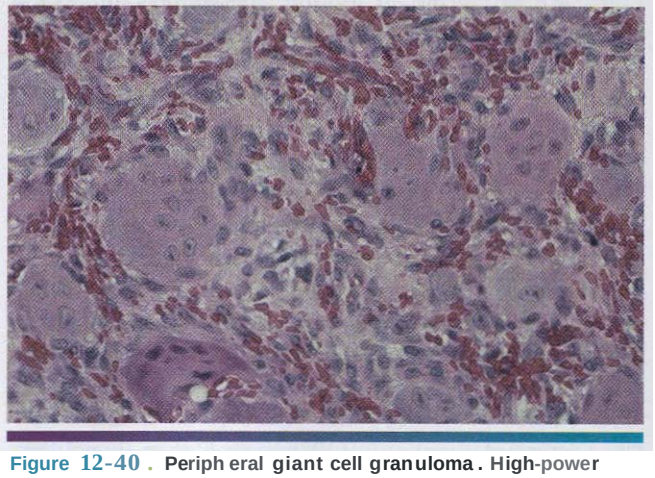


Figure 12-40 . Peripheral giant cell granuloma. High-power view showing scattered multinucleated giant cells within a hemorrhagic background of ovoid and spindle-shaped mesenchymal cells.

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% 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 724). 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, some peripheral ossifying fibromas are thought to 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 634) 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 563).

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 (Figures 12-41 and 12-42). 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

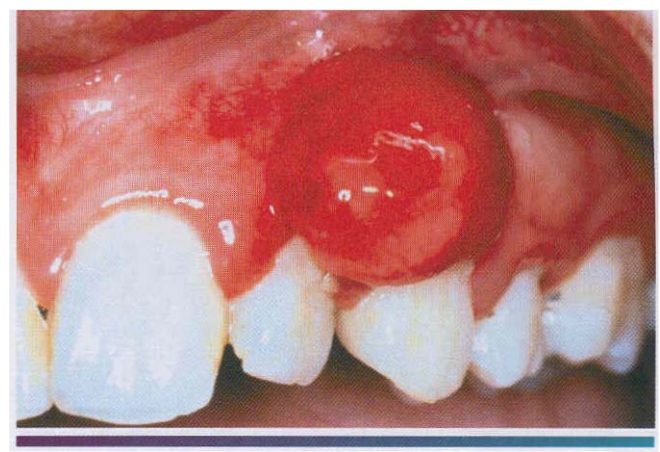


Figure 12-41 • Peripheral ossifying fibroma. Red, ulcerated mass of the maxillary gingiva. Such ulcerated lesions are easily mistaken for a pyogenic granuloma.

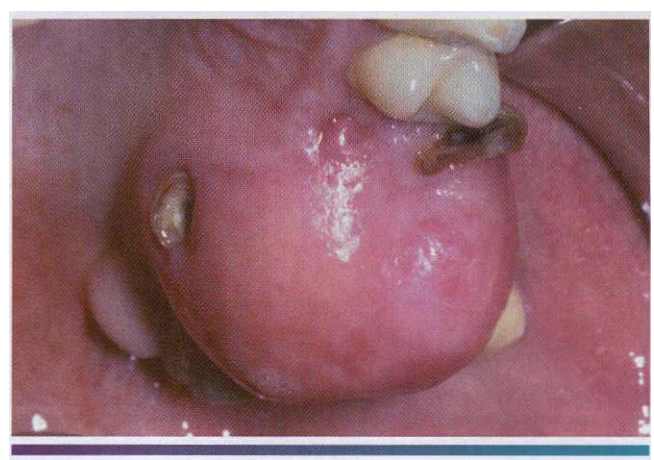


Figure 12-42 • Peripheral ossifying fibroma. Pink, nonulcerated mass arising from the maxillary gingiva. The remaining roots of the first molar are present.

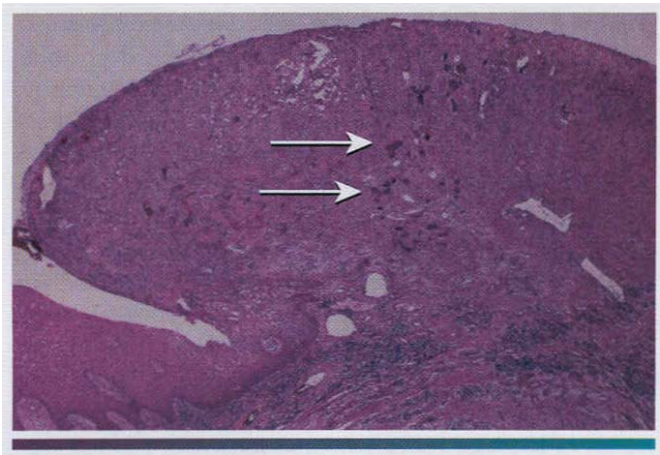


Figure 12-43 • Peripheral ossifying fibroma. Ulcerated gingival mass demonstrating focal early mineralization *(arrows)*.

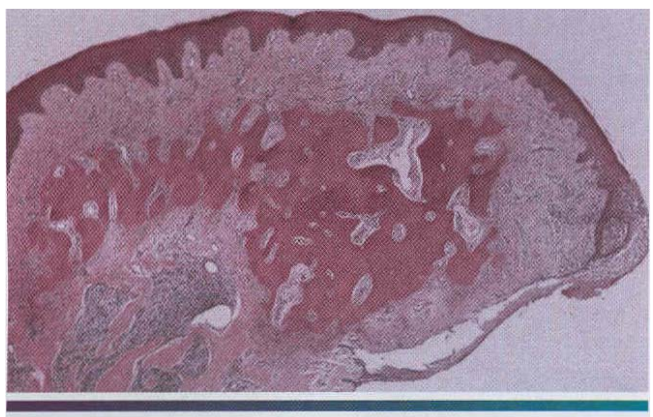


Figure 12-44 • Peripheral ossifying fibroma. Nonulcerated fibrous mass of the gingiva showing central bone formation.

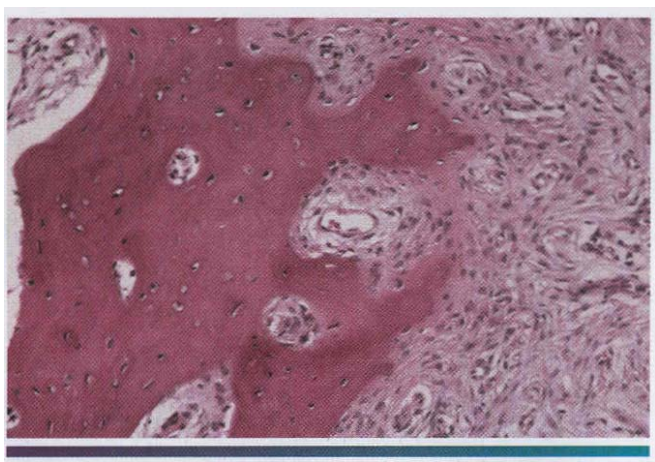


Figure 12-45 • Peripheral ossifying fibroma. High-power view showing formation of bone within a moderately cellular fibrous stroma.

cases occur in the incisor-cuspid region. Usually, the teeth are unaffected; rarely, there can be migration and loosening of adjacent teeth.

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 (Figures 12-43 to 12-45). If the epithelium is ulcerated, 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 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.

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. Although excision is usually curative, a recurrence rate of 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. 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, lipomas do not decrease in size, although normai body fat may be lost.

Clinical Features

Oral lipomas are usually soft, smooth-surfaced nodular masses that can be sessile or pedunculated (Figure 12-46). 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 50% of all cases. Some buccal cases may not represent true tumors, but rather herniation of the buccal fat pad, which may occur subsequent to surgical removal of third molars. 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. Although lipomas elsewhere in the body are reported to be twice as common in females as in males. oral lipomas are characterized by a more balanced sex distribution,

Histopathologic Features

Most oral lipomas are composed of mature fat cells that differ little in microscopic appearance from the surrounding normal fat (Figures 12-47 and i2-48). 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, 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. Myxoid lipomas exhibit a mucoid background and may be confused with myxoid liposarcomas. The spindle cell lipoma demon-

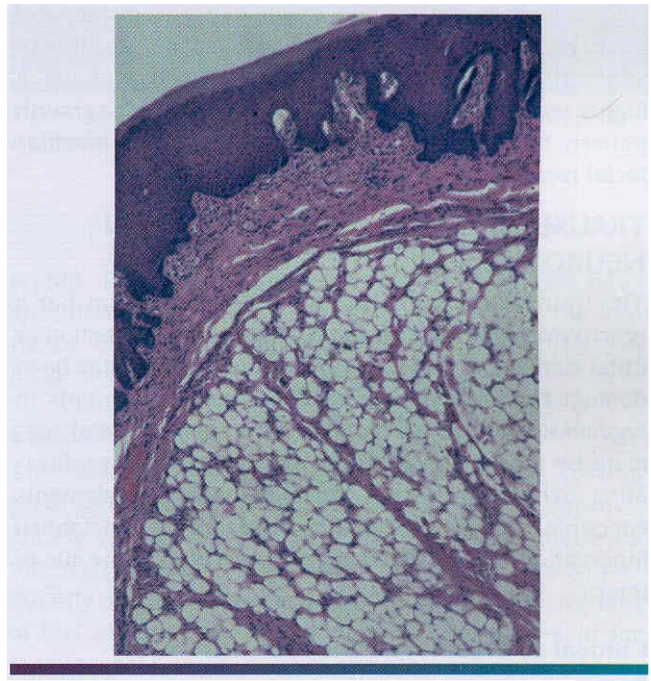


Figure 12-47 • Lipoma. Low-power view of a tumor of the tongue demonstrating a mass of mature adipose tissue,

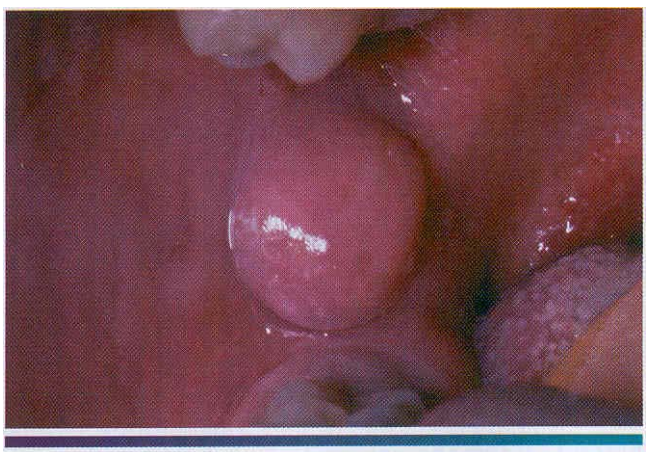


Figure 12-46 • Lipoma. Nodular mass of the posterior buccal mucosa.

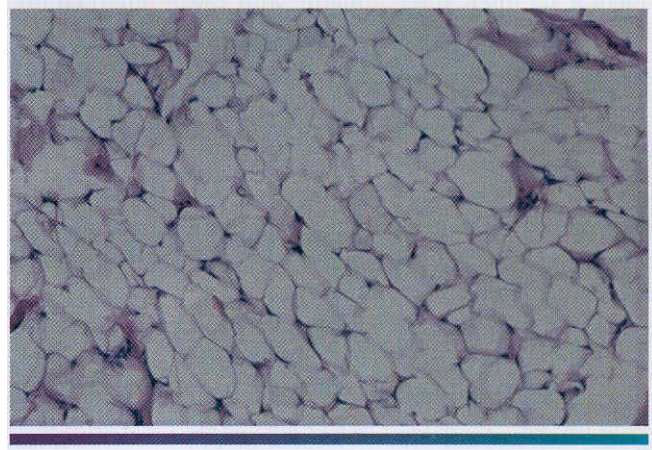


Figure 12-48 • Lipoma. High-power view of the same lesion depicted in Figure 12-4Z Note the similarity of the tumor cells to normal fat.

strates variable amounts of uniform-appearing spindle cells in conjunction with a more typical lipomatous component. 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.

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 Schwarm cells. If these regenerating elements encounter scar tissue or otherwise cannot reestablish innervation. 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 at any location but are most common in the mental foramen area, tongue. and lower lip (Figures 12-49 and 12-50). A history of trauma often can be elicited; some lesions arise subsequent to tooth extraction or other surgical procedures.tntraosseous 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 females. 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.

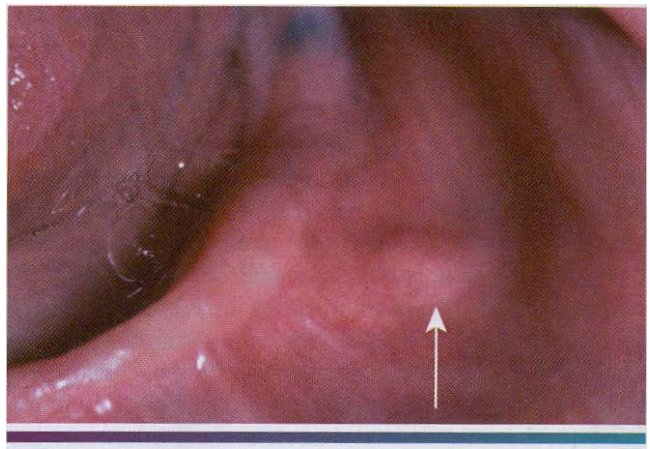


Figure 12-49 • Traumatic neuroma. Painful nodule of the mental nerve as it exits the mental foramen *(arrow)*.

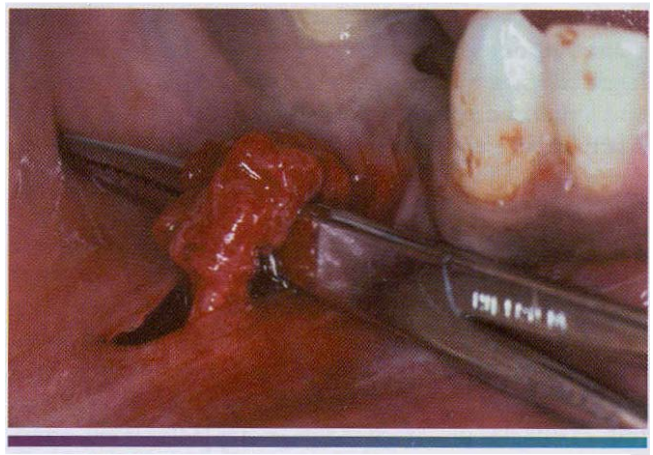


Figure 12-50. Traumatic neuroma. Note the irregular nodular proliferation along the mental nerve that is being exposed at the time of surgery.

Histopathologic Features

Microscopic examination of traumatic neuromas shows a haphazard proliferation of mature. myelinated nerve bundles within a fibrous connective tissue stroma that ranges from densely collagenized to myxomatous in nature (Figures 12-51and 12-521. 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.

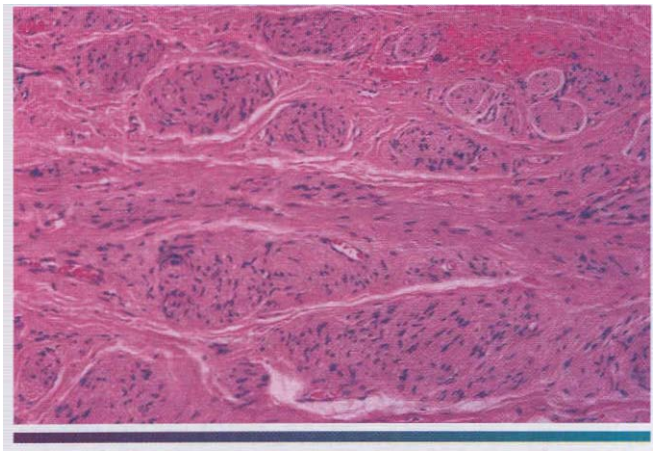


Figure 12·51 • Traumatic neuroma. Low-power view showing the haphazard arrangement of nerve bundles within the background fibrous connective tissue.

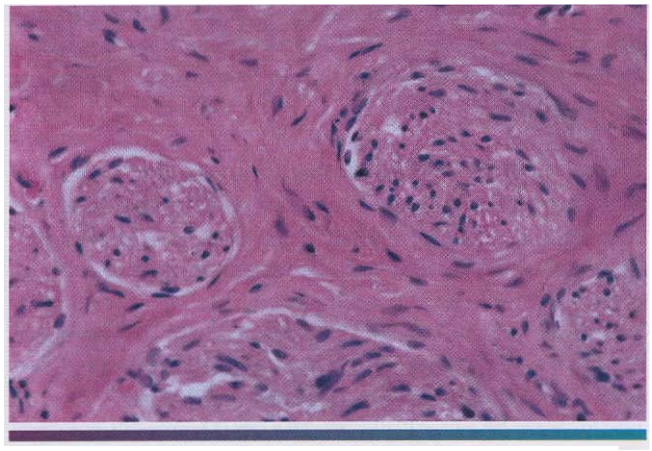


Figure 12·52 • Traumatic neuroma. High-power view showing cross-sectioned nerve bundles within dense fibrous connective tissue.

Treatment and Prognosis

The treatment of choice for the patient with a traumatic neuroma is surgical excision, including a small portion of the involved nerve bundle. Most lesions do not recur; in some cases, however, the pain persists or returns at a later date.

PALISADED ENCAPSULATED NEUROMA (SOLITARY CIRCUMSCRIBED NEUROMA)

The palisaded encapsulated neuroma is a benign neural tumor with distinctive clinical and histopathologic features. Although it was first recognized only as recently as 1972. 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.

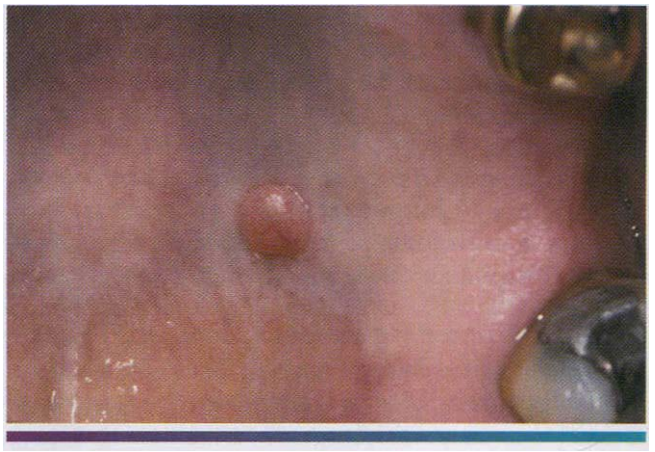


Figure 12·53 . Palisaded encapsulated neuroma. Small. painless nodule of the lateral hard palate.

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 I cm in diameter. There is no sex predilection.

Oral palisaded encapsulated neuromas are not uncommon, although many are probably diagnosed microscopically as neurofibromas or neurilemomas. The lesion appears most frequently on the hard palate (Figure 12-53) and maxillary labial mucosa, although it also may occur in other oral locations.

Histopathologic Features

Palisaded encapsulated neuromas appear well circumscribed and often encapsulated (Figure t2-54), 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 Schwarm 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 neurilemoma are usually not seen. Special stains reveal the presence of numerous axons within the tumor and the cells show a positive immuno-**histochemical reaction for S-100 protein (Figure 12-55). 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.

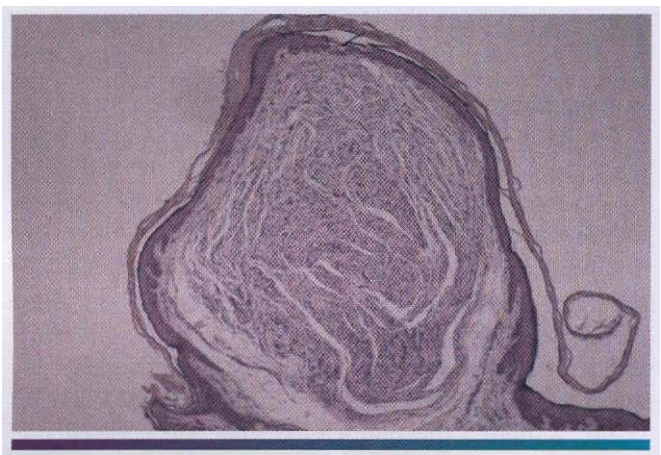


Figure 12-54 • Palisaded encapsulated neuroma. low-power **view showing a well-circumscribed, nodular proliferation of neural tissue.**

NEURILEMOMA (SCHWANNOMA)

The neurilemoma 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.

Clinical and Radiographic Features

The neurilemoma 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 asyrnpro mattc, 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 neurilemomas. although the tumor can occur almost anywhere in the mouth (Figure 12-56). On occasion. the tumor arises centrally within bone and may produce **bony expansion.** Intraosseous examples **are most com-**mon in the posterior mandible and usually appear as **either unilocular or** multilocular **radiolucencies on** radio-**graphs. Pain** and paresthesia **are not unusual for intra-**bony tumors.

Histopathologic Features

The neurilemoma is usually an encapsulated tumor that **demonstrates two microscopic patterns in varying** amounts: (1) Antoni A and (2) Antoni B. Antoni A tissue is characterized by streaming fascicles of spindle-shaped Schwarm cells. These cells often form a palisaded **arrangement around central acellular, eosinophilic areas** known as Verocay bodies (Figure 12-57). These verocav bodies consist of reduplicated basement membrane and

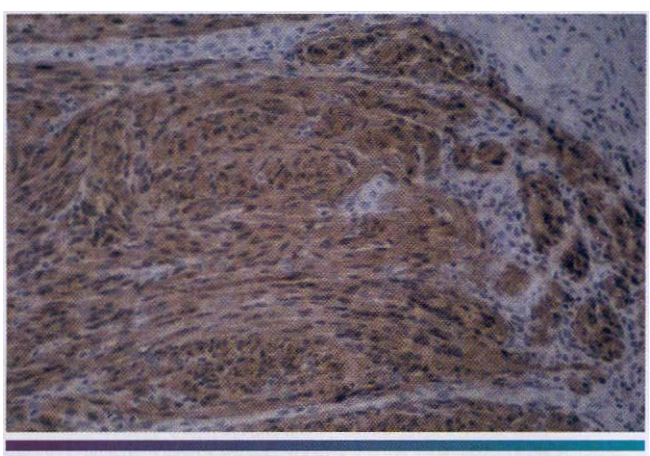


Figure 12-55 • Palisaded encapsulated neuroma. Immunohisto-chemical reaction demonstrating spindle-shaped cells that are strongly positive for $-100 protein.

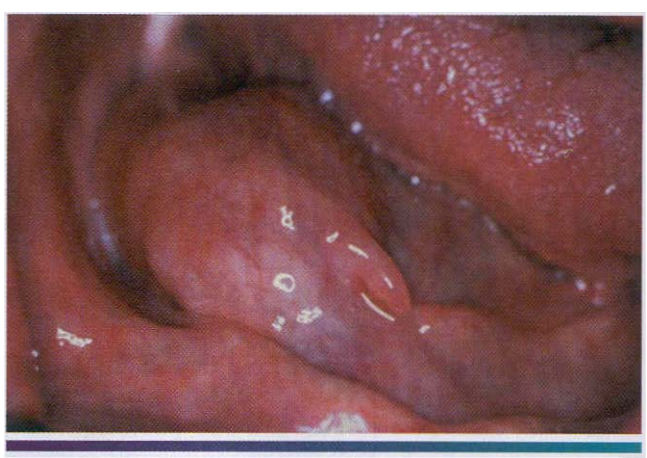


Figure 12-56 . Neurilemoma. Nodular mass in the floor of the mouth. (Courtesy of Dr. Art A. Gonty.)

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 neurilemomas). 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.**

Treatment and Prognosis

The neurilemoma is treated by surgical excision, and the lesion should not recur. Malignant transformation does not occur or is extremely rare.

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 458). 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 (Figures 12-58 and 12-59). 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 (Figure 12-60).

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 of 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 (Figures 12-61 and 12-62). 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

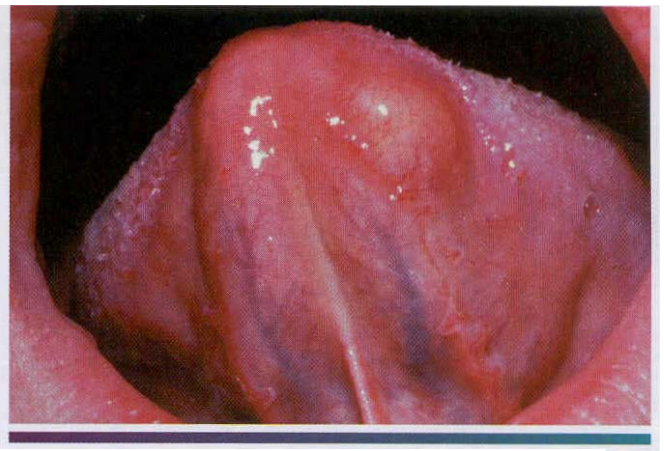


Figure 12-58 • Neurofibroma. Nodular mass of the anterior ventral tongue. (Courtesy of Dr. lindsey Douglas.)

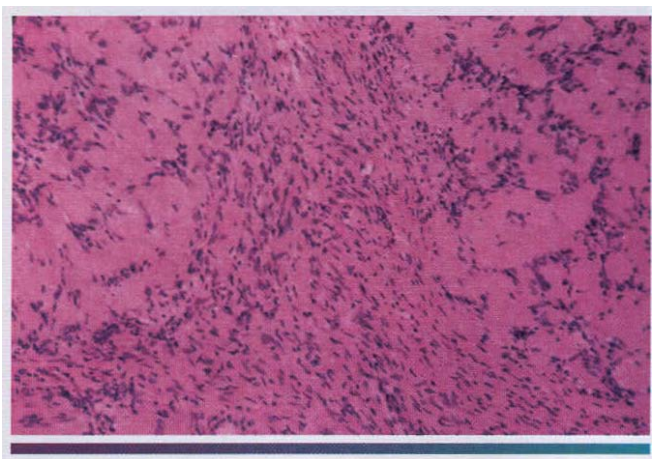


Figure 12-57 • Neurilemoma. Medium-power view showing a central zone of Antoni B tissue that is bordered on both sides by better-organized Antoni A tissue. The Schwann cells of the Antoni A tissue form a palisaded arrangement around acellular zones known as Verocay bodies.

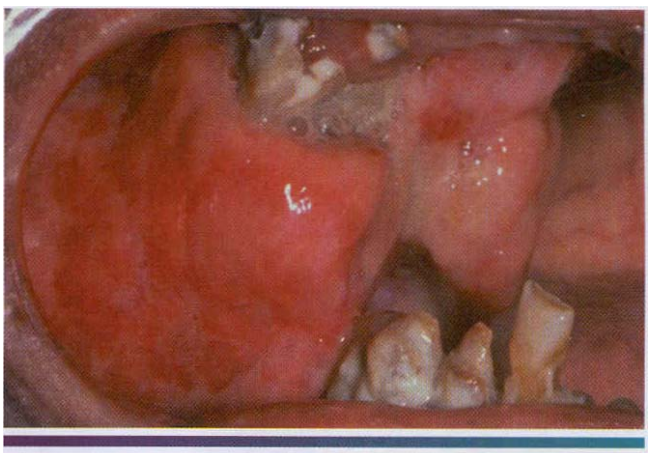


Figure 12-59 • Neurofibroma. Huge tumor involving the maxillary gingiva and hard palate.

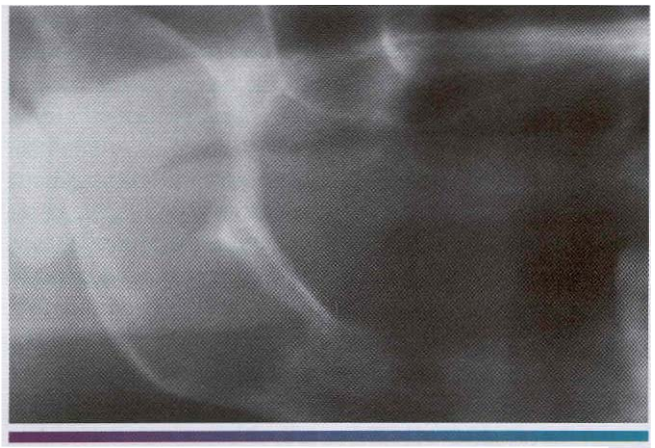


Figure 12-60. Neurofibroma. Intraosseous tumor filling the right mandibular ramus. (Courtesy of Dr. Paul Allen.)

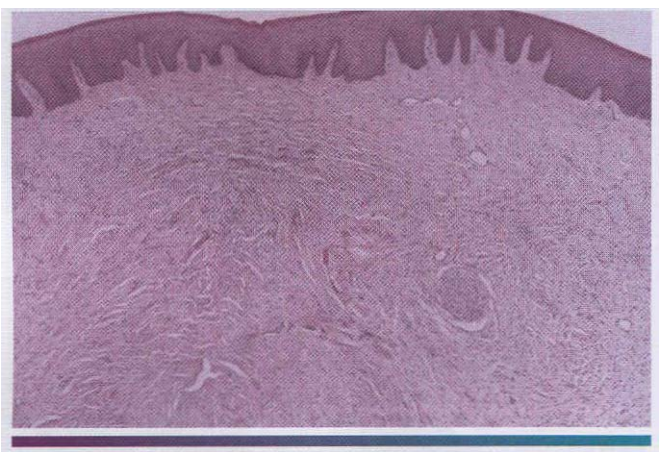


figure 12-61 • Neurofibroma. Low-power view showing a cellular tumor mass below the epithelial surface.

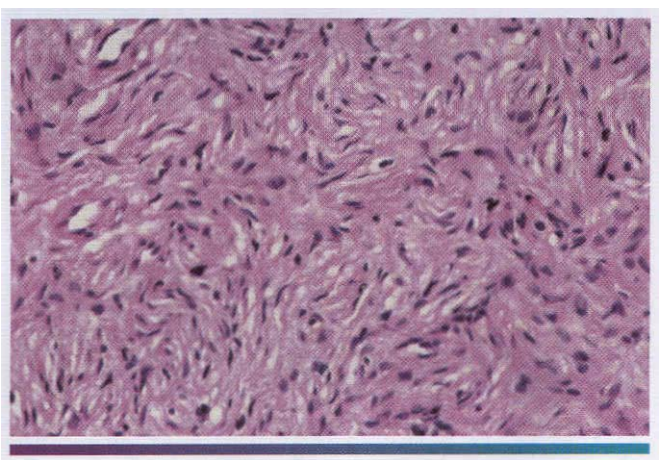


Figure 12-62 • Neurofibroma. High-power view showing spindle-shaped cells with wavy nuclei.

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 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 (VON RECKLINGHAUSEN'S DISEASE OF THE SKIN)

Neurofibromatosis is a relatively common hereditary condition that is estimated to occur in one of every 3000 births. At least eight forms of neurofibromatosis have been recognized. but the most common form is neurofibromatosis type I (discussed here). This form of the disease, also known as von Rccklinghauscn's disease of the skin, accounts for 85% to 97% of cases and is inherited as an autosomal dominant trait (although 50% of all patients have no family history and apparently represent new mutations). The gene responsible for neurofibromatosis type I has been mapped to chromosome 17.

Clinical and Radiographic Features

The diagnostic criteria for neurofibromatosis are summarized in Box 12-1. Patients have multiple neurofi-

Box 12-1 *Diagnostic Criteria for Neurofibromatosis Type I*

The diagnostic criteria are met if a patient has two or more of the following features:

1. Six or more *café au lait* macules over 5 mm in greatest diameter in prepubertal persons and over 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 neurofibromatosis type I, based on the above criteria

bromas 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, pendu ious masses (elephantiasis neurornatosa) on the skin (Figures 12-63 and i2-64). The plexiform variant of neurofibroma, which feels like a "bag of worms," is considered pathognomonic for neurofibromatosis. 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/ait* (coffee with milk) pigmentation on the skin (Figure i2-65). These spots are smooth-edged, yellowish-tan to dark-brown macules that vary in diameter from I to 2 mm to several centimeters. They are usually present at birth or may develop during the first year of life. Axillary freckling (Crowe's sign) is also a highly suggestive sign.

Lisch nodules, translucent brown-pigmented spots on the iris, are found in nearly all affected individuals. Other possible abnormalities may be seen, including central nervous system (eNS) tumors, macrocephaly. mental deficiency. seizures, short stature. and scoliosis.

In the past, oral lesions were estimated to occur in 4% to 7% of cases (Figure 12-66). However, two studies suggest that oral manifestations may occur in as high as 72% to 92% of cases, especially if a detailed clinical and radiographic examination is performed. The most common reported finding is enlargement of the fungiform papillae lin about 50% of all affected patients); however, the specificity of this finding for neurofibromatosis is unknown. Only about 25% of patients examined in these two studies exhibited actual intraoral neurofibromas. 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.

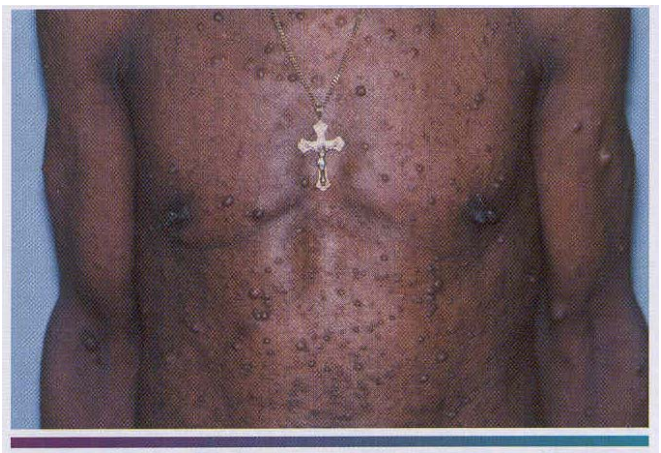


Figure 12-63 • Neurofibromatosis. Multiple tumors of the trunk and arms.

Treatment and Prognosis

There is no specific therapy for neurofibromatosis, and treatment often is directed toward prevention or management of complications. Facial neurofibromas can be removed for cosmetic purposes. Carbon dioxide laser and dermabrasion have been used successfully for extensive lesions.

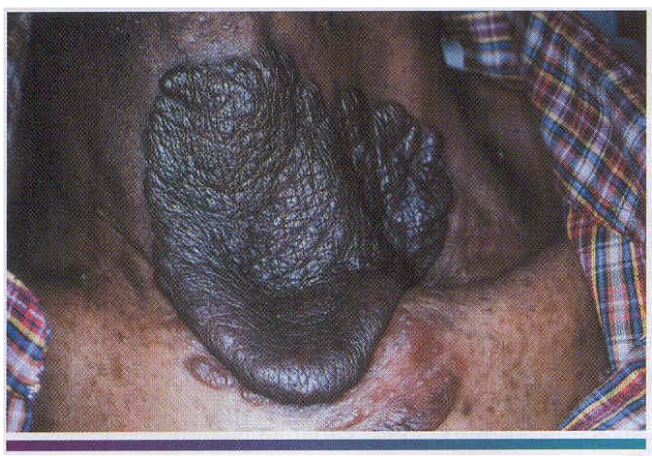


Figure 12-64 • Neurofibromatosis. Baggy, pendulous neurofibroma of the lower neck.

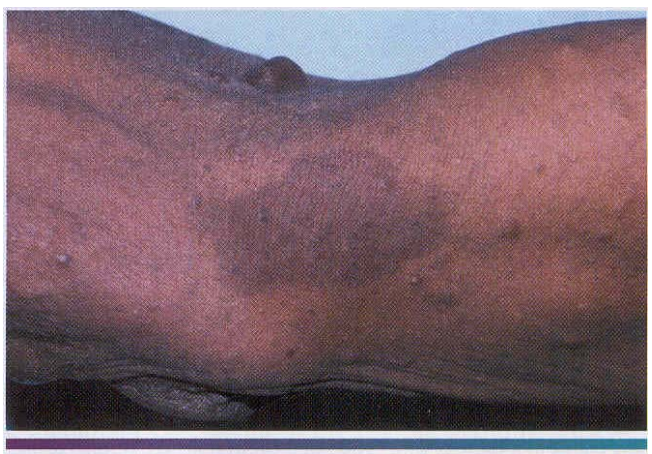


Figure 12-65 • Neurofibromatosis. Same patient as depicted in Figure 12-63. Note the *café au fait* pigmentation on the arm.

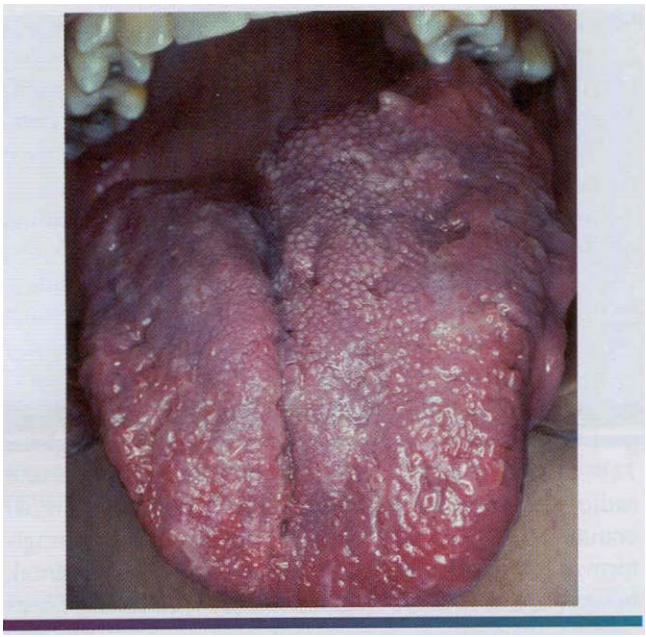


Figure 12-66 • Neurofibromatosis. Intraoral involvement characterized by unilateral enlargement of the tongue.

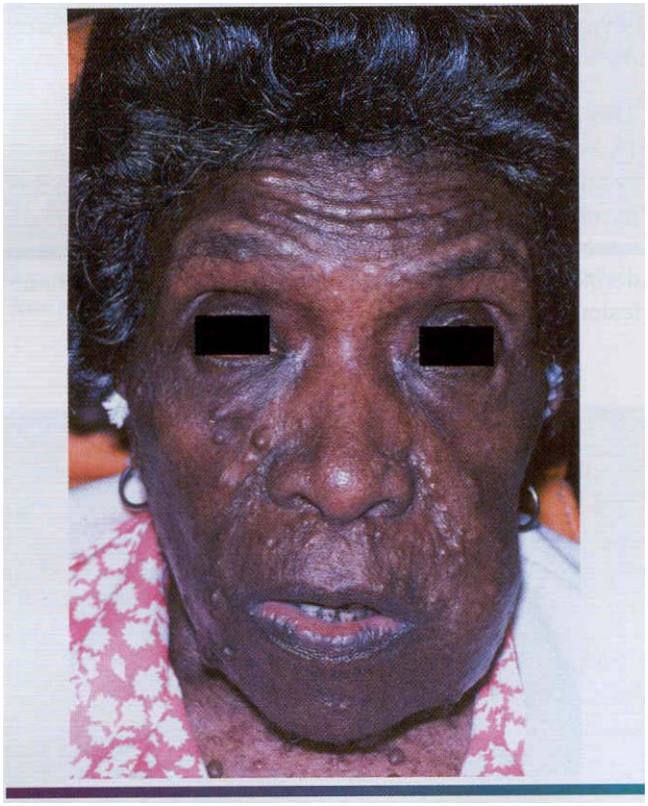


Figure 12-67 • Neurofibromatosis. Neurofibrosarcoma of the left cheek in a patient with type I neurofibromatosis. (From Neville BW, Hann J. Narang R, et al: Oral neurofibrosarcoma associated with neurofibromatosis type I. *Oral Surg Oral Med Oral Pathol* 72:456-461. 1991.)

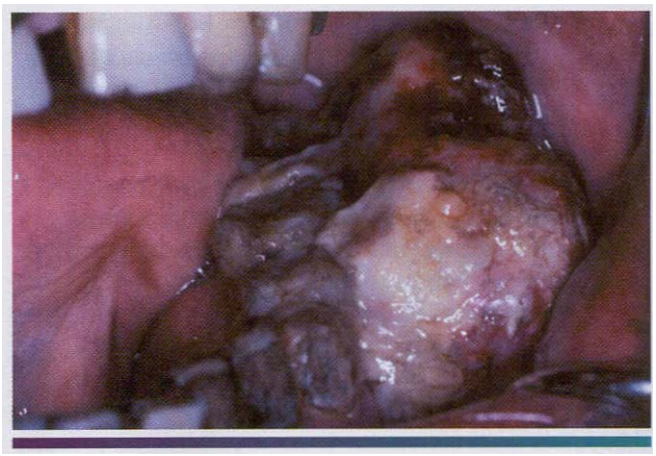


Figure 12-68 • Neurofibromatosis. Same patient as depicted in Figure 12-67. Note the intraoral appearance of neurofibrosarcoma of the mandibular buccal vestibule. The patient eventually died of this tumor. (From Neville BW, Hann J. Narang R, et al: Oral neurofibrosarcoma associated with neurofibromatosis type I, *Oral Surg Oral Med Oral Pathol* 72:456-461. 1991.)

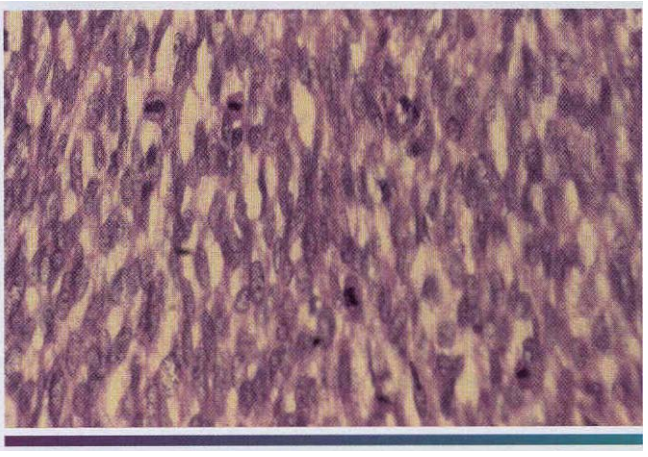


Figure 12-69 • Neurofibrosarcoma. High-power view of an intraoral tumor that developed in a patient with neurofibromatosis. There is a cellular spindle cell proliferation with numerous mitotic figures.

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 (Figures 12-67 to 12-69). The prognosis for malignant peripheral nerve sheath tumors associated with neurofibromatosis is poor, with a 5-year survival rate of only 15%. Other malignancies also have been associated with neurofibromatosis, including CNS tumors, pheochromocytoma, leukemia, rhabdomyosarcoma, and Wilms tumor.

In recent years. there has been considerable interest in [oseph (not John) Merrick, the so-called "Elephant Man." Although Merrick once was mistakenly considered to have neurofibromatosis. it is now generally accepted that his horribly disfigured appearance was not because of neurofibromatosis but that he most likely had a rare condition known as Proteus syndrome. Because patients with neurofibromatosis may fear acquiring a similar clinical appearance. they should be reassured that they have a different condition. The phrase "Elephant Man disease" is incorrect. misleading. and should be avoided. Genetic counseling is extremely important for all patients with neurofibromatosis.

MUITIPLE ENDOCRINE NEOPLASIA TYPE 28 (MULTIPLE ENDOCRINE NEOPLASIA TYPE III; MULTIPLE MUCOSAL NEUROMA SYNDROME)

The multiple endocrine neoplasia (MEN) syndromes are a group of rare conditions characterized by tumors or hyperplasias of neuroendocrine tissues. For example, patients with MEN type 1 have benign tumors of the pancreatic islets. adrenal cortex. parathyroid glands. and pituitary giand. MEN type 2A. also known as Sipple syndrome. is characterized by the development of adrenal pheochromocytomas and medullary thyroid carcinoma. In addition to pheochromocytomas and medullary thyroid carcinoma. patients with MEN type 2B have mucosal neuromas that especially involve the oral mucous membranes. Because oral manifestations are most prominent in MEN type 2B. the remainder of the discussion is limited to this condition.

Similar to the other MEN syndromes. MEN type 2B is inherited as an autosomal dominant trait. However. 50% of cases are thought to represent spontaneous mutations. The condition is caused by a mutation of the RET protooncogene on chromosome 10. which has been detected in 95% of affected individuals.

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 (Figure 12-70). Small. pedunculated neuromas may be observable on the conjunctiva. eyelid margin. or cornea.

Oral mucosal neuromas are usually the first sign of the condition. These present as soft. painless papules or nodules that prineipally affect the lips and anterior tongue but also may be seen on the buccal mucosa. gingiva, and palate (Figure 12-71). Bilateral neuromas of the commissural mucosa are highly characteristic.

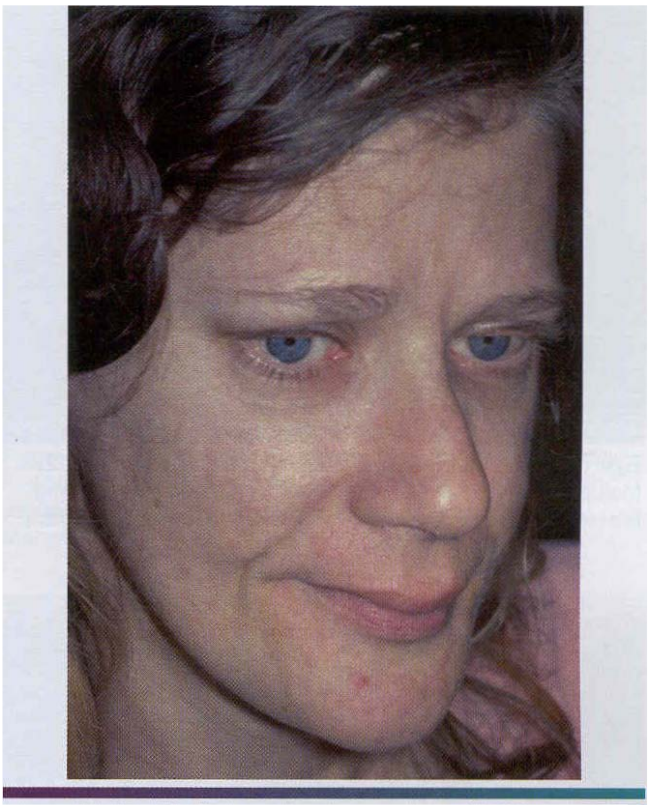


Figure 12-70 • Multiple endocrine neoplasia (MEN) type 2B. Note the narrow face and eversion of the upper eyelids.

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 catecholarnines, which result in symptoms such as profuse sweating. intractable diarrhea. headaches. flushing. heart palpitations. and severe hypertension.

The most significant aspect of this condition is the development of medullary carcinoma of the thyroid gland. which occurs in more than 90% of cases. This aggressive tumor arises from the parafollicular cells (C cells). which are responsible for calcitonin production. Medullary carcinoma most often is diagnosed in patients between the ages of 18 and 25. and it shows a marked propensity for metastasis. The average age at death from this neoplasm is 21 years.

Laboratory Values

If medullary carcinoma of the thyroid gland is present. serum or urinary levels of calcitonin arc elevated. An increase in calcitonin levels may herald the onset of the tumor. and calcitonin also can be monitored to detect

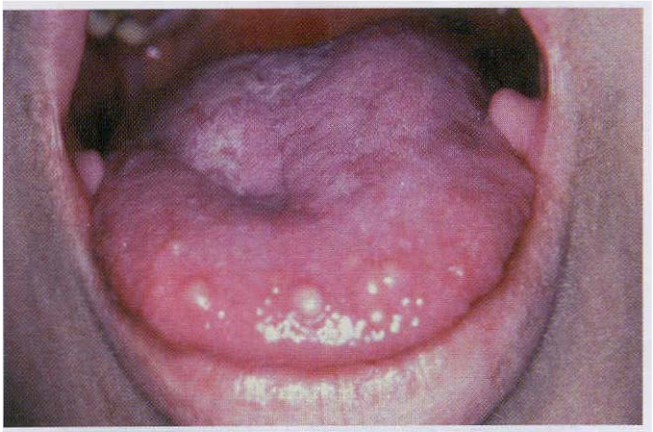


Figure 12-71 • Multiple endocrine neoplasia (MEN) type 2B. Multiple neuromas along the anterior margin of the tongue and bilaterally at the commissures. (Courtesy of Dr. Emmitt Costich.)

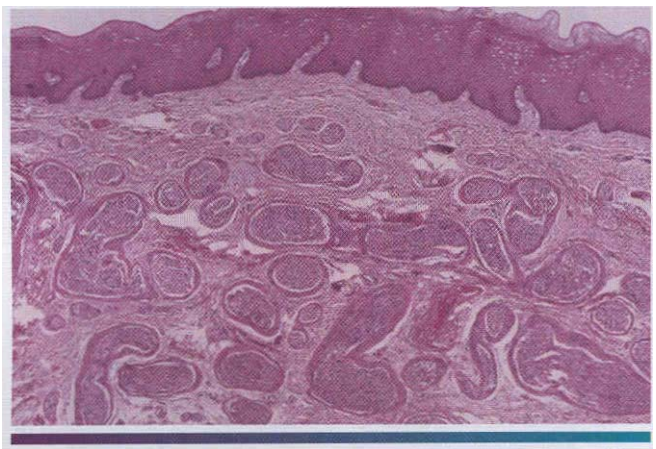


figure 12-72 • Multiple endocrine neoplasia (MEN) type 2B. low-power view of an oral mucosal neuroma showing marked hyperplasia of nerve bundles.

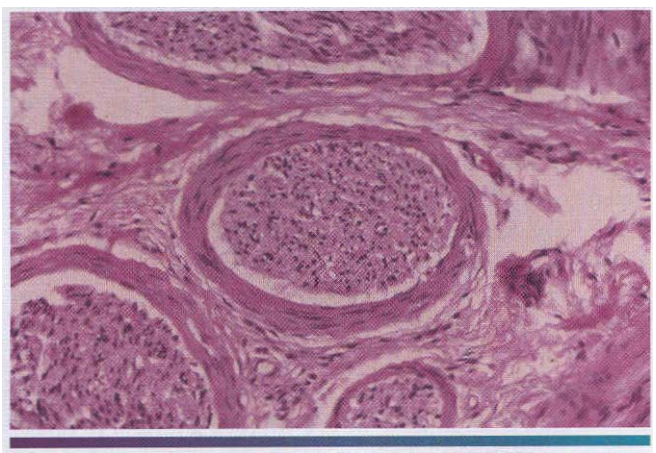


Figure 12-73 • Multiple endocrine neoplasia (MEN) type 2B. High-power view of the same neuroma as depicted in Figure 12-72. Note the prominent thickening of the perineurium.

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 (Figures 12-72 and 12-73). 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, given the serious nature of the medullary thyroid carcinoma. Some *investigators* advocate prophylactic *removal* of the thyroid gland at an early age because medullary carcinoma is almost certain to occur. Once it has developed, this tumor often exhibits an aggressive behavior with a poor prognosis. The patient also should be *observed* for the development of pheochromocytomas because they may 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. Melanotic (pigmented) neuroectodermal tumor of infancy is the preferred term.

Clinical and Radiographic Features

Melanotic neuroectodermal tumor of infancy almost always develops during the first year of life; some patients are affected at birth. There is a striking predilection for the maxilla: two thirds of all reported cases occur there. 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 (Figure 12-74). The tumor often destroys the underlying bone and may be associated with displacement of the developing teeth (Figure 12-75). In some instances, there may be an associated osteogenic reaction, which exhibits a "sun ray" radiographic pattern that can be mistaken for

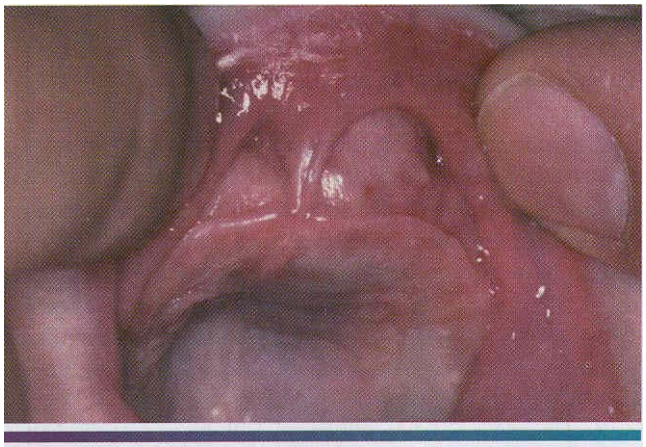


Figure 12-74 • Melanotic neuroectodermal tumor of infancy. Infant with an expansIle mass of the anterior maxilla. (From Steinberg B, Shuler C. Wilson S: Melanotic neuroectodermal tumor of infancy: evidence for multicentricity, *Oral Surg Oral Med Oral PathoI66:666-669, 1988.)*

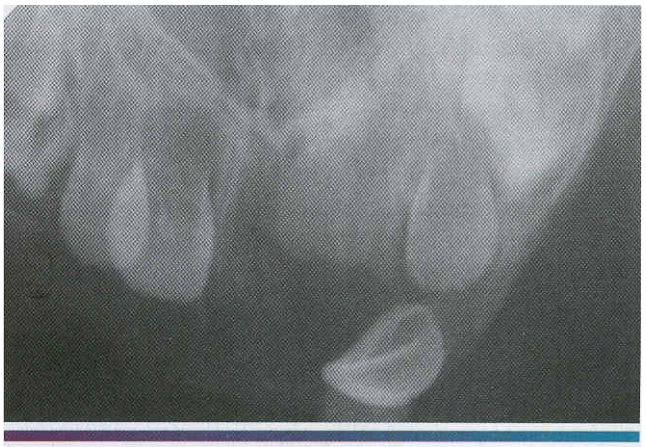


Figure 12-75 • Melanotic neuroectodermal tumor of infancy. Radiolucent destruction of the anterior maxilla associated with displacement of the developing teeth. (Courtesy of Dr. Ien Morrow.)

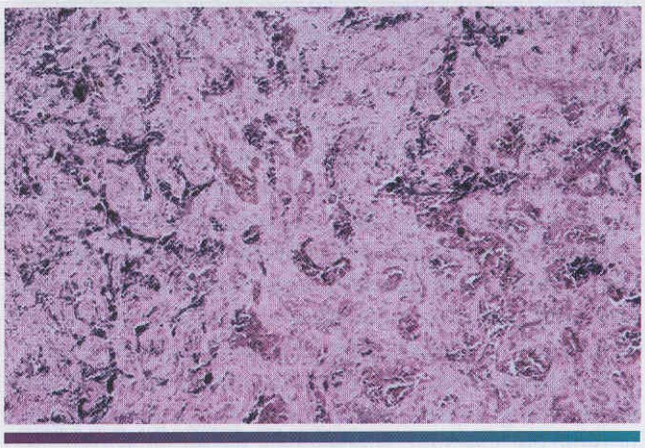


Figure 12-76 • Melanotic neuroectodermal tumor of infancy. low-power view showing nests of epithelioid cells within a fibrous stroma.

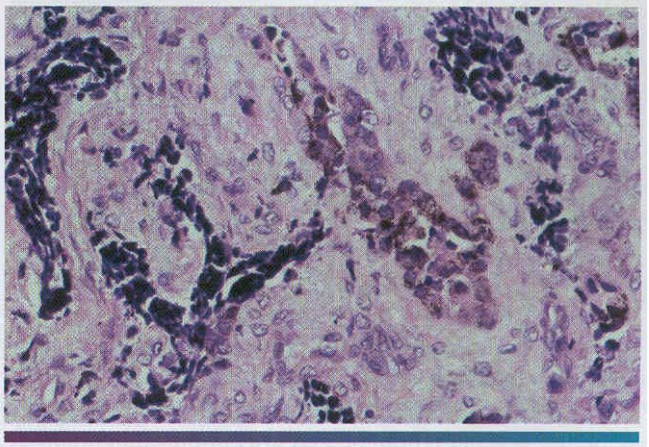


Figure 12-77 • Melanotic neuroectodermal tumor of infancy. High-power view of a tumor nest demonstrating two cell types: (') small, hyperchromatic round cells and (2) larger epithelioid cells with vesicular nuclei. Some stippled melanin pigment is also present.

osteosarcoma. The tumor also can occur at other locations; the skull, mandible, brain, and epididymis or testis **are the most frequent** extra maxillary **sites. There is no** apparent sex prcdllcction.

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** the tumor has been resected. This finding supports the **hypothesis of neural crest origin because other tumors** from this tissue (c.g.. pheochromocytoma, 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 (Figures i 2-76 and 12-77). The *alveo*lar 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.**

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 15% of cases. In addition, about 6% of reported cases have acted in a malignant fashion, resulting in metastasis and death. Although this 6% figure is probably high (because unusual malignant cases are more likely to be reported), it does underscore 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); those that develop in the temporal bone and middle ear are called jugulotympanic paragangliomas. jugulotympanic paragangliomas also are commonly known as glomus jugulare tumors, although some authors prefer to reserve this term only for those examples that arise from the jugular bulb and to use the term glomus tympanicum tumors for those that arise in the middle ear.

Clinical and Radiographic Features

Although paragangliomas are rare, the head and neck **area is the most common site for these lesions. The most** common paraganglioma is the carotid body tumor, which develops at the bifurcation of the internal and external carotid arteries. This tumor usually occurs in middle-aged adults. 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.**

Jugulotympanic paragangliomas are the second most common type of these tumors. They also are most frequent in middle-aged individuals but show a 2:1 female **predilection. The most common symptoms include dizzi**ness, tinnitus (a ringing or other noise in the ear), hearing **loss, and cranial nerve palsies. Other less common para**gangliomas of the head and neck include vagal, nasopharyngeal. laryngeal. and orbital paragangliomas.

Approximately 10% of affected patients have multifocal tumors. In 7% to 10% of cases. there is a family history of such tumors, with an autosomal dominant pattern of inheritance that is modified by genomic imprinting. In genomic imprinting. the gene is transmitted in a mendelian manner, but expression of that gene is determined by the sex of the transmitting parent. **Paternal transmission results in development of tumors** in the offspring. even if the father is clinically unaffected. Maternal transmission does not result in development of tumors in the offspring. although these children will carry the gene and have the ability to pass it down to subsequent **generations. Hereditary cases have an even greater** chance of being multicentric; about one third of affected **patients have more than one tumor.**

Histopathologic Features

The paraganglioma is characterized by round or polygonal epithelioid cells that are organized into nests or *Zellbailen* (Figure 12-78). 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. The tumor is typically vascular and may be surrounded by a thin fibrous capsule.

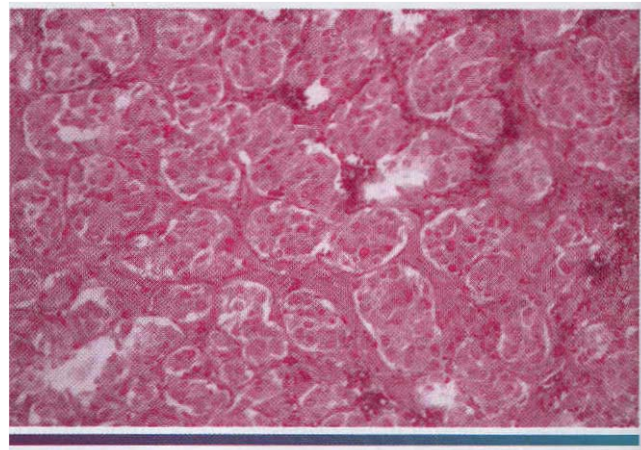


Figure 12-78 • Carotid body tumor. Nested arrangement of tumor cells.

Treatment and Prognosis

The treatment of paragangliomas may include surgery. radiario n therapy. Dr both, depending on the extent and location of the turner. 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. fDllowed by vascular grafting. Radiation therapy may be **used as adjunctive treatment or for** unresectable **carotid** body turnors,

Although most carotid body paragangliomas are benign and can be controlled with surgery and radiation therapy. vascular compltcatlons can lead to considerable surgical morbidity Dr mortality. In addirlon, 6% to 9% of carotid body paragangliomas metastasize. either to regional lymph nodes Dr distant sites. unfortunately, it is usually difficult tD predict which tumors will act in a malignant **fashion based on their microscopic features. Because such** metastases may develop many years after the orlgl nal dlagnosis is made, long-term follow-up is Important.

Because of their location near the base of the brain, [ugulotyrnparuc paragangliornas are more difficult to manage. Recent advances in both diagnostic radiology and neurosurgery have greatly improved the potential for resection of these turners. Radiation therapy may be used **in conjunction with surgery or as a primary treatment for** unresectable tumors. Stereotactic radiosurgery (gamma knife treatment) has recently shown promise in the management of primary Dr recurrent glomus jugulare tumors in patients who are poor surgical candidates. This technique allows the delivery ot a focused, large, single dose of radlatlon under stereotactic guidance.

GRANULAR CEIL 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 has long been debated. Originally. it was believed to be of skeletal muscle orlgin and was called the granular cell rnyoblas- **toma. *However,* more recent investigations do not sup-** port a muscle origln but point tD a derivation from Schwann cells (granular cell schwannorna) Dr neuroen- **docrine cells. At present, it seems best to use the non-committal term granular cell tumor for this lesion.**

Clinical Features

Granular cell tumors arc most common in the ora] cavity **and on the skin. The single most common site is the** tongue, which accounts for one third to one 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:I female predtlectlon.

The granular cell tumDr is typically an asyrnptomatlc sessile nodule that is usually 2 cm Dr less in size (Figures 12-79 and 12-80). The lesion often has been rioted for many months Dr years. although sornetirnes the patient is unaware of its presence. The mass is typically pink. but occasional granular ceil tumors appear yellow. The granular cell tumor is usually solitary, although multiple, sep- **arate tumors sometimes occur, especially in black patients.**

Histopathologic Features

The granular cell turner is composed of large. polygonal cells with abundant pale eosinophilic, granular cytoplasm and small, vesicular nuclei (Figure 12-81). The cells are usually arranged **in** sheets, but they also may be found **in** cords and nests. The cell borders often are

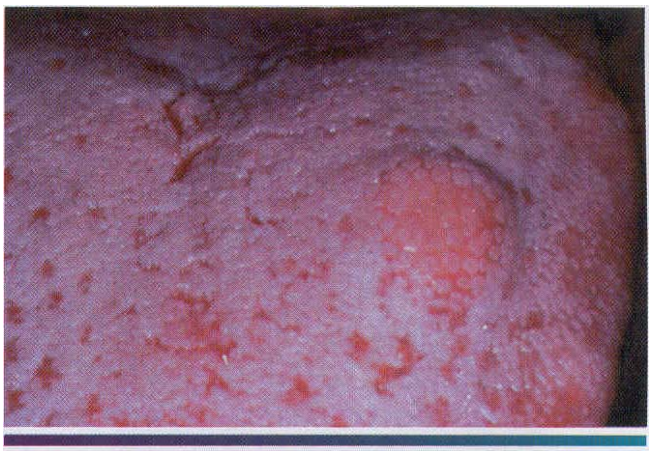


Figure 12-79 • Granular cell tumor. Submucosal nodule on the dorsum of the tongue.

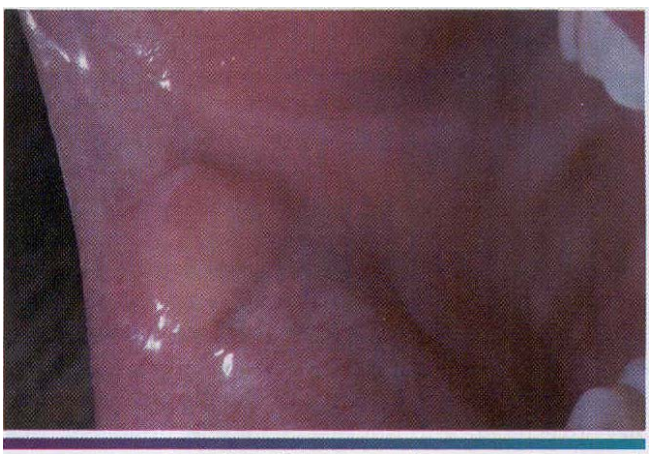


Figure 12-80 • Granular cell tumor. Nodular mass of the buccal mucosa near the commissure.

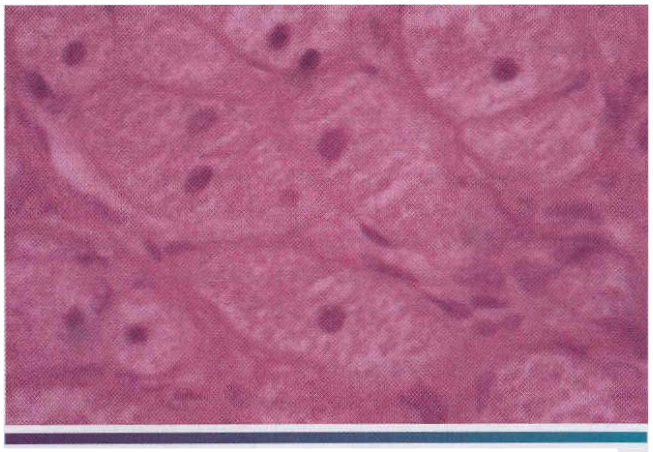


Figure 12-81 • Granular cell tumor. High-power view showing polygonal cells with abundant granular cytoplasm.

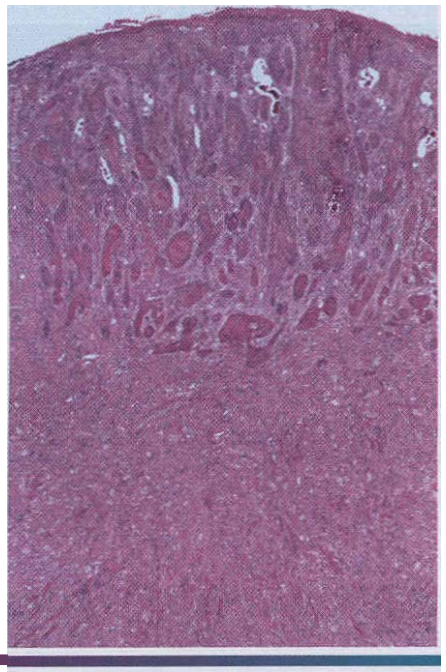


Figure 12-82 • Granular cell tumor. Marked pseudoepitheliomataus hyperplasia overlying a granular cell tumor. Such cases may easily be mistaken for squamous cell carcinoma.

indistinct, which results in a syncytial appearance. The lesion is not encapsulated and sometimes appears to infiltrate the adjacent connective tissues. Often, there appears to be a transition from normal adjacent skeletal muscle fibers to granular tumor 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.

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 (Figure 12-82). 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. 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 light 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.

Clinical Features

The congenital epulis typically appears as a pink-to-red, smooth-surfaced, polypoid mass on the alveolar ridge of a newborn infant (Figure 12-83). 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.

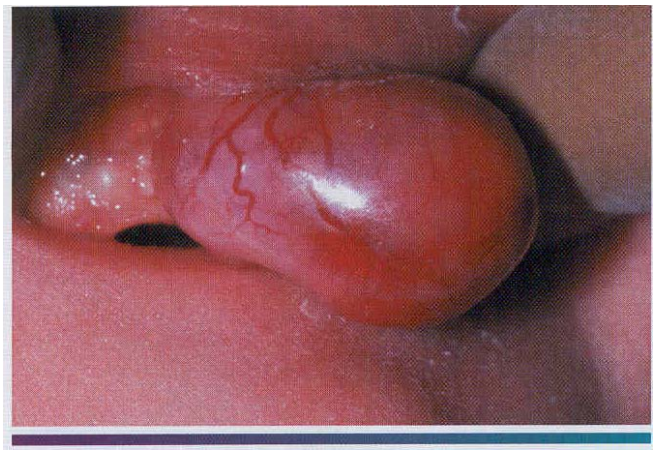


Figure 12-83 • Congenital epulis. Polypoid mass of the anterior maxillary alveolar ridge in a newborn infant.

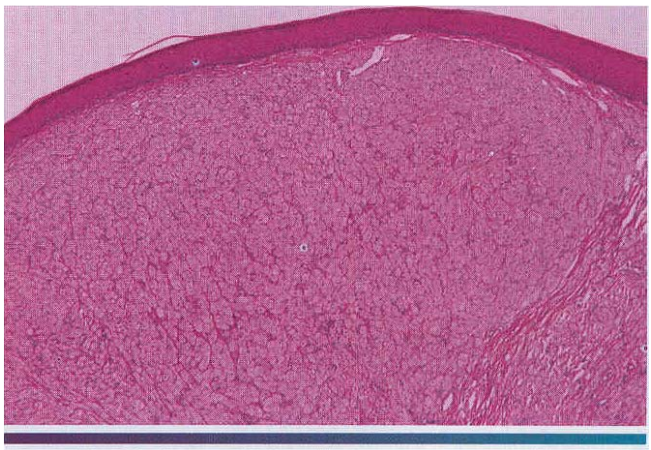


Figure 12-84 • Congenital epulis. Low-power photomicrograph showing a nodular tumor mass. Note the atrophy of the rete ridges.

Histopathologic Features

The congenital epulis is characterized by large, rounded cells with abundant granular, eosinophilic cytoplasm and round to oval, lightly basophilic nuclei (Figures 12-84 and 12-85). 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.

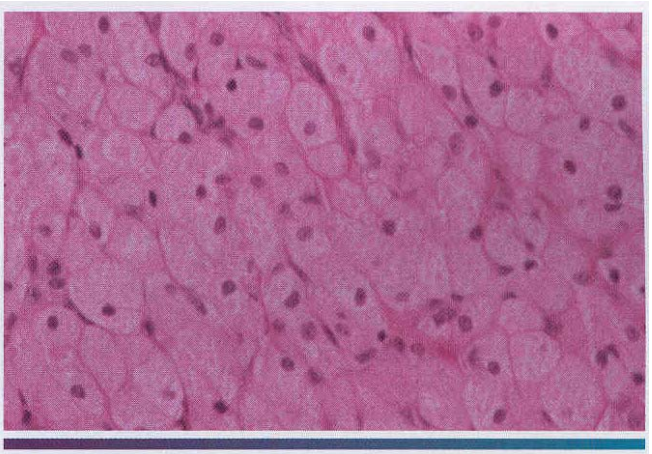


Figure 12-85 • Congenital epulis. High-power view of rounded cells with abundant granular cytoplasm.

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 (Figure 12-86).

HEMANGIOMA AND VASCULAR MALFORMATIONS

The term hemangioma has traditionally been used to describe a *variety* of developmental vascular anomalies. In recent years, great progress has been made in the classification and understanding of these vascular lesions. Currently, hemangiomas are considered to be benign tumors of infancy that are characterized by 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 hand, vascular malformations are structural anomalies of blood vessels without endothelial proliferation. 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, arterial) and according to hemodynamic features (low flow or high flow).

Clinical and Radiographic Features

Hemangioma. Hemangiomas are the most common tumors of infancy, occurring in 5% to 10% of 1-year-old children. They are much more common in females than males (ratio = 3:1), 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.

Fully developed 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

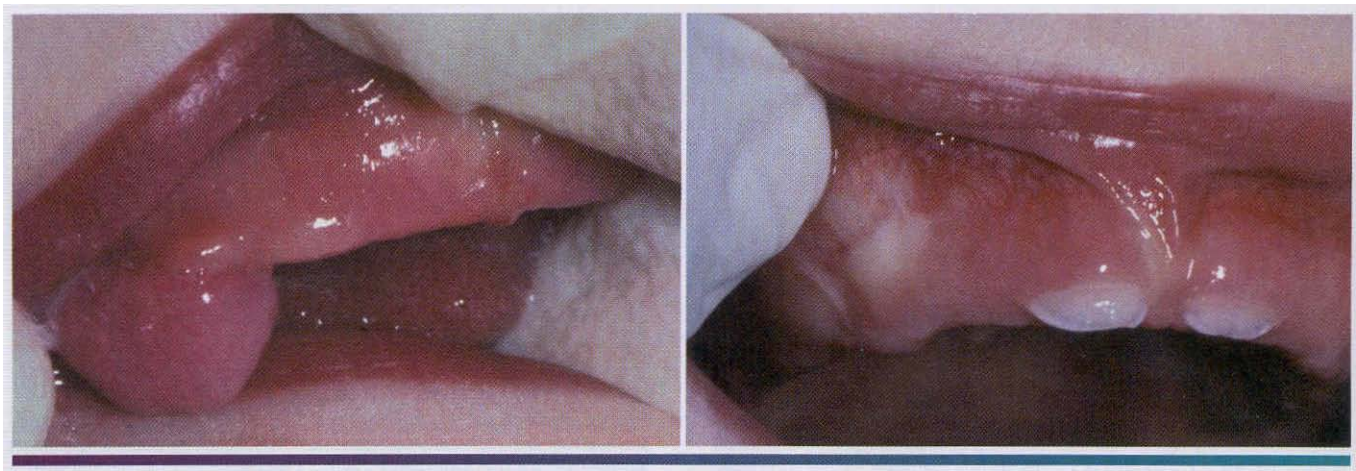


Figure 12-86 • Congenital epulis. A, Nodular mass on the maxillary alveolar ridge. Instead of being excised, the lesion was monitored clinically. B, Clinical appearance of the child at 1 year of age. The mass has disappeared without treatment. (Courtesy of Dr. Irwin Turner.)

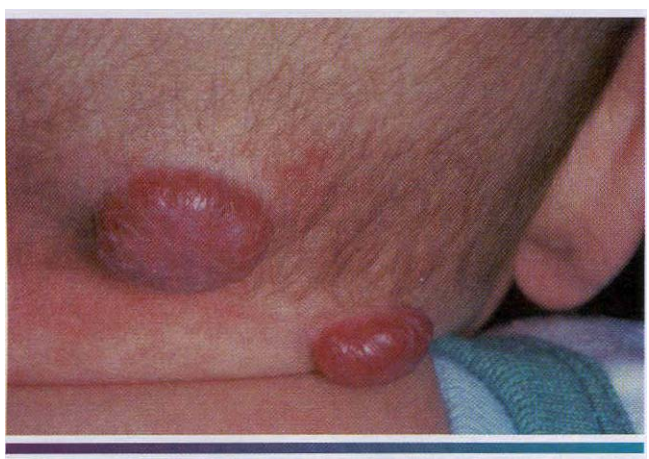


Figure 12-87 . Hemangioma. Infant with two red, nodular masses on the posterior scalp and neck ("strawberry" hemangioma).

growth. Superficial tumors of the skin appear raised and bosselated with a bright-red color (rstrawberrv' hemangioma) (Figure 12-87). 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 proliferative phase usually lasts for 6 to 10 months. after which the tumor slows in growth and begins to involute. 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. Atter 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.

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 mul**tiple cutaneous hemangiomas or large facial hemangiomas are at increased risk tor concomitant visceral** hemangiomas. Tumors in the neck and laryngeal region **can lead to airway obstruction.**

Kasabach-Merritl syndrome is a serious coagulopathy **that has been associated with large or extensive hemangiomas** in infants. This disorder is characterized by severe thrombocytopenia and hemorrhage because of platelet trapping within the tumor. The mortality rate is as high as 30% to 40%. Recent studies suggest that this complication may not be associated with the typical hemangioma. but a different vascular tumor known as a tufted hemangioma or kaposiform hemangioendothelioma.

***Vascular** maltormations*. **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% to I% of newborns. They are most common on the face. particularly along the distribution of the trigeminal nerve. In Sturge-**Weber angiomatosis. associated intracranial lesions are** present (see page 471). 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.

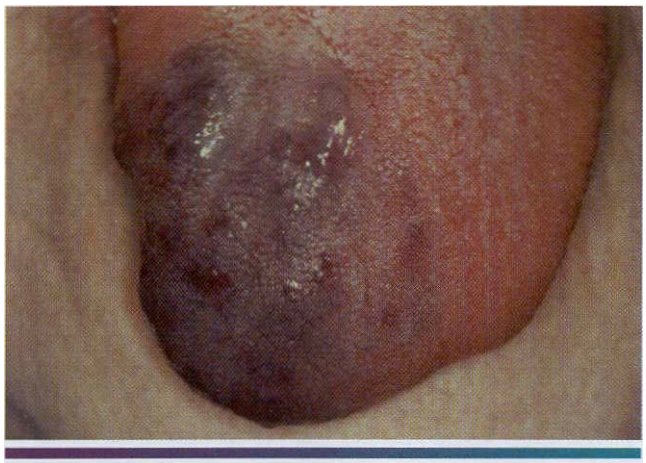


Figure 12-88 • Venous malformation. Bluish-purple mass of the anterior tongue.

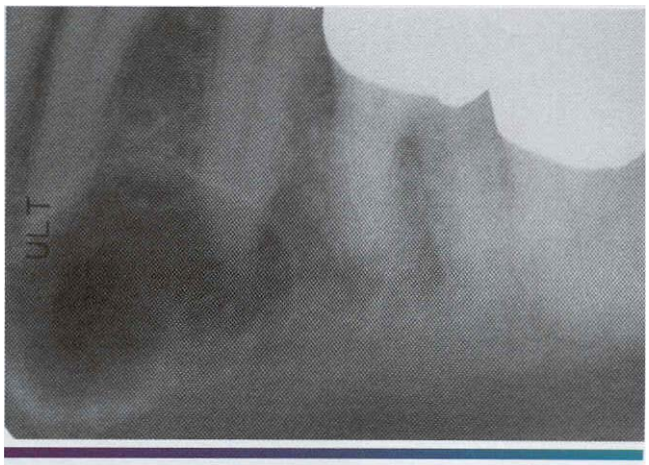


Figure 12-89 • Intrabony venous malformation. Well-circumscribed radiolucency that contains fine trabeculations.

They are present at birth. although they may not always be immediately apparent. Typically, venous malformations have a blue color and are easily compressible (Figure 12-88). 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 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 probably represent either venous or arteriovenous malformations. In the jaws, such lesions are detected most often in patients between 10 and 20 years of age. They are considerably more common in females than males and occur twice as often in the mandible as 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 (Figure 12-89). Large malformations may cause cortical expansion, and occasionally a "sunburst" radiographic pattern is produced (Figure 12-90). Angiography can be helpful in demonstrating the vascular nature of the lesion (Figure 12-91).

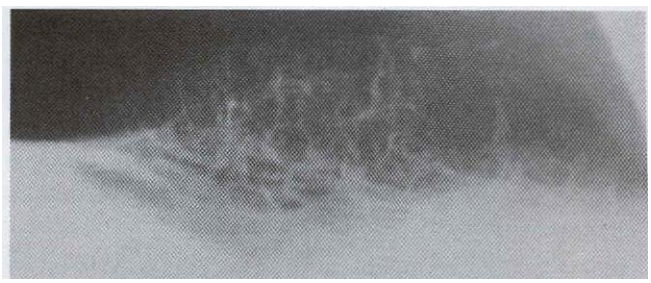


Figure 12-90 . Intrabony venous malformation. Occlusal radiograph demonstrating cortical destruction and a "sunburst" periosteal reaction resembling osteosarcoma.

Histopathologic Features

Early hemangiomas are characterized by numerous plump endothelial cells and often-indistinct vascular lumina (Figures 12-92 and 12-93). At this stage, such lesions often are known as *tuvenue* or *cellular* hemangiomas. Because of their cellular nature, these lesions also have been called juvenile hemangioendothelioma. although this term should be avoided because 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

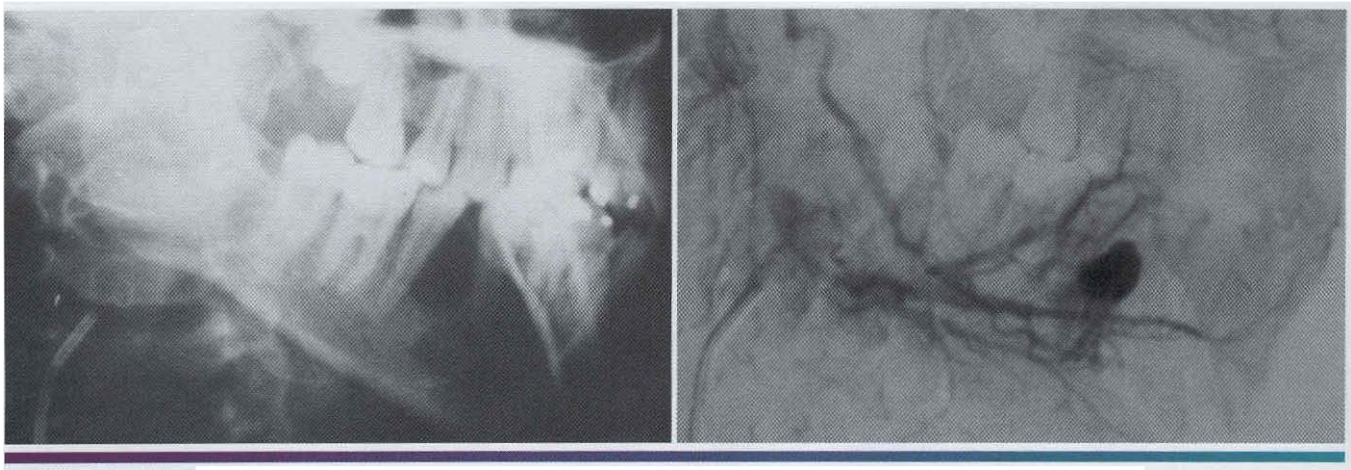


Figure 12-91 • Intrabony arteriovenous malformation. A, lateral jaw film showing a radiolucent lesion between the mandibular premolar roots. This was believed to be a lateral periodontal cyst, but pulsation was noted during palpation of the area. B, Subtraction angiogram demonstrating the vascular nature of the defect. (Courtesy of Dr. H.W. Allsup.)

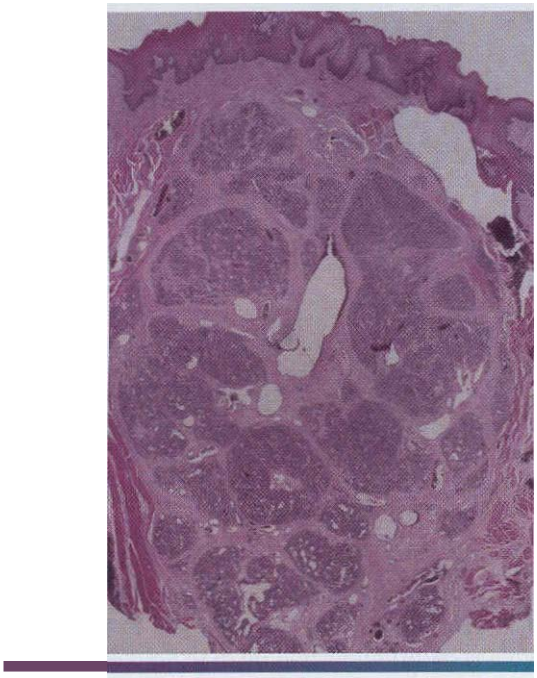


Figure 12-92 • Juvenile (cellular) hemangioma. Low-power photomicrograph showing a cellular mass of vascular endothelial cells arranged in lobular aggregates.

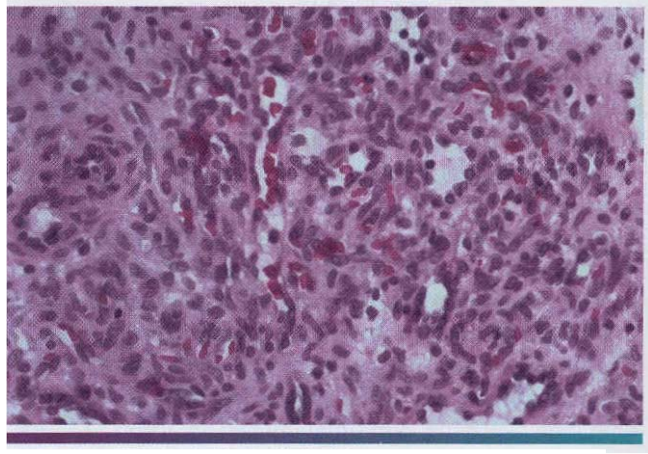


Figure 12-93 . Juvenile (cellular) hemangioma. High-power view showing a highly cellular endothelial proliferation forming occasional indistinct vascular lumina.

more evident (Figures 12-94 and 12-95). As the hemangioma undergoes involution, the vascular spaces become more dilated (cavernous) and widely spaced (Figure 12-96).

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 dilated vessels that resemble the cavernous stage of hemangioma. Because of these similar features, many vascular malformations are incorrectly categorized as hemangiomas. Arteriovenous malformations demonstrate a mixture of thick-walled arteries and veins, along with capillary vessels.

Treatment and Prognosis

Because most hemangiomas undergo involution, management often consists of "watchful neglect." It is important to educate parents that although rapid growth may be seen, regression will occur. Surgical resection is rarely warranted during infancy. For problematic or life-threatening hemangiomas, pharmacologic therapy may be indicated. Systemic corticosteroids may help to reduce

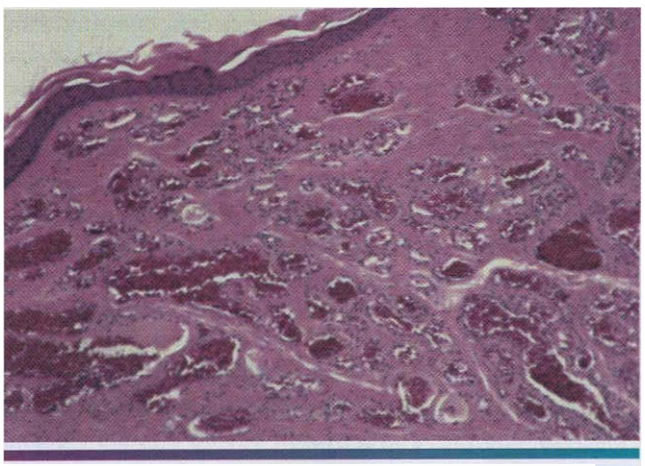


Figure 12-94 • Capillary hemangioma. Low-power view of a vascular tumor forming multiple capillary blood vessels.

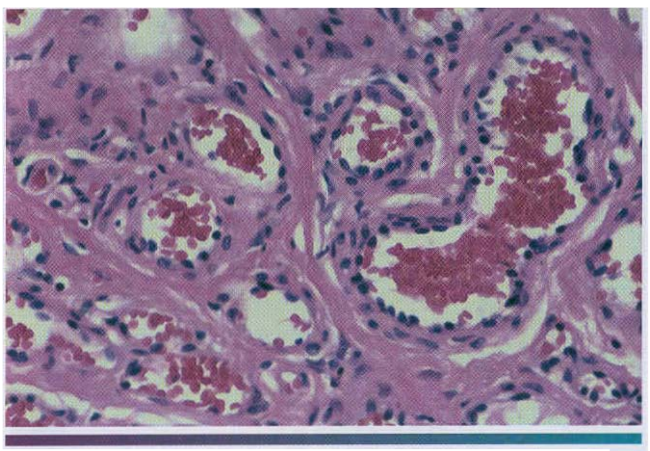


Figure 12-95 • Capillary hemangioma. High-power photomicrograph demonstrating well-formed capillary-sized vessels.

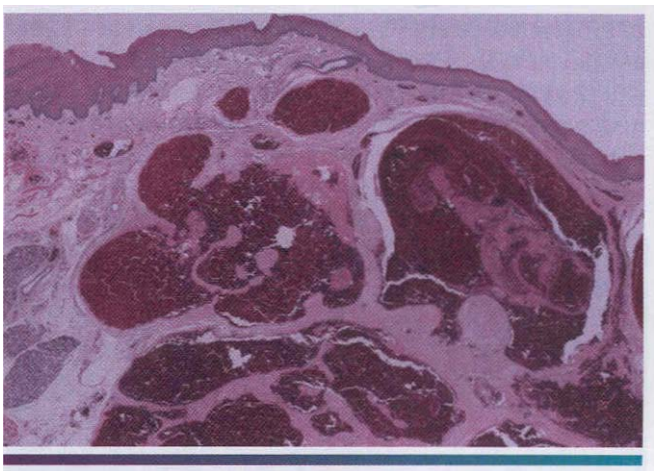


Figure 12-96 • Cavernous hemangioma. Low-power photomicrograph showing multiple large. dilated blood vessels.

the size of the lesion in some cases. Hemangiomas that are unresponsive to corticosteroids can be treated with tnterferon-u-za.

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. directly into the lesion in order 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 in order 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 ANGIOMATOSIS (ENCEPHALOTRIGEMINAL ANGIOMATOSIS; STURGE-WEBER SYNDROME)

Sturge-Weber angiomatosis is a rare. nonhereditary developmental condition that is characterized by **a hamartomatous vascular proliferation involving the tis-**sues of the brain and face. It is believed to be caused by **the persistence of a vascular plexus around the cephalic** portion of the neural tube. This plexus develops during the sixth week of intrauterine development but normally **undergoes regression during the ninth week.**

Clinical and Radiographic Features

Patients with Sturge-Weber angiomatosis 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. Not all patients with facial port wine nevi have sturge-weber angiomatosis. in one study of patients with facial port wine nevi. only slightly more than 10% had sturge-weber angiomatosis. Only patients with involvement along the distribution of the ophthalmic branch of the trigeminal nerve were at risk for the full condition (Figures i 2-9 7 and 12-98).

in addition to the facial port wine nevus. affected individuals also have leptomeningeal angiomas that overlie the ipsilateral cerebral cortex. This meningeal angiomatosis is usually associated with a convulsive disorder and often results in mental retardation or contralateral hemiplegia. Radiographs of the skull may reveal gyriform "tramline" calcifications on the affected side (Figure 12-99). Ocular involvement may be manifested by glaucoma and vascular malformations of the conjunctiva, episclera, choroid. and retina.

Intraoral involvement in Sturge-Weber **angiomatosis** is common, resulting in hypervascular changes to the ipsilateral mucosa (Figure 12-100). 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,

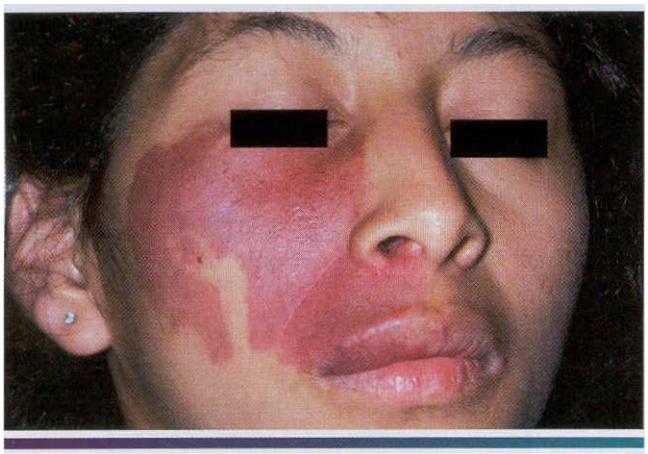


Figure 12-97 • Port wine stain. Nevus flammeus of the malar area in a patient without Sturge-weber **angiomatosis. Unless the vascular lesion includes the region innervated by the ophthalmic branch of the trigeminal nerve, usually the patient does not have central nervous system involvement.**

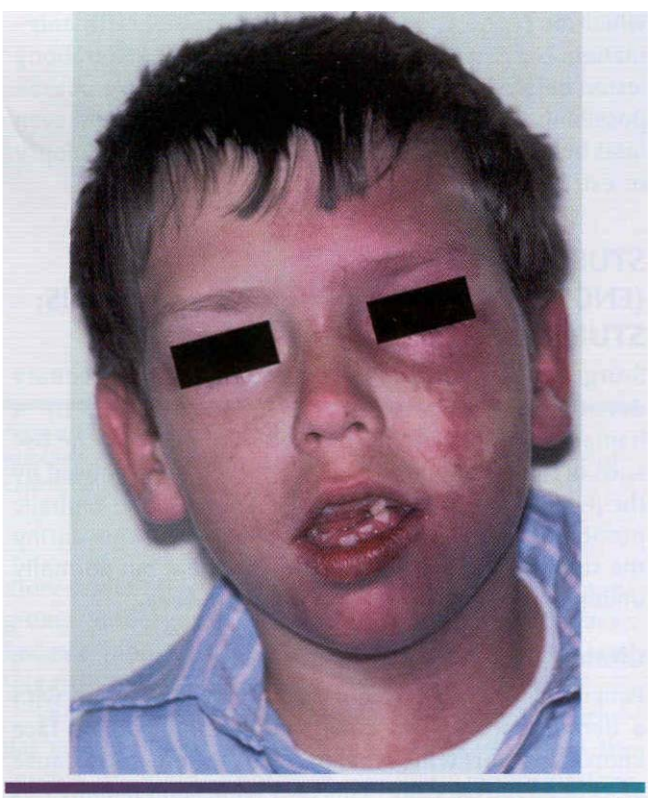


Figure 12-98 • Sturge-Weber angiomatosis. Port wine stain of the left face, including involvement along the ophthalmic branch of the trigeminal nerve. The patient also was mentally retarded and had a seizure disorder.

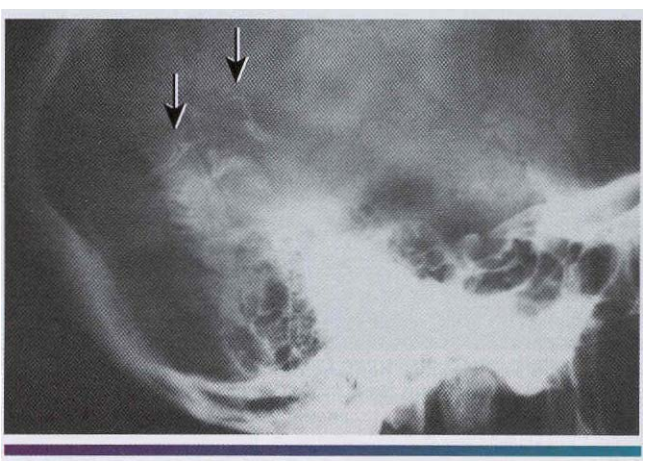


Figure 12-99 • Sturge-Weber angiomatosis. Skull film showing "tramline" calcifications *(arrows)*. (Courtesy of Dr. Reg Munden.)

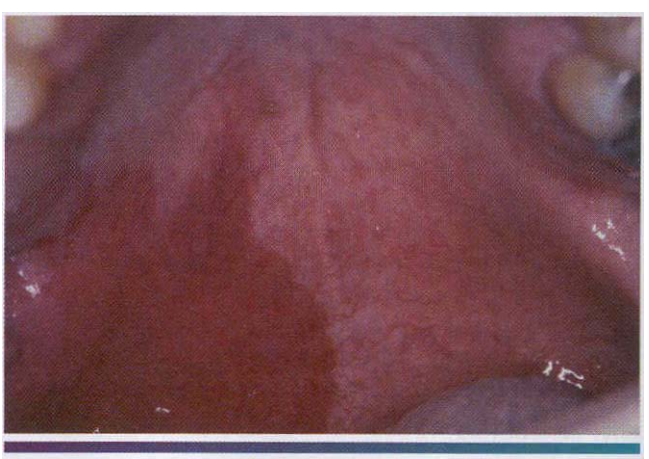


Figure 12-100 . Sturge-Weber angiomatosis. Unilateral vascular involvement of the soft palate.

phenytoin 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 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 angiomatosis depend on the nature and severity of the possible clinical features. Usually, facial port wine nevi can be improved by using the newer flashlarnp-pulsed dye lasers. Neurosurgical removal of angiomatous meningeal lesions may be necessary in some cases.

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 severe 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 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 ltkelv, 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 will show extension into the paranasal sinuses, orbits. or middle cranial fossa. Invasion into the oral cavity or cheek rarely has been reported. Computed tornographtc ICT) 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 (Figure 12-101). Angiograms can be used to confirm the vascular nature of the lesion (Figure 12-102).

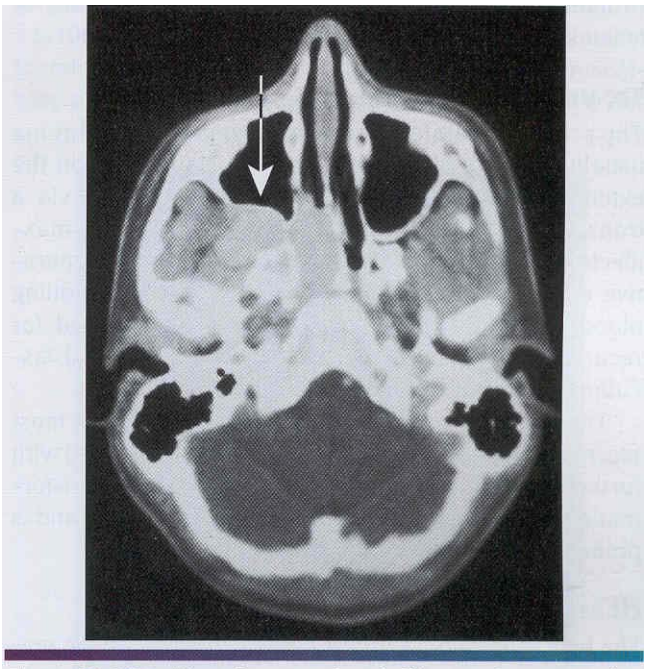


Figure 12-101 • Nasopharyngeal angiofibroma. A contrasted computed tomography (CT) scan showing a tumor of the nasopharynx and pterygopalatine fossa, with characteristic anterior bowing of the posterior wall of the right maxillary sinus *(arrow)*. (Courtesy of Dr. Pamela Van Tassel.)

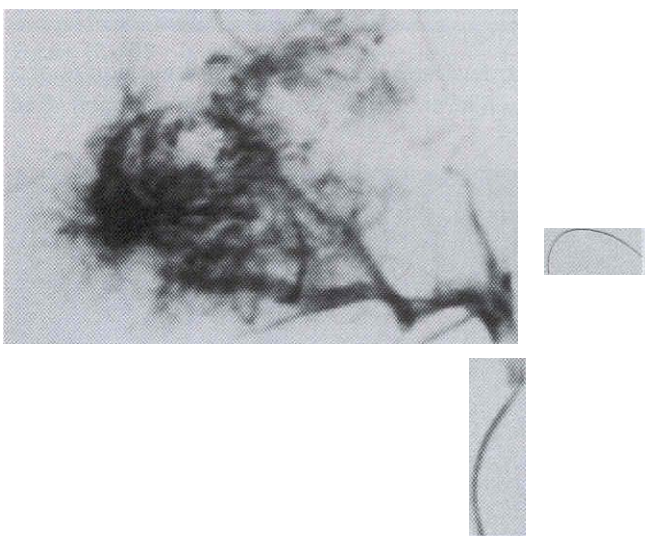


Figure 12-102 • Nasopharyngeal angiofibroma. A digital subtraction angiogram of the external carotid artery showing the intense vascular blush of the tumor, (Courtesy of Dr. Pamela *Van* TasseL)

Histopathologic Features

The nasopharyngeal angiofibroma consists of dense fibrous connective tissue that contains numerous dilated, thin-walled blood vessels of variable size (Figure 12-103). Typically, the vascular component is more prominent at the periphery of the tumor, especially in lesions from younger patients.

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 a transpalatal approach, Le Fort I approach, medial maxillectomy, or a midfacial degloving procedure. Preoperative embolization of the tumor is helpful in controlling blood loss. Radiation therapy is usually reserved for recurrent lesions and extensive tumors with unusual vascular supplies or intracranial extension.

The recurrence rate varies from 20% to 40% in most recent studies. Such recurrences are usually retreated with further surgery or radiation therapy. Malignant transformation into fibrosarcoma has rarely been reported and is probably associated with prior radiation therapy.

HEMANGIOPERICYTOMA

The hemangiopericytoma is a rare neoplasm that is presumably derived from pericytes, (i.e., cells whose processes encircle the endothelial cells of capillaries). However, some investigators have recently questioned the existence of the hemangiopericytoma, suggesting that many cases actually represent examples of the so-called solitary fibrous tumor. Hemangiopericytomas have been reported most commonly in the lower extremity, and approximately 16% of cases occur in the head and neck region.

Clinical Features

Hemangiopericytomas are seen primarily in adults and are rare in children. There is no sex predilection. The tumor is usually a slow-growing, painless mass. Superficial lesions may demonstrate vascular pigmentation.

A distinctive form of hemangiopericytoma (hemangiopericytoma-like tumor) occurs in the nasal cavity and paranasal sinuses. The lesion primarily occurs in middle-aged and older adults and usually results in symptoms of nasal obstruction or epistaxis.

Histopathologic Features

The hemangiopericytoma is usually fairly well circumscribed and exhibits tightly packed cells that surround endothelium-lined vascular channels. The cells are haphazardly arranged and demonstrate round to ovoid nuclei and indistinct cytoplasmic borders. Occasionally, they are spindle-shaped. The blood vessels often show irregular branching, which results in a characteristic "staghorn" and "antlerlike" appearance (Figure 12-104). A reticulin stain demonstrates a dense reticulin network that surrounds the vessels and individual tumor cells.

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 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.

Treatment and Prognosis

For hemangiopericytomas with a benign histopathologic appearance, local excision is the treatment of choice. More extensive surgery is required for tumors with malignant characteristics. Most tumors appear to behave in a benign fashion, although the reported metastatic rate has

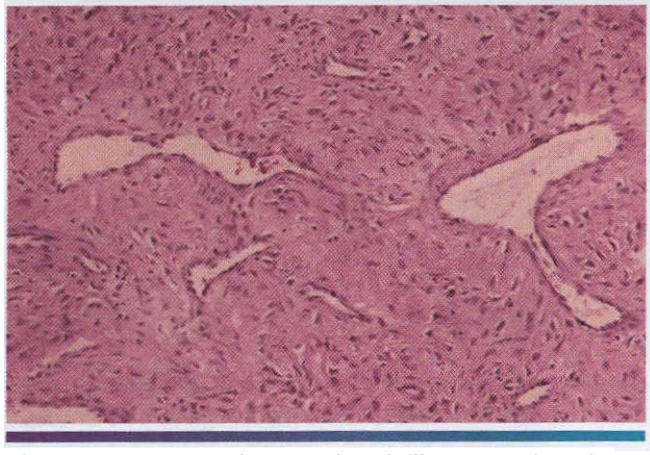


Figure 12-103 • **Nasopharyngeal angiofibroma.** Moderately cellular fibrous connective tissue with prominent blood vessels.

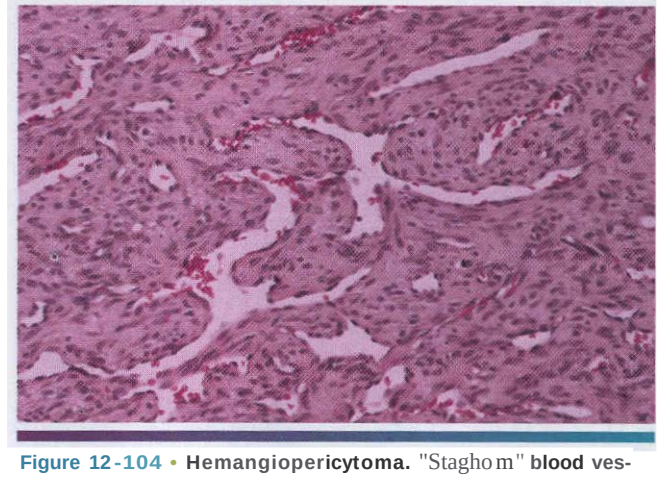


Figure 12-104 • **Hemangiopericytoma.** "Staghorn" blood vessels with surrounding pericytes.

varied from 11.7% to 56.5%. Local recurrence has been reported in up to 40% to 50% of cases and may develop many years after the primary excision. Recurrence is a worrisome sign because many of these tumors eventually metastasize.

Studies show that patients with sinonasal hemangiopericytomas have a better prognosis than do those with tumors at other sites. Because of its different clinical features, microscopic appearance, and prognosis, some authors prefer to designate it as a hemangiopericytoma-like tumor because they believe that it represents a related but separate entity.

LYMPHANGIOMA

Lymphangiomas are benign, hamartomatous tumors of lymphatic vessels. It is doubtful that they are true neoplasms; instead, they most likely represent developmental malformations that arise from sequestrations of lymphatic tissue that do not communicate normally with the rest of the lymphatic system.

There are three types of lymphangioma:

1. Lymphangioma simplex <capillary lymphangioma), which consists of small, capillary-sized vessels
2. Cavernous lymphangioma, which is composed of larger, dilated lymphatic vessels
3. Cystic lymphangioma <Cystic hygroma), which exhibits large, macroscopic cystic spaces

However, this classification system is rather arbitrary because all three sizes of vessels often can be found within the same lesion.

The subtypes are probably variants of the same pathologic process, and the size of the vessels may depend on the nature of the surrounding tissues. Cystic lymphangiomas most often occur in the neck and axilla, where the loose adjacent connective tissues allow for more expansion of the vessels. Cavernous lymphangiomas are more frequent in the mouth, where the denser surrounding connective tissue and skeletal muscle limit vessel expansion.

Clinical Features

Lymphangiomas have a marked predilection for the head and neck, which accounts for 50% to 75% of all cases (Figure 12-105). About half of all lesions are noted at birth, and around 90% develop by 2 years of age.

Cervical lymphangiomas 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 lymphangiomas extend into the mediastinum or upward into the oral cavity. Such tumors can become massive and can measure 15 ern or greater in size. Rapid tumor 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 lymphangiomas may occur at various sites but are most frequent on the anterior two thirds of the tongue, where they often result in macroglossia (Figures 12-106 and 12-107). Usually, the tumor is superficial in location and demonstrates a pebbly surface that resembles a cluster of translucent vesicles. The surface has

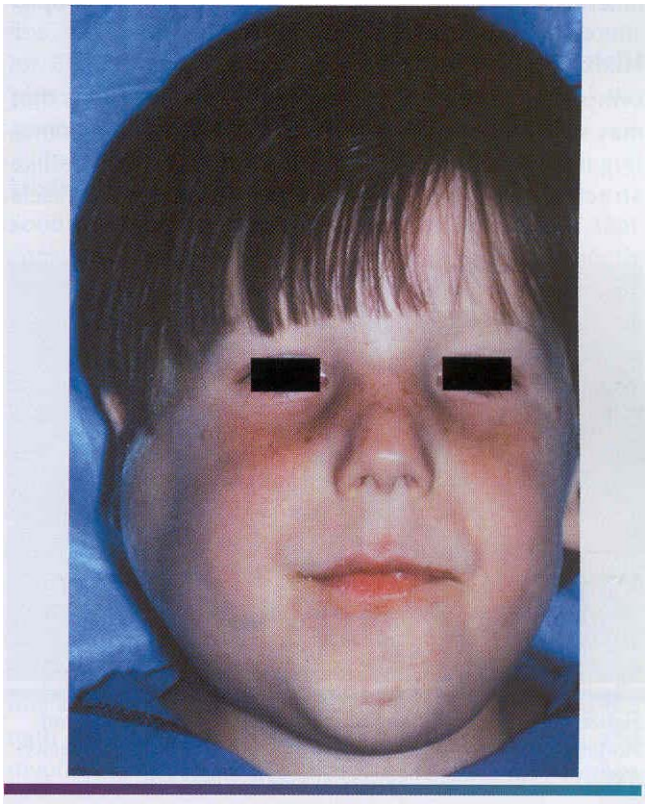


Figure 12-105 • Lymphangioma. Young boy with a cystic hygroma primarily involving the right side of the face. (Courtesy of Dr. Frank Kendrick)

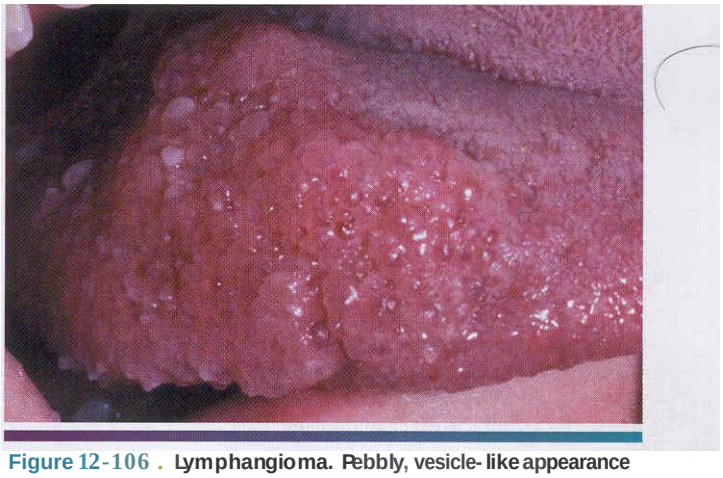


Figure 12-106 . Lymphangioma. Pebbly, vesicle-like appearance of a tumor of the right lateral tongue.

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 lymphangiomas 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

Lymphangiomas are composed of lymphatic vessels that may show marked dilatation (cavernous lymphangioma) (Figures 12-108 and 12-109) or macroscopic cystlike structures (cystic hygroma) (Figure 12-110). 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 contain red blood cells. which creates uncertainty as to whether they are lymphatic or blood vessels. Although many of these llkcly represent secondary hemorrhage into a lymphatic vessel, some actually may be examples of mixed lymphangioma and hemangioma.

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.

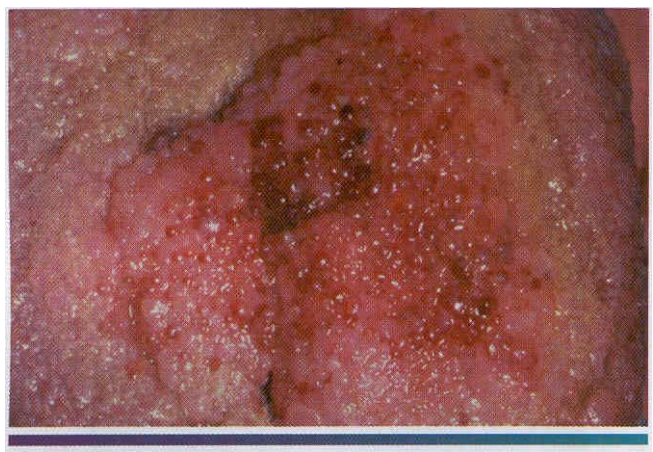


Figure 12-107 • lymphangioma. Dorsal tongue lesion demonstrating a purple color, which can be caused by secondary hemorrhage or an associated hemangiomatous component.

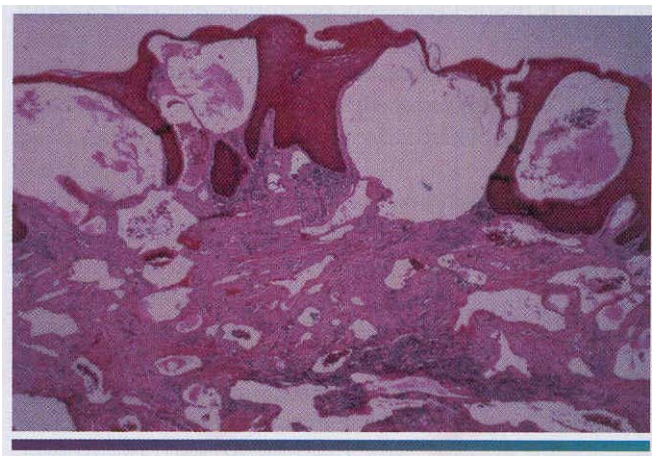


Figure 12-108. Cavernous lymphangioma. Lesion of the tongue showing dilated lymphatic vessels beneath the epithelium and in the deeper connective tissues.

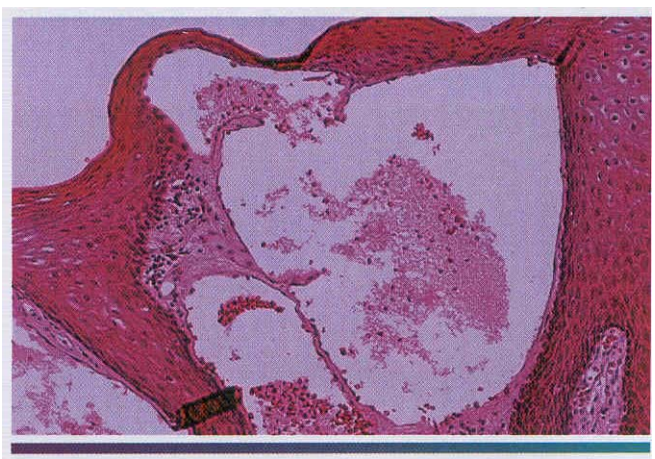


Figure 12-109 • Cavernous lymphangioma. High-power photomicrograph showing dilated, lymph-filled vessels immediately below the atrophic surface epithelium.

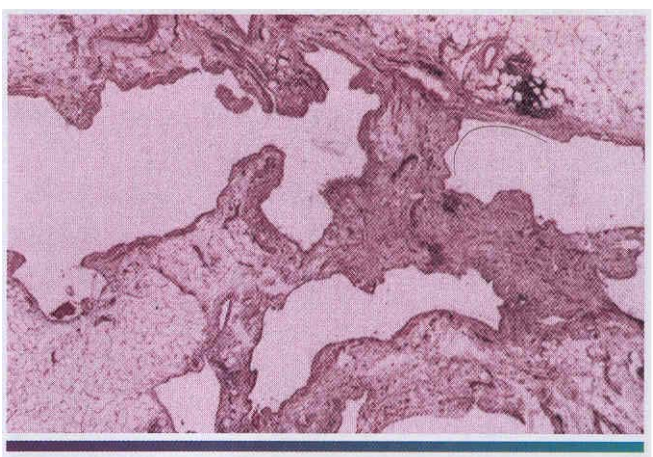


Figure 12-110. Cystic hygroma. Lesion from the neck showing markedly dilated lymphatic vessels.

Treatment and Prognosis

The treatment of lymphangiomas usually consists of surgical excision, although total removal may not be possible **in all cases because of large size or involvement of vital structures, Recurrence is common, especially for cavernous lymphangiomas of the oral cavity, because of their infiltrative nature. Some clinicians do not recommend** treatment for nonenlarging lymphangiomas of the tongue because of the difficulty in removal and high recurrence rate. Cystic lymphangiomas of the cervical region are **often well circumscribed and have a lower rate of recurrence, Spontaneous regression of lymphangiomas is rare.**

Unfortunately, lymphangiomas do not respond to **sclerosing agents as do hemangiomas, However, some** success with sclerosant therapy for unresectable lymphangiomas has been reported using OK-432, a **lyophilized incubation mixture of a low-virulent strain of** *Streptococcus pyogenes* with penicillin G potassium, which has lost its streptolysin S-producing ability.

The prognosis is good for most patients, although **large tumors of the neck or tongue may result in airway** obstruction and death. The mortality rate for cystic **hygromas ranges from 2% to 5% in most series.**

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:

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.**

Clinical and Radiographic Features

The oral leiomyoma can occur at any age and is usually a slow-growing firm mucosal nodule (Figure 12-111). 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 exam**ples 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 (Figures 12-112 and 12-113). 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 (Figure 12-114). 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 (Figure 12-115), and myofibrils may be demonstrated by Mallory's phospho-

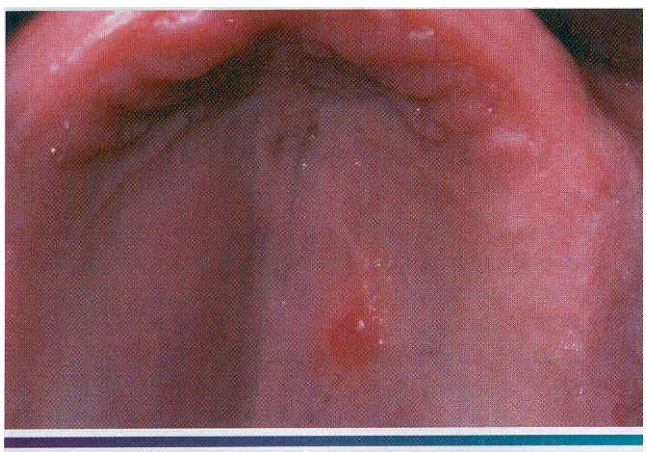


Figure 12-111 • Leiomyoma. Small, pinkish-red nodule on the posterior hard palate lateral to the midline.

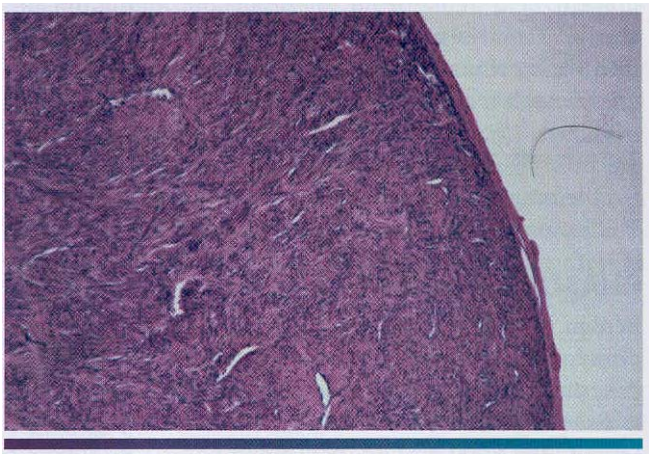


Figure 12-112 • Leiomyoma. Low-power view showing a well-circumscribed cellular mass of spindle-shaped smooth muscle cells.

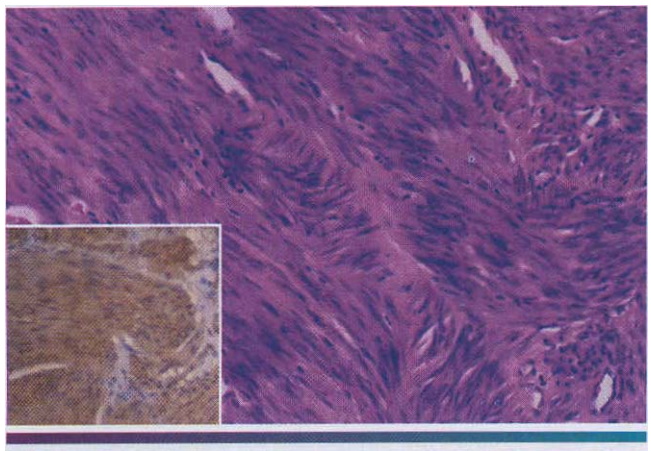


Figure 12-113 • Leiomyoma. High-power view showing spindle-shaped cells with blunt-ended nuclei. Immunohistochemical analysis shows strong positivity for smooth muscle actin *(inset)*.

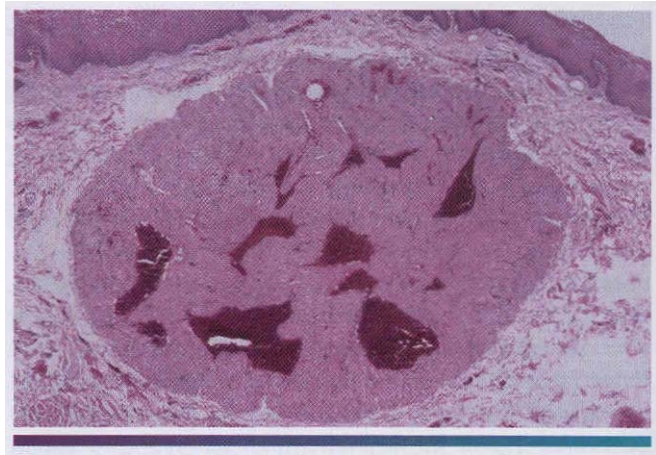


Figure 12-114 . Angiomyoma. Well-circumscribed tumor exhibiting prominent blood vessels surrounded by smooth muscle.

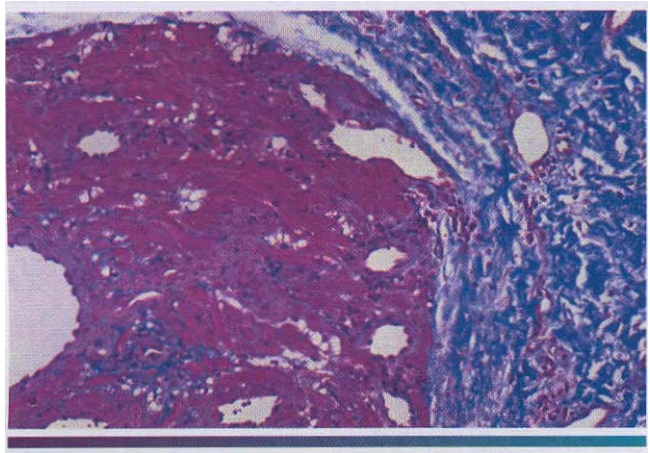


Figure 12-115 • Angiomyoma. Masson trichrome stain demonstrating bundles of smooth muscle *(red)* with adjacent normal collagen *(blue)*.

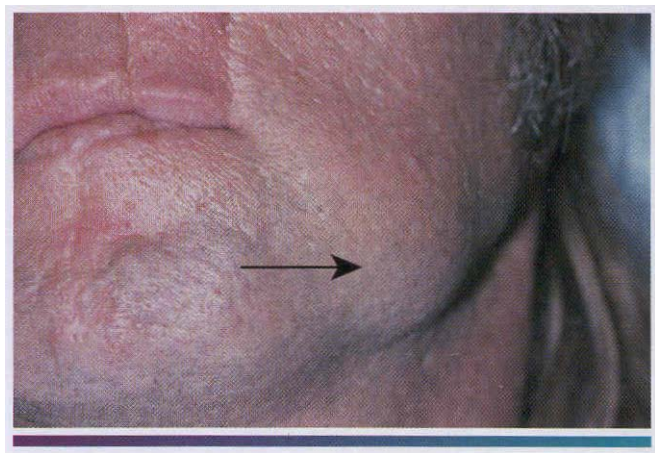


Figure 12-116 • Adult rhabdomyoma. Nodular mass *(arrow)* in the left cheek. (Courtesy of Dr; Craig Iillie.)

tungstic actd-hernatoxylin (PTAH) stain. Immunohistochemical 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 lciornyornas arc 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 (sec page 657). 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. adult and fetal rhabdomyomas.

Clinical Features

Adult rhabdomyomas. Adult rhabdomyomas of the head and neck occur primarily in middle-aged and older patients, with about 70% 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 to many centimeters before discovery (Figures 12-116 and 12-117). 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. Occasional cases are multicentric. with separate, distinct tumors at different sites.

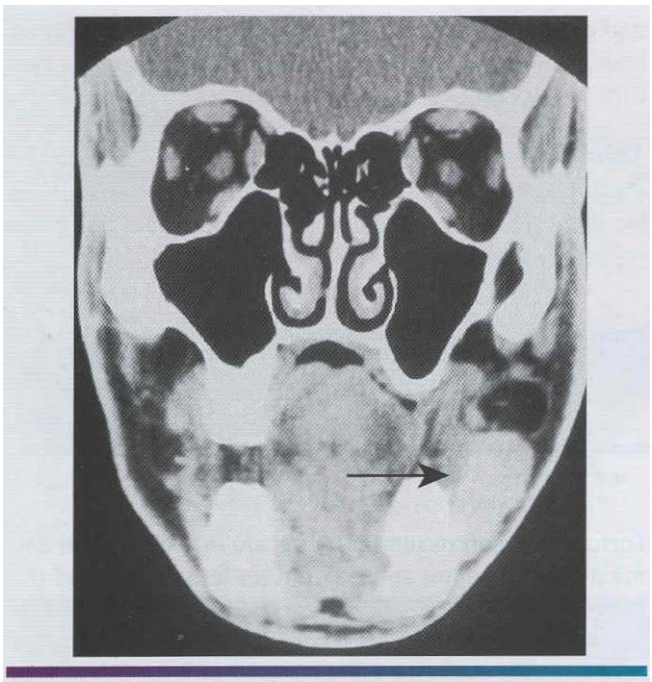


Figure 12-117 • Adult rhabdomyoma. Computed tomography (CT) scan of the same tumor depicted in Figure 12-116. Note the mass *(arrow)* lateral to the left body of the mandible. (Courtesy of Dr. Craig Little.)

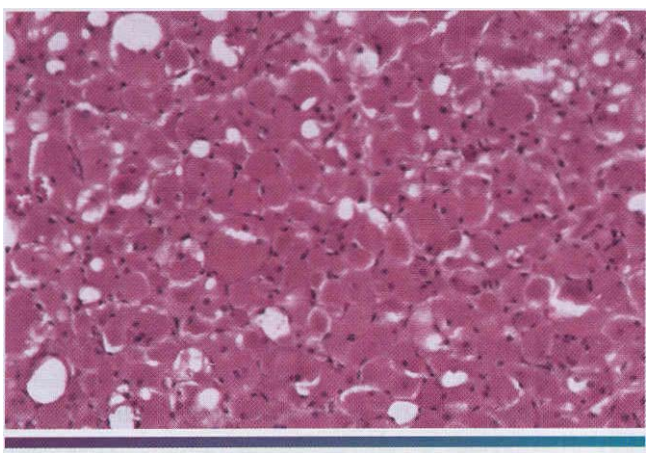


Figure 12-118 • Adult rhabdomyoma. Medium-power view showing a uniform tumor composed of rounded and polygonal cells with focal vacuolization.

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.

Histopathologic Features

Adult rhabdomyomas. The adult rhabdomyoma is composed of well-circumscribed lobules of large, polygonal cells, which exhibit abundant granular, eosinophilic cytoplasm (Figure 12-118). 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 (Figure 12-119).

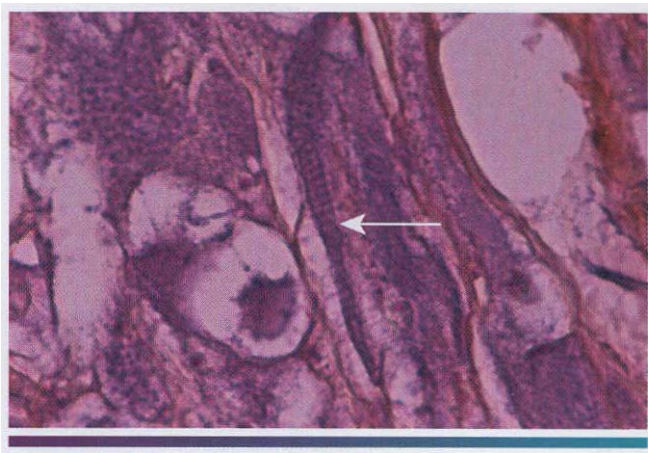


Figure 12-119 • Adult rhabdomyoma. Phosphotungstic acid-hematoxylin (PTAH) stain that demonstrates focal cross striations in some cells *(arrow)*.

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 is uncommon but has been reported in a few cases.

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 chortstomas. 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 choristorna 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-

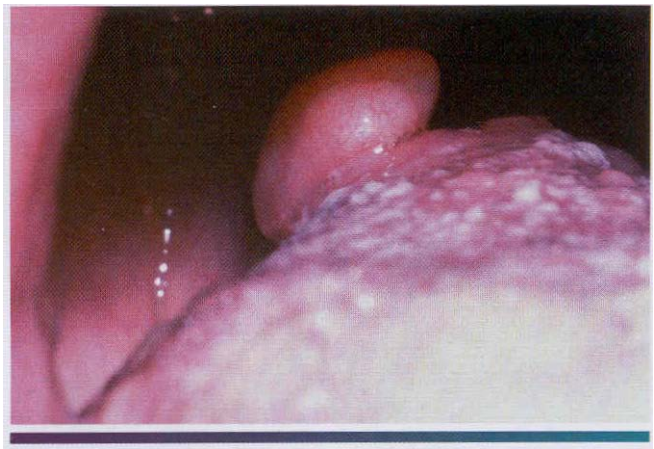


Figure 12-120 • Osseous choristoma. Hard pedunculated nodule on the posterior dorsum of the tongue. (Courtesy of Dr. Michael Meyrowitz.)

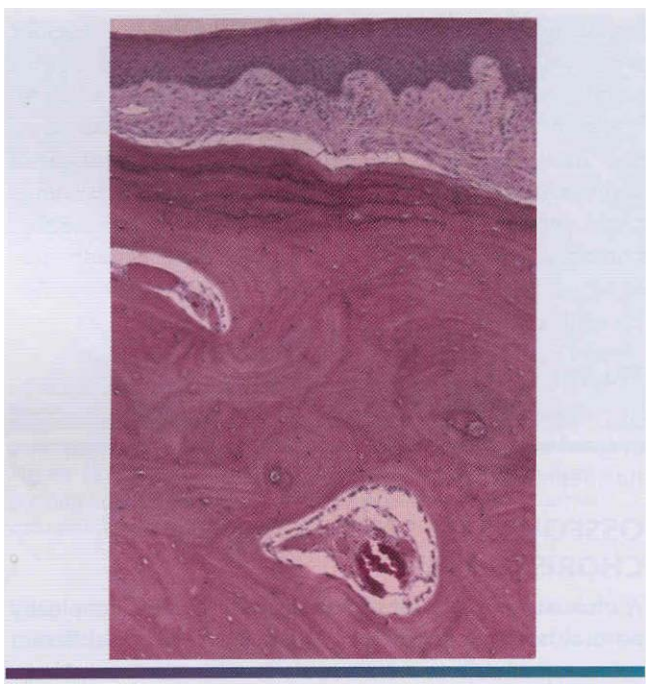


Figure 12-121 • Osseous choristoma. Mass of dense lamellar bone beneath the surface epithelium.

surfaced. sessile or pedunculated nodule between 0.5 and 2.0 cm In diameter (Figure 12-120). Many patients are unaware of the lesion. although some complain of gagging or dysphagia. More than 70% of osseous chertstornas have been reported in women.

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 (Figure 12-121). 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% 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 (Figure 12-122). They can 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. (They can occur at any age but are most common in young adults and children.

Histopathologic Features

Well-differentiated fibrosarcomas consist of fascicles of spindle-shaped cells that classically form a "herringbone" pattern (Figure 12- 123). The cells often show little variation in size and shape, although variable numbers of mitotic figures can usually be identified. In 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. Poorly differentiated tumors tend to produce less collagen than do well-differentiated tumors.

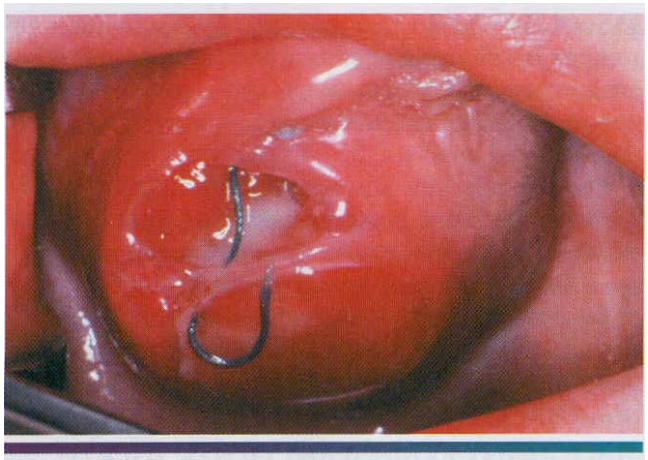


Figure 12-122 • Fibrosarcoma. Child with a large mass of the hard palate and maxillary alveolar ridge. (Courtesy of Dr. John McDonald.)

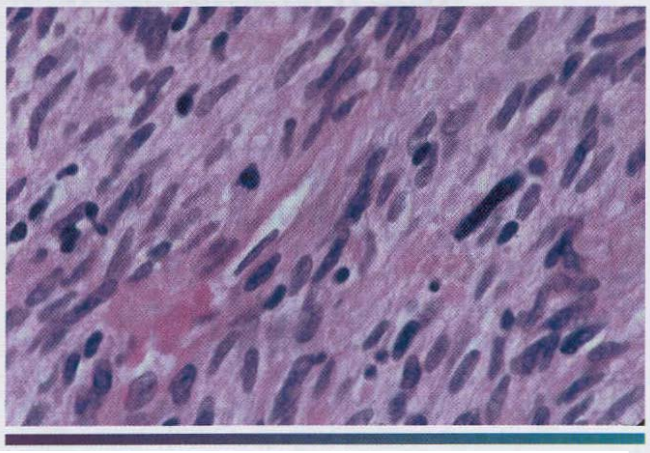


Figure 12-123 • Fibrosarcoma. Cellular mass of spindle-shaped cells demonstrating mild pleomorphism.

Treatment and Prognosis

The treatment of choice is usually surgical excrsron, **including a wide margin of adjacent normal tissue.** Recurrence is noted in about half of cases, and s-year **survival rates range from 40% to 70%.**

MALIGNANT FIBROUS HISTIOCYTOMA

The malignant fibrous histiocytoma is a sarcoma with both fibroblastic and histiocytic features. Although this **term was first introduced in 1963. this tumor is now considered to be the most common soft tissue sarcoma in adults. The extremities and retroperitoneum are the most common sites; lesions in the head and neck are rare.**

Clinical Features

The malignant fibrous histiocytoma is primarily a tumor of older age groups. The most common complaint is an expanding mass that may or may not be painful or ulcerated. **Tumors of the nasal cavity and paranasal sinuses** produce obstructive symptoms.

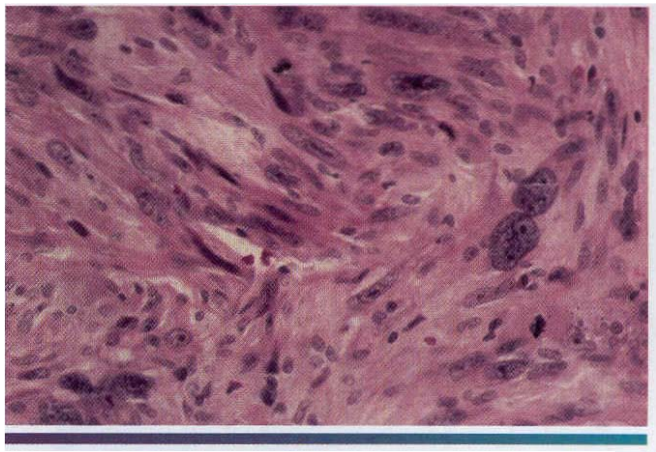


Figure 12-124 • Malignant fibrous histiocytoma. Spindle cell neoplasm demonstrating marked pleomorphism of some of the larger histiocytic cells.

Histopathologic Features

Several histopathologic subtypes have been described. The storiform-pleomorphic type is the most common. This pattern is characterized by short fascicles of plump spindle cells arranged in a storiform pattern, admixed with areas of pleomorphic giant cells (Figure 12-124). Myxoid. giant cell. inflammatory. and angiomatoid subtypes also are recognized.

Treatment and Prognosis

The malignant fibrous histiocytoma is an aggressive tumor that is usually treated by radical surgical resection. Approximately 40% of patients have local recurrences. **A similar percentage develops metastases, usu**ally within 2 years of the initial diagnosis. The survival **rate for patients with oral tumors appears to be worse** than for those with tumors at other body sites.

LIPOSARCOMA

The liposarcoma is a malignant neoplasm of fatty origin. **It is the second most common soft tissue sarcoma of adult** life, after the malignant fibrous histiocytoma. The most **common sites are the thigh, retroperitoneum, and** inguinal region. Liposarcomas of the head and neck are **rare.**

Clinical Features

Liposarcomas are primarily seen in adults. with peak prevalence between the ages of 40 and 60. 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 oral location is the cheek, which accounts for slightly over half of all cases. The tongue is the second most common intraoral site.

Histopathologic Features

There are five histopathologic categories of liposarcoma:

1. Myxoid
2. Round cell
3. Well-differentiated
4. Dedifferentiated
5. Pleomorphic

The most common of these is the myxoid liposarcoma, which accounts for nearly 50% of all cases. These tumors 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.

Well-differentiated liposarcomas resemble benign lipomas but demonstrate scattered lipoblasts with atypical hyperchromatic nuclei (Figure 12-125).

Dedifferentiated liposarcomas are characterized by the combination of well-differentiated liposarcoma with poorly differentiated, nonlipogenic sarcomatous changes. These features may coexist in the same neoplasm, or the dedifferentiated changes may develop in a recurrent tumor or metastasis.

Pleomorphic liposarcomas exhibit extreme cellular pleomorphism and bizarre giant cells.

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 round cell and pleomorphic liposarcomas is much worse than for myxoid and well-differentiated tumors.

Because relatively few tumors from the mouth have been reported, it is difficult to estimate accurately the survival rate for oral liposarcomas. However, the prognosis for oral tumors is generally more favorable because of the predominance of myxoid and well-differentiated subtypes, and because most tumors are small when diagnosed.

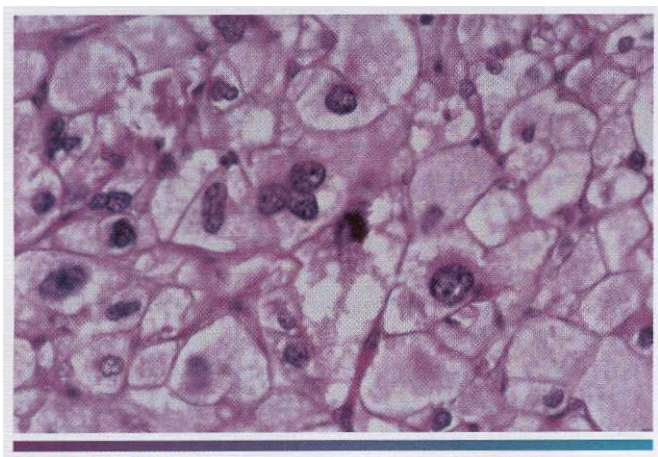


Figure 12-125 • Liposarcoma. High-power view showing vacuolated lipoblasts with pleomorphic nuclei.

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 10% of all soft tissue sarcomas, with about half of such cases occurring in patients with neurofibromatosis (see page 458). The lesion is most common on the proximal portions of the extremities and the trunk; it is rare 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 Figures 12-67 and 12-68 on page 460). 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 Figure 12-69 on page 460). However, these cells are frequently 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 is often difficult, especially in the absence of neurofibromatosis. Positive immunostaining for S-100 protein is a helpful clue, but this is found in only about 50% of all cases.

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 poor, especially in patients with neurofibromatosis. One study showed the 5-year **survival rate in individuals with neurofibromatosis** to be only 16%. For other patients, the 5-year survival **rate was 53%; this rate dropped to 38% at 10 years. However, another study showed an overall 5-year survival rate of 44%, which was nearly equal** between both groups.

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.** Traditionally, it is believed to arise from the olfactory epithelium.

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 and occurs over a wide age range. The tumor arises high in the nasal** cavity close to the cribriform plate. From here it may extend into the adjacent paranasal sinuses (especially the ethmoid sinus), the orbit, and the anterior cranial fossa (Figure 12-126). The most common symptoms are **nasal obstruction, epistaxis, and pain.**

Histopathologic Features

Olfactory neuroblastomas consist of small, round to ovoid basophilic cells that are arranged in sheets and lobules (Figure 12-127). 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 may approach 90%. The 5-year survival rate drops to 70% 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 has improved to **nearly 50% or even greater with newer treatment regimens. Death is usually a result of local recurrence; metastasis occurs in approximately 20% to 37% of cases.**

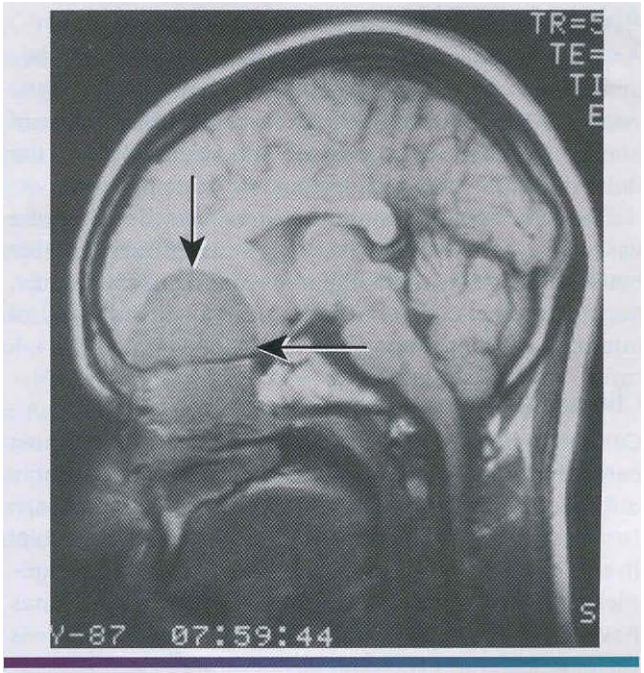


Figure 12-126 . Olfactory neuroblastoma. A T1-weighted sagittal magnetic resonance image (MRI) showing a tumor filling the superior nasal cavity and ethmoid sinus, with extension into the anterior cranial fossa *(arrows).* (Courtesy of Dr. Pamela Van Tassel.)

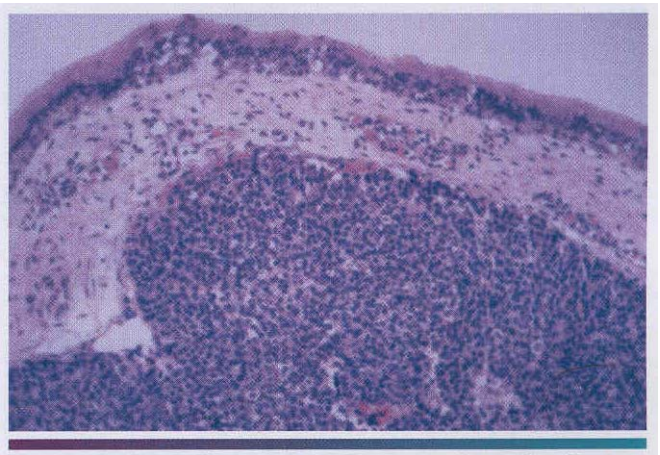


Figure 12-127 . Olfactory neuroblastoma. Sheet of small, basophilic cells adjacent to the sinonasal epithelium *(top).*

ANGIOSARCOMA

Angiosarcoma is a rare malignancy of vascular endothelium, which may arise from either blood or lymphatic vessels. More than SO% 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 arc considered to be of intermediate malignancy.**

Clinical Features

Cutaneous angiosarcomas of the head and neck are most common in elderly 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. Many examples** appear multifocal in nature. Oral angiosarcomas have been reported in various locations: the mandible is the most common site (Figure 12- 128).

Histopathologic Features

Angiosarcoma is characterized by an infiltrative proliferation of endothelium-lined biood vessels that form an anastomosing network (Figure 12- 129). The endothelial cells appear hyperchromatic and atypicai: they often **tend to pile up within the vascular lumina. Increased** rnttotlc activity may be seen.

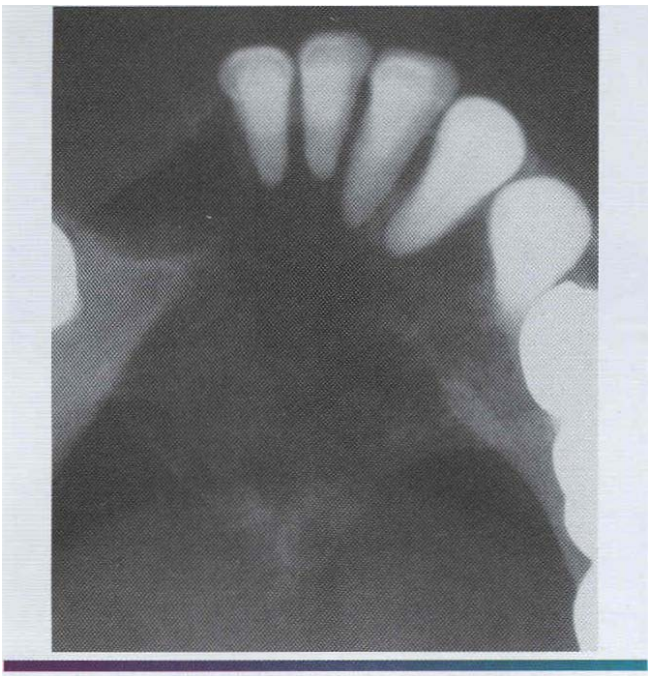


Figure 12-128 • Angiosarcoma. Occlusal radiograph showing a destructive, expansile **tumor of the anterior mandible. (Courtesy** of Dr. W.e. Jdhn.)

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 21 %.

KAPOSI'S SARCOMA

Kaposi's sarcoma is an unusual vascular neoplasm that was first described in 1872 by Moritz Kaposi (correct pronunciation. *KOP-osh-ee).* Before the advent of the acquired immunodeficiency syndrome (AIDS) epidemic, **it was a rare tumor; however, since the early 1980s it has** become quite common because of its propensity to develop in individuals infected by human immunodeficiency virus (HIV).

Current evidence suggests that Kaposi's sarcoma is caused by human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus). The lesion most likely arises from endothelial cells, with some evidence of lymphatic **origin. Four clinical presentations are recognized:**

1. Classic
2. Endemic (Afrlcan)
3. **Iatrogenic immunosuppression-associated**
4. AiDS-reiated

The first three forms are discussed here: AIDS-related **Kaposi's sarcoma is covered in the section on HIV disease** (see page 242).

Clinical Features

Classic type. **Classic (chronic) Kaposi's sarcoma is** primarily a disease of late adult life, and about 90% of cases occur in men. It mostly affects individuals of italian. lewish, or Slavic ancestry. Multiple bluish-purple macules and plaques are present on the skin of the lower extremities (Figure 12- 130). These lesions grow slowly over many years and develop into painless tumor nod-

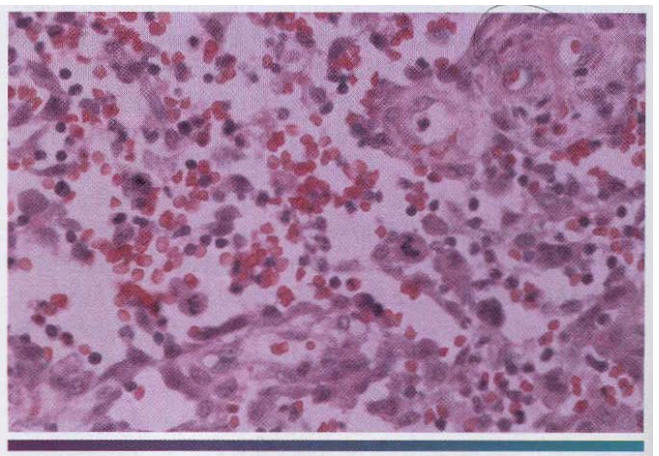


Figure 12-129 • Angiosarcoma. Sinusoidal vascular spaces lined by pleomorphic endothelial cells.

ules. Oral lesions are rare and most frequently involve the palate. Some earlier reports suggested that patients with classic Kaposi's sarcoma had an increased prevalence of lymphoreticular malignancies, but more recent analysis has questioned any significant association.

Endemic type. Endemic Kaposi's sarcoma in Africa has been divided into four subtypes:

1. A benign nodular type, similar to classic Kaposi's sarcoma
2. An aggressive or infiltrative type, characterized by progressive development of locally invasive lesions that involve the underlying soft tissues and bone
3. A florid form, characterized by rapidly progressive and Widely disseminated. aggressive lesions with frequent visceral involvement
4. A unique lymphadenopathic type, which occurs primarily in young black children and exhibits generalized, rapidly growing tumors of the lymph nodes, occasional visceral organ lesions, and sparse skin involvement

Iatrogenic type. Iatrogenic immunosuppression-associated Kaposi's sarcoma most often occurs in recipients of organ transplants. It affects 0.4 % of renal transplant patients, usually several months to a few years after the transplant. It is probably related to the loss of cellular immunity. which occurs as a result of immunosuppressive drugs. Like classic Kaposi's sarcoma, iatrogenic immunosuppression-associated cases are most common in individuals of Italian, Jewish, and Slavic ancestry. However, the disease may run a more aggressive course.

Histopathologic Features

Kaposi's sarcoma typically evolves through three stages:

1. Patch (macular)
2. Plaque
3. Nodular

The patch stage is characterized by a proliferation of miniature vessels. 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 (Figures 12-131 and 12-132). However, numerous extravasated erythrocytes are present, and slitlike vascular spaces may be discerned.

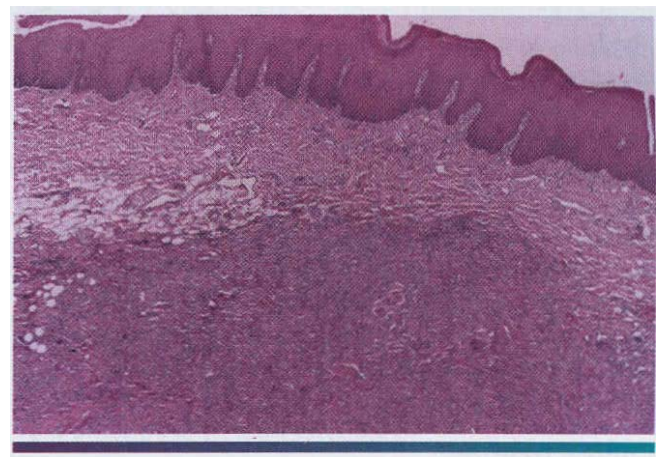


Figure 12-131 • Kaposi's sarcoma. Low-power photomicrograph showing a cellular spindle cell tumor within the connective tissue.

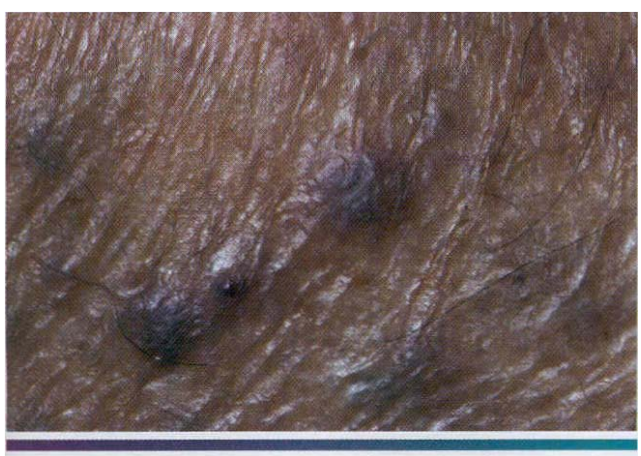


Figure 12-130 • Kaposi's sarcoma. Classic Kaposi's sarcoma in an older man presenting as multiple purple macules and plaques on the lower leg.

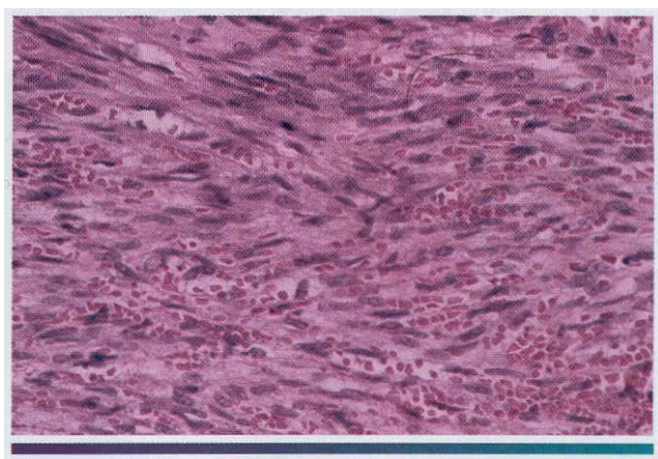


Figure 12-132 • Kaposi's sarcoma. High-power photomicrograph showing spindle cells and poorly defined vascular slits.

Treatment and Prognosis

The treatment of Kaposi's 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, especially vinblastine, also may be helpful. Intralesional injection of chemotherapeutic agents 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% die of the disease after 8 to 10 years. However, 25% die of a secondary malignancy, sometimes of lymphoreticular origin. The benign nodular, endemic African form of the disease **is similar in behavior to classic non-African Kaposi's 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 some**what more aggressive, although the tumors may regress if **immunosuppressive therapy is discontinued or reduced.**

LEIOMYOSARCOMA

The leiomyosarcoma is a malignant neoplasm of smooth muscle origin, 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 (Figure 12-133). 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 (Figure 12-134). 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 can usually be demonstrated within the cells with a periodic acid-Schiff (PAS) stain, and the cell cytoplasm appears bright red with a Masson trichrome stain. Longitudinal striations may be seen with a phosphotungstic acid-hematoxylin (PTAH) stain. Immunohistochemical analysis usually reveals the presence of desrnln. muscle-**specific actin. 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 poor, with a high rate of local recurrence and** distant metastasis. Although few cases are available for analysis, a 5-year survival rate of 32% has been reported.

RHABDOMYOSARCOMA

Rhabdomyosarcoma, a malignant neoplasm of skeletal **muscle origin. is the most common soft tissue sarcoma** of children. The mosf'Ircquent site is the head and neck,

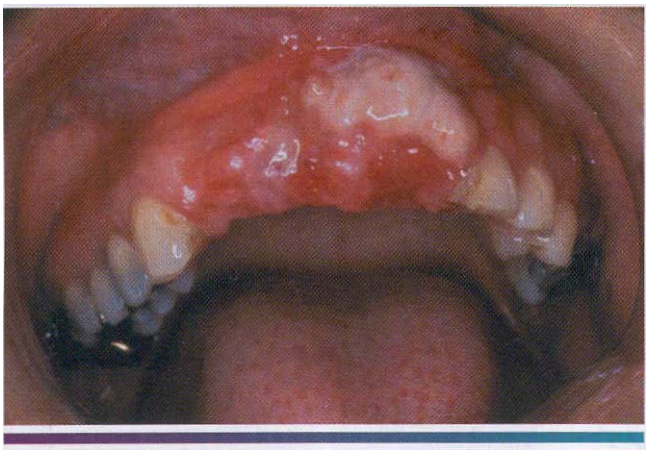


Figure 12-133 • Leiomyosarcoma. Ulcerated mass of the anterior maxillary alveolar ridge. (Courtesy of Dr. Jim Weir.)

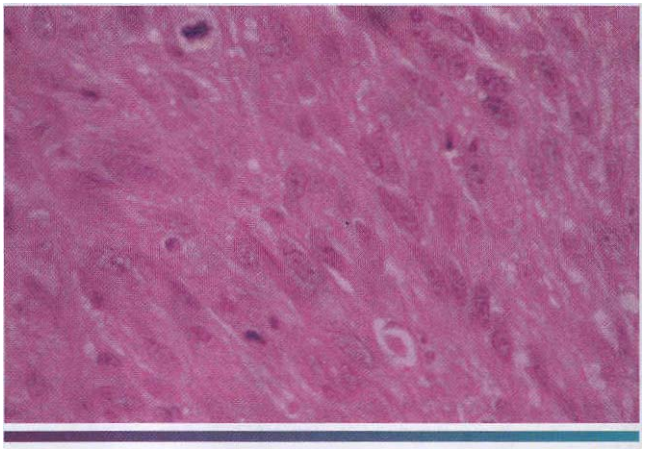


Figure 12-134 • Leiomyosarcoma. High-power view of a pleomorphic spindle cell proliferation.

which accounts for 40% of all cases. The genitourinary tract is the second most common location. Three basic microscopic patterns are recognized:

1. Embryonal
2. Alveolar
3. Pleomorphic

Clinical Features

Rhabdomyosarcoma primarily occurs in the first decade of life. but also is seen in teenagers and young adults. It is rare in people older than age 45. and approximately 60% of all cases occur in males. Embryonal rhabdomyosarcomas are most common in the first 10 years of life and account for about60% 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 a peak prevalence in patients over 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 grolV rapidly (Figures t2-135 and 12-136). In the head and neck region. the orbit is the most frequent location. followed by the nasal cavity and nasopharynx. 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* (grapelikel rhabdomyosarcoma has been used for these lesions.

Histopathologtc 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 (Figure 12-137). 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 nudeus. Cross striations are rarely found. Some tumors show better-differentiated. elongated. strap-shaped rhabdomyoblasts.

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. muscle-specific actin. and myoglobin 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. The alveolar rhabdomyosarcoma 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 in a single layer. The central cells appear to float freely within the alveolar spaces. Mitoses arc common, and multinucleated giant cells also may be seen.

Pleomorphic type. The pleomorphic rhabdomyosarcoma is characterized by loosely arranged and haphazardly oriented cells of variable morphology. Both small and large cells with round or pleomorphic shapes may be present. Deeply eosinophilic cytoplasm may be noted in some cells. Positive immunostains for desmin and myoglobin are helpful in distinguishing these tumors from other pleomorphic sarcomas.

Treatment and Prognosis

Before 1960. the prognosis for a patient with rhabdomyosarcoma was extremely poor. with more than 90%

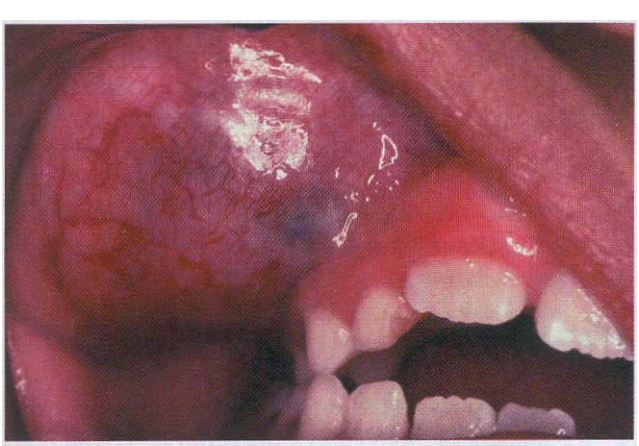


Figure 12-135 • Embryonal rhabdomyosarcoma. Young child with a mass of the right maxilla. (Courtesy of Dr. Robert Achterberg.)

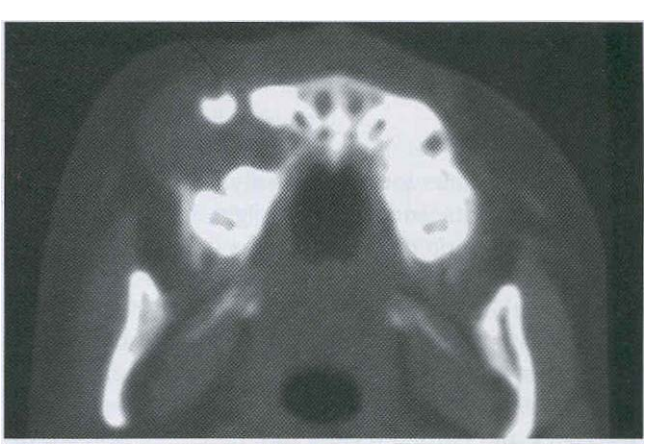


Figure 12-136 . Embryonal rhabdomyosarcoma. CT scan of patient from Figure 12-135 showing expansile lytic lesion of the maxilla. (Courtesy of Dr. Robert Achterberg.)

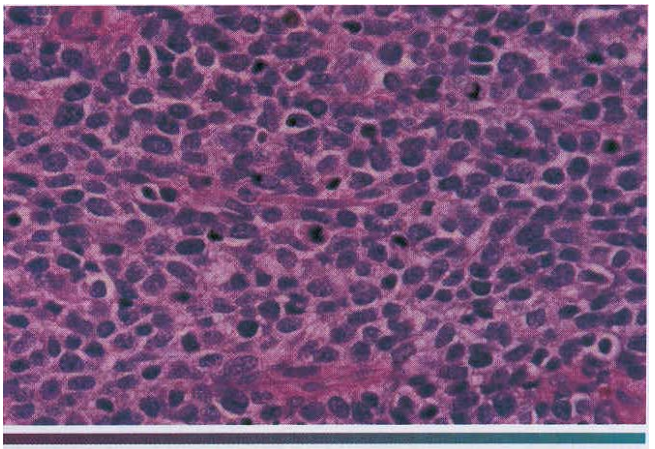


Figure 12-137. Embryonal rhabdomyosarcoma. Medium-power view showing a sheet of small, round cells with hyperchromatic nuclei.

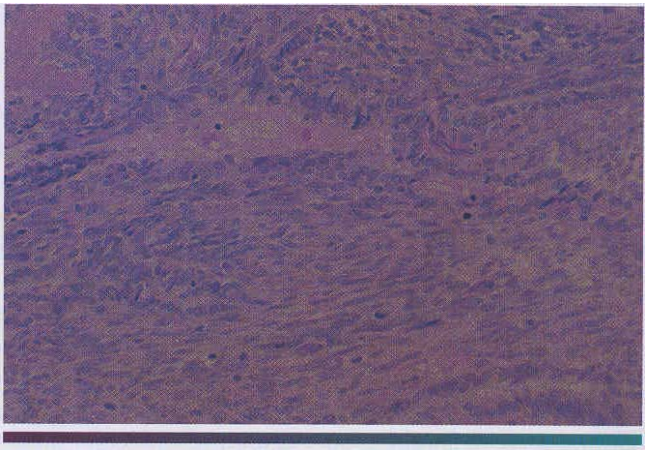


Figure 12-138 • Synovial sarcoma. Biphasic tumor consisting of spindle cells along with cuboidal to columnar epithelial cells that line glandlike spaces.

of patients dying. With the advent of multimodal therapy during the past several decades, the prognosis has improved dramatically.

Treatment typically consists of local surgical excision followed by multiagent chemotherapy (vincristine, actinomycin 0, 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 is around 60% to 70% for newly diagnosed patients without metastatic disease; however, the survival rate drops to less than 30% if metastases are** present.

SYNOVIAL SARCOMA

Synovial sarcoma is an uncommon tumor that primarily occurs near large joints and bursae, especially in the extremities. However. most authorities now agree that the tumor 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, and many of these are apparently unrelated to joint areas.

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. Orofacial **tumors most often have been reported in** the cheek and parotid region.

Histopathologic Features

Classic **synovial sarcoma is a** biphasic **tumor that consists of a combination of spindle cells and epithelial cells** (Figure 12-138). 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.**

Less 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. Rare examples** of monophasic epithelial synovial sarcomas also have been reported.

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 to-year survival rate drops to 20% ro 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. About 25% of all cases occur in the head and neck.

Clinical Features

The alveolar soft-part sarcoma is usually a slow-growing, **painless mass. The tumor is most common in young** adults and children. In adults, the lower extremity is the

most frequent location; in younger patients, the head and neck region is the most common site. The orbit and tongue are the most common head and neck locations. 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 spaces (Figure 12-139). 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 lattice-work pattern.

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 poor because the tumor often metastasizes. The 5-year survival rate is 60%, but the 20-year survival rate drops to only 15%. The prognosis for children appears to be better than for adults.

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 582) 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's plexus, a valveless vertebral venous plexus that might allow retrograde spread of tumor cells, bypassing filtration through the lungs.

Clinical Features

The most common site for oral soft tissue metastases is the gingiva, which accounts for slightly more than 50% of all cases. This is followed by the tongue, which is the site for 25% of cases. The lesion usually appears as a nodular mass that often resembles a hyperplastic or reactive growth, such as a pyogenic granuloma (Figures 12-140 to 12-142). 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.

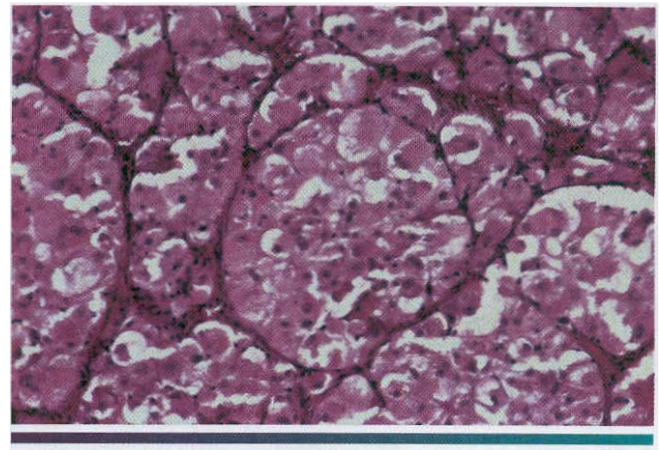


Figure 12-139 • Alveolar soft-part sarcoma. Alveolar collections of large, polygonal cells containing abundant granular cytoplasm.

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 more than 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 25% of all cases, followed by malignancies of the genital organs, lung, bone, and kidney. It is probable that in the future we will see an increased number of metastatic lung cancers in women (today this is the most common cancer killer of women in the United States).

In most cases, the primary tumor already is known when the metastatic lesion is discovered. In some cases, 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 (Figure 12-143). Most cases represent carcinomas; metastatic sarcomas to the oral region are rare.

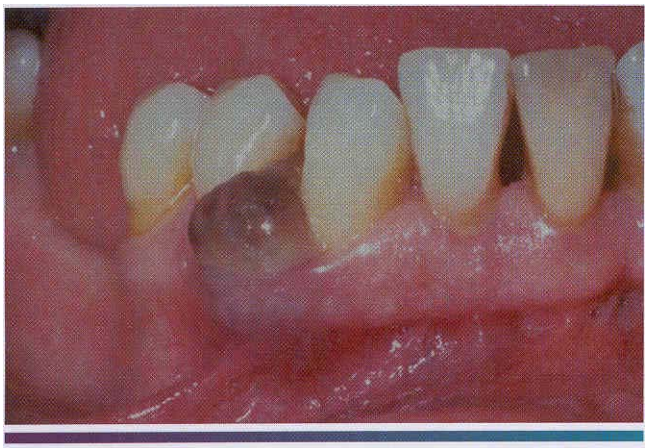


Figure 12-140 . Metastatic melanoma. Pigmented nodule of the mandibular gingiva.

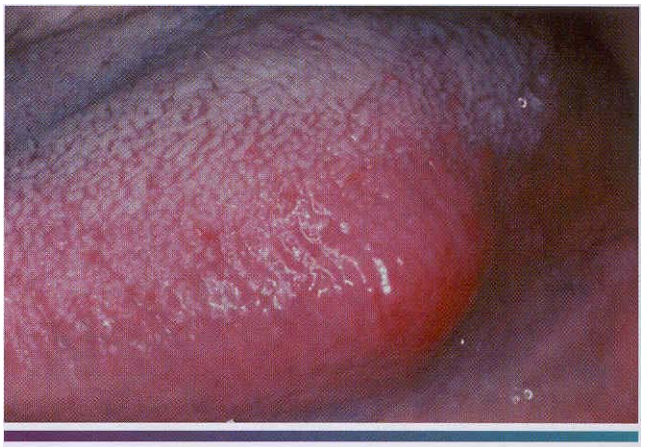
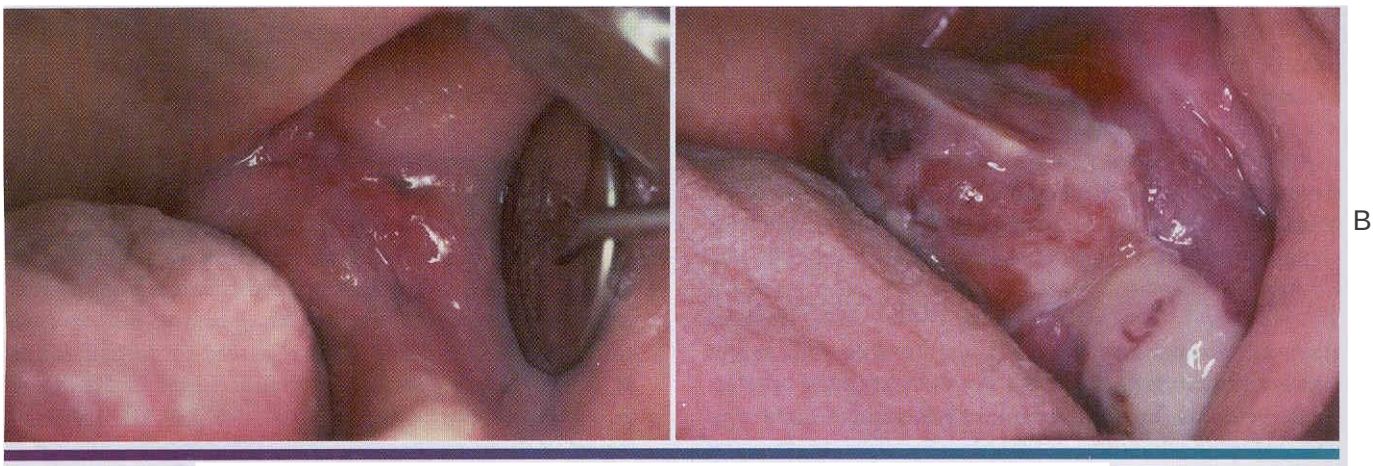


Figure 12-141 • Metastatic renal carcinoma. Nodular mass of the left lateral border of the tongue. (Courtesy of Dr. Mark Bowden.)

A



B

Figure 12-142 • 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.)

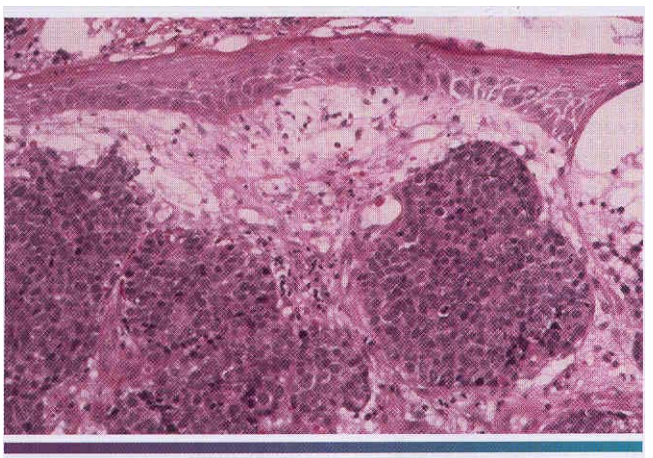


Figure 12-143 • Metastatic carcinoma of the lung. Aggregates of malignant epithelial cells below the surface epithelium.

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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CHAPTER 13

Hematologic Disorders

CHAPTER OUTLINE

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's 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 237).

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 symmetric and asymptomatic (Figure 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 present as discrete. nontcnder, submucosal swellings. usually **less than I em in diameter, which may appear normal or** dark pink in color if the aggregate is deeper or may have a creamy yellowish-orange hue if the collection of lymphocytes is closer to the surface (Figures 13-2 and 13-3). Lymphoid hyperplasia commonly involves the posterior lateral tongue. where it may appear somewhat ominous. The enlargement is usually bilaterally symmetric. however. which helps to distinguish the condition from a malignancy. The buccal lymph node may also become hyperplastic and present as a nontender, solitary. freely movable nodule. usually less than i em 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 cen-

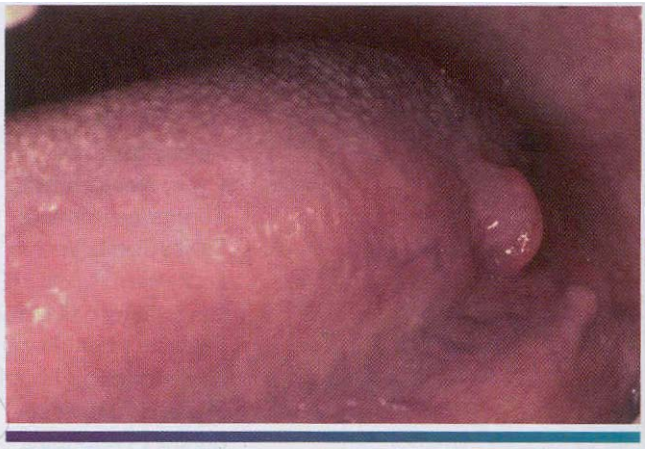

Figure 13-2 • lymphoid hyperplasia. The smooth-surfaced papule of the posterior lateral tongue represents an enlarged lymphoid aggregate. The lesion exhibits a lighter color as a result of the accumulation of lymphocytes. which are white blood cells. (Courtesy of D, Dean White.)

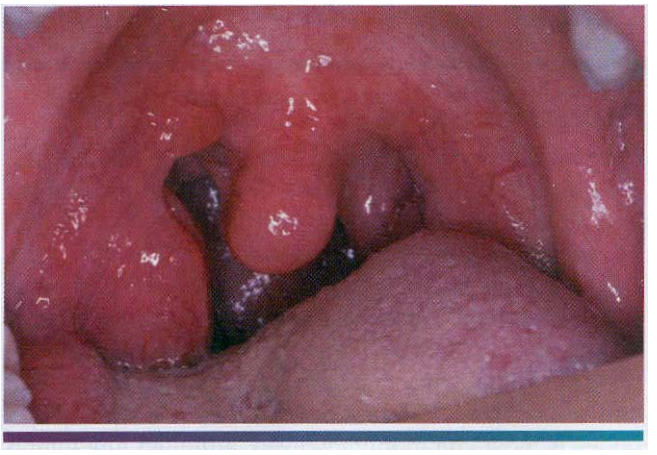

Figure 13-1 • Lymphoid hyperplasia. The large tonsil observed in this patient represents a benign hyperplasia of the lymphoid cells. If significant asymmetry is observed. further investigation may be warranted to rule out the possibility of lymphoma.

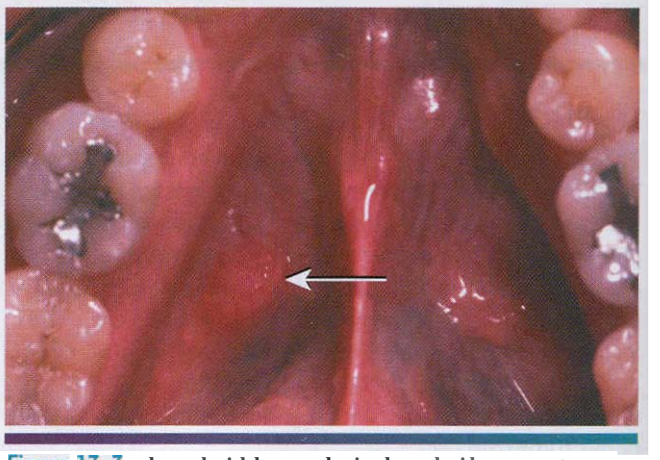

Figure 13-3 • lymphoid hyperplasia. lymphoid aggregates *(arrow)* are frequently noted in the floor of the mouth, as in this photograph.

ters. 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 (tingtble bodies) in their cytoplasm as they engulf nuclear debris *tram* the proliferating lymphocytes.

Treatment and Prognosis

Once the diagnosis of lymphoid hyperplasia is confirmed. notreatment 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.

HEMOPHILIA

Hemophilia *(hemo* = blood; *phtlia* = loving) represents a variety of bleeding disorders associated with a genetic deficiency of any one of the clotting factors of the blood ITable 13-1). This condition was common in certain European royal families. many of whom carried an X-linked hereditary deficiency of either factor VIII or factor IX. Consequently, as a result of inbreeding, 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. it is not known whether these people had factor VIII or factor IX deficiency, because all of the affected individuals died before the definitive diagnostic studies were developed to determine precisely which deficiency was present. 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,

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 presentation, being transmitted in an X-linked fashion. Hemophilia B is much less common than hemophilia A, occurring with a prevalence of I in 50.000. Another clotting disorder that is sometimes seen, von Willebrand's disease. is caused by a genetic deficiency of a plasma glycoprotein called von Willebrand's 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's 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 t in every 800 to 1000 persons, However, many cases of von Willebrand's 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 i in 8000 to 10.000 males are born with this genetic disease. 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 anyone of a variety of mutations associated with the gene for factor VIII. Because the mutations occur at different sites in the factor VIII gene (over 80 different mutations have been identified). a clinical spectrum of deficiency of factor VIII is seen. This results in varying degrees *at* disease expression. Not all patients have an absolute lack of the particularclotting 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 toddlers, 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, 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 (Figure 13-4). The result of

Table 13-1 *Comparisoll of Ihe Mosl Commollly Ellcollfllered Illherited Bleedillg 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 wmebrand's disease	Abnormal von Willebrand's factor, abnormal platelets	Autosomal dominant	Abnormal BT, abnormal PIT

Bf, Bleeding time; PIT, partial thromboplastin time,

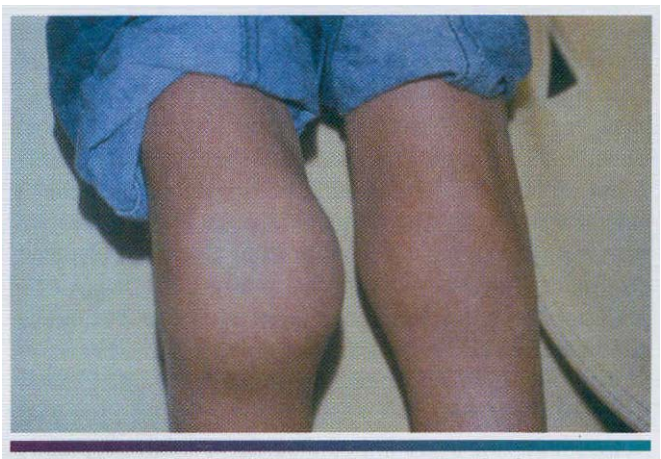

Figure 13-4 • **Hemophilia. The enlargement of the knees of this patient with factor VIII deficiency is due to repeated episodes of bleeding into the joints (hemarthrosis). Inflammation and scarring have resulted.**

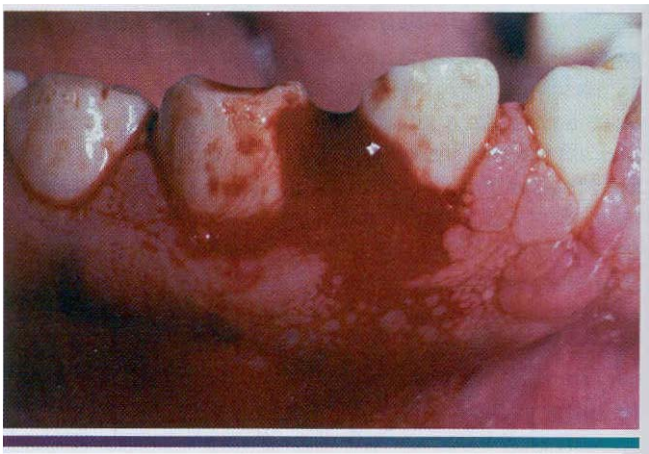

Figure 13-5 • **Hemophilia. Hemorrhage in a patient with factor IX deficiency occurred after routine periodontal curettage.**

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 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 (Figure 13-5). Measurements of the platelet count, bleeding time, prothrombin time (PT), and partial thromboplastin time (PTT) should be ordered as screening tests for any patient with a suspected 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 50% of normal levels of factor VIII), no special treatment is typically required for normal activities. If surgery is to be performed, 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 elective termination of the pregnancy may be an option.

Optimal dental care is strongly encouraged for these patients to prevent oral problems that might require surgery. If oral or periodontal surgery is necessary, 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, which can be given just before surgery. 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 I von Willebrand's 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 traglc complication

for many of these patients. Cryoprecipitation. the traditional method of concentrating clotting factors from the serum. also resulted in the concentration of several viruses. including the hepatitis viruses and human immunodeficiency virus (HIV). Consequently, as many as 80% to 90% of hemophiliac patients treated with multiple doses of factor VIII cryoprecipitate are now positive for HIV. The methods of preparing the clotting factors have been modified to eliminate the risk of acquiring HIV from the preparation; however. many hemophiliac patients who have already been infected still face the prospect of acquired immunodeficiency syndrome (AIDS). Recombinant DNA technology now provides a source of factor VIII that is manufactured by inserting the human factor VIII gene into bacteria that then synthesize the protein. Thus, this product can now be manufactured without contamination by any viral organisms.

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 hemogiobin 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.

Clinical Features

The symptoms of anemia are typicaliy 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. or lightheadedness are often present.

Palior 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.

Box 13-1 *Causes of Anemia*

ANEMIAS WITH DtSTURBED 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, pyelonephritis)
- Anemia of inflammatory connective tissue disorders (rheumatoid arthritis. lupus erythematosus. sarcoidosis, temporal arteritis, 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, 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

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 lhymine molecule for an adenine in DNA. the codon is altered to code for the amino acid valine rather than glutamic acid in the beta-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 of patients with sickle celi anemia have a marked tendency to undergo deformation

from the normal biconcave disc shape to a rigid-and-curved (sickle) shape. Because the genes for hemoglobin synthesis arc codominant. if only one allele is affected, 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, however, particularly with low-oxygen tensions associated with 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 red blood cells contain primarily sickle hcrnoglobln. This results in the condition called sickle cell disease. In the United States, about I 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 arc more fragile than normal 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 experience 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 10 days. Pulmonary involvement. known as acute chest syndrome. is particularly serious. and a recent 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 I year or longer without problems, Often fever accompanies the crisis: therefore. infection must be considered in the differential diagnosis.

Patients with sickle cell disease arc susceptible to infections, especially those caused by *Streptococcuspneumoniae*. 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 vasa-occlusive episodes in the capillary networks of those organs. if the patient lives long enough, 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-an-end" appearance is seen on the skull radiograph. although this is less prominent than that seen in thalassemia (Figure 13-6). Other oral problems that have been reported include an increased prevalence of osteomyelitis of the mandible, 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

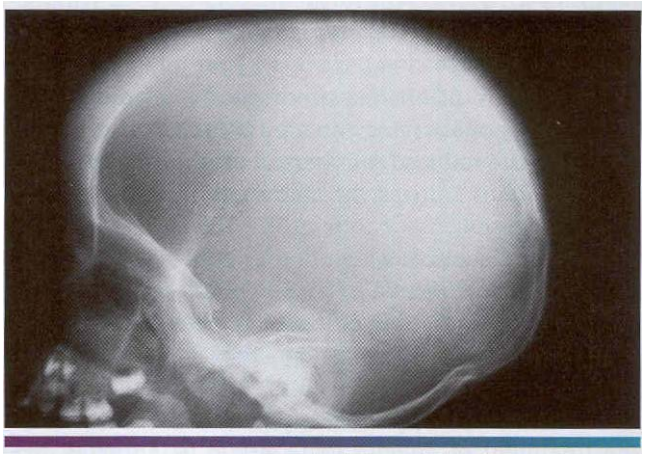

Figure 13-6 • Sickle cell anemia. Lateral skull radiograph reveals an altered trabecular pattern, including a slight degree of "hair-on-end" appearance of the cranial bones. (Courtesy of Dr. Reg Munden.)

appropriate analgesic therapy (usually narcotic preparations). It is important. but often difficult. to rule out the possibility of infection.

As of this writing. 46 states 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 vaccination. 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 Fl. which may inhibit polymerization of hemoglobin 5 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, 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 either 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. Recently, 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 alpha-globin or beta-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."** By **some estimates.** thalassernia **is the most common inherited disorder that affects 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 alpha and two beta chains; if one of the chains is not being made in adequate quantities, 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). The net result is that the patient **has hypochromic. microcytic anemia.**

Because two genes code for the beta chain and four genes code for the alpha 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 arc 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 over 200 different mutations **have been documented for this condition.**

Clinical and Radiographic Features

Beta-thalassemia, If only one defective gene for the beta-globin molecule is inherited (thalassemia minor), **no significant clinical manifestations are usually present.**

When two defective genes for the beta-globin molecule are inherited, the patient is affected with thalassemia major. also called Cooley'S anemia or Mediterranean fever. 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 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 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 marked but painless enlargement of the mandible and maxilla. This results in a characteristic "chipmunk" facies. Frontal bossing is also present. and a skull radiograph shows a prominent "hair-an-end" appearance of the calvaria (Figure 13-7).

Without therapy. tissue hypoxia worsens and serious bacterial infections with pneumococcal organisms often develop. Eventually. high-output cardiac failure occurs; many patients die by I year of age as a result of infection or heart problems.

Alpha-thalassemia. Alpha-thalassemia has a broader spectrum of involvement than does beta-thalassemia because there are four alpha-globin genes that may be affected.

With the alteration of only one gene. no disease can be detected. With the Inheritance of two altered genes. the condition is known as alpha-thalassemia trait; these patients have a mild degree of anemia and microcytosis that is usually not clinically significant. With three altered genes. the term Hb (hemoglobin) II disease is applied. Patients have problems with hemolytic anemia and splenomegaiy. For patients with severe hemolysis. splenectomy may be indicated.

The homozygous state. in which all four genes are abnormal. is called hydrops fetalis. This condition is typically fatal 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 develops because of the constant infusion of exogenous red blood cells. 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 desfcrrioxaminc). must be given. If such therapy is used steadfastly. patients with beta-thalassemia may have a relatively normal life span. Bone marrow transplantation has also been used with considerable success for individuals who arc relatively young. have little organ damage. and have an HLA-matched donor.

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 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. 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, which normally induce the production and maturation of several types of white blood cells.

Although the underlying cause is unknown. some cases are associated with exposure to certain environmental toxins (such as benzene), treatment with certain drugs (especially the antibiotic chloramphenicol), or infection with certain viruses (particularly non-A. non-B. non-C. non-G hepatitis). In many instances. the destruction of the bone marrow appears to be mediated by lymphocytes that attack and destroy the bone marrow stem cells. In some instances, the abnormal immune response is perhaps triggered by exposure to drugs or viruses. A few genetic disorders. such as Fanconi's anemia and dyskeratosis congenita (sec page 648). 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 (neu-

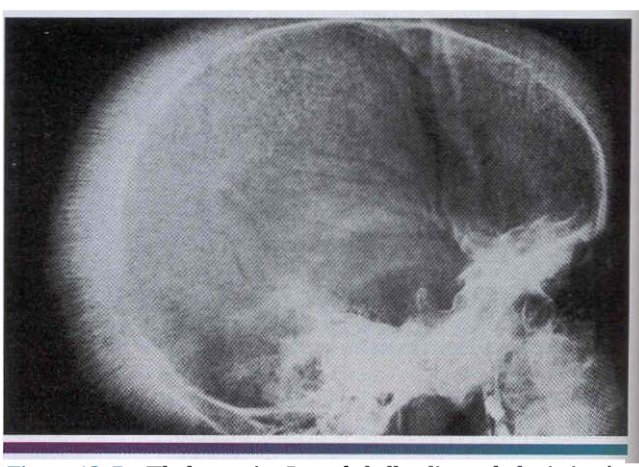

Figure 13-7 • Thalassemia. Lateral skull radiograph depicting the characteristic "heir-on-end" **appearance in a patient with thalassemia.**

tropcnla. leukopenia, or granulocytopenia) is the most significant complication of this disease, predisposing the patient to bacterial and fungal infections that often arc the cause of death.

The oral findings related to thrombocytopenia include gingival hemorrhage, oral mucosal petechiae. purpura. and ecchymoses. The oral mucosa may appear pale because of the decreased numbers of red blood cells. Oral ulcerations associated with infection, particularly those that invoive 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.**

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/ut,
- Fewer than 20.000 platelets/ut,
- Fewer than 10,000 reticulocytes/pl,

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;** progresslon **to severe aplastic anemia may be seen in** others. Generally. in severe cases, the chances of spon**taneous recovery arc slim. If a particular environmental** toxin or drug is associated with the process, withdrawal of the offending agent may sometimes result in recovery.

The treatment Is initially supportive. Appropriate antibiotics arc given for the infections that develop, and transfusions of packed red blood cells or platelets are **administered for symptomatic treatment of anemia and** bleeding problems. respectively.

Attempts to stimulate the bone marrow have met with variable success. Androgenic steroids appear to benefit patients with mild disease. but they have little effect on **the severe form.**

One approach to therapy is to replace the defective **marrow with normal marrow, either by bone marrow** transplantation or peripheral blood stem cell transplantation from a matched donor. This treatment has been gaining acceptance despite the risk of graft-versus-host disease. Patients must be carefully selected; patients younger than 40 years of age and those with an HLA-matched donor (usually a sibling) have the best prognosis.

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 (in the United States) or antilymphocyte globulin (in Europe) combined with cyclosporine produces a response in the majority of these patients. Recent findings from a large **randomized trial have documented a 3-year survival rate** of 90% with a combination of antilymphocyte globulin and cyclosporine.

Typically, the prognosis for this condition is guarded at best. 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. Today, even if the disease is con**trolled, the patient remains at risk for recurrent marrow aplasia and is 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 impact on the health of the patient because neutrophil counts respond to bacterial challenge.

A decrease in neutrophils may be precipitated by sev**eral 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 caused by a congenital or genetic abnormality, such as **Schwachman-Diamond syndrome. dyskeratosis con**genita (see page 6481. 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 neutropenias have an **unknown cause; however, others are clearly associated with various causes. A decreased production of neutro**phils and the other formed clements of the blood may result from the destruction of the bone marrow by malignancies, such as leukemia (see page 510l. or by metabolic diseases. such as Gaucher disease (see page 707), and osteopetrosis (see page 535).

Many drugs may affect neutrophil production, either through direct toxic effects on the bone marrow progen-

itor cells or by unknown idiosyncratic mechanisms. These drugs include the following:

- Antican cer chemotherapeutic agents (e.g., nitrogen mustard. busulfan. chlorambucil. and cyclophosphamide)
- Antibiotics (e.g.. penicillins and sulfonamides)
- Phenothiazines
- Tranquilizers
- Diuretics

Nutritional deficiencies of vitamin B_{12} or folate. which may be a consequence of malabsorption syndromes. can inhibit neutrophil production.

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. Viruses that have been implicated include:

- 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 the neutropenic patient. 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.

Histopathologic Features

A biopsy specimen of a 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-CSFl. 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.

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). which is caused by 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 140).

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 agranulocytosis is thought to be caused by a particular drug, 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 antibiotics.

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 related to a defect in the hematopoietic stem cells in the marrow. The best estimated frequency of this disease in the population is about one in one 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 (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 cajon.** rectum, and anus, may be affected by recurrent ulcerations.

The oral ulcerations develop on any oral mucosal surface that is exposed to even minor trauma, particularly the lips, tongue, buccal mucosa, and oropharynx (Figure 13-8). 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 are also characteristic (Figure 13-9).

Diagnosis

The diagnosis of cyclic neutropenia should be established by sequential complete blood counts (typically two to three times per week for 8 weeks) to determine whether cycling of the neutrophil levels occurs. The neu-

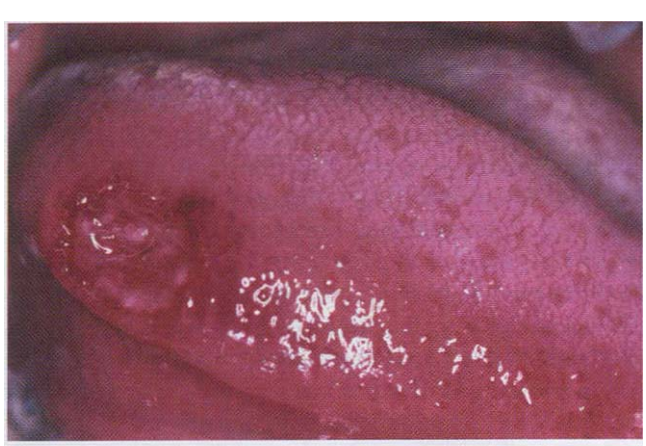

Figure 13-8 • Cyclic neutropenia. Ulceration of the lateral tongue is typical of the lesions associated with cyclic neutropenia. (From Allen CM. Camisa C: Diseases of the mouth and lips. In Sams WM. Lynch P, editors: *Principles and practice of dermatology.* ed 2. New York, 1996, Churchill Livingstone.)

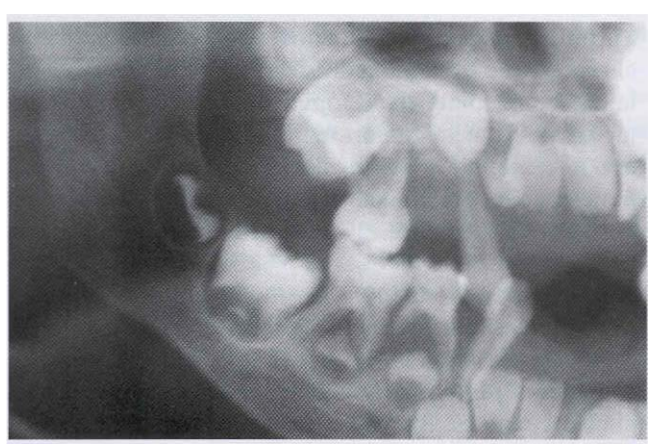

Figure 13-9 • Cyclic neutropenia. Cyclic neutropenia is one of several conditions that may produce premature bone loss. as shown in the interradicular regions of the mandibular deciduous molar teeth.

trophil count should be less than SOO/ 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. Studies have shown that 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 I day, which improves the clinical course of the disease. The cycles are reduced from \8 to 2\ days to II 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 orai 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 toO 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 and HIV infection. Increased destruction may also occur by nonimmunologic means because of increased consumption of platelets associated with abnormal blood clot formation. This occurs in patients with conditions such as thrombotic thrombocytopenic purpura (TTP).

*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, or 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^J. 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 arc continuously inflicted on the oral mucosa during chewing and swallowing of food. The small capillaries that arc 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, an ecchymosis or bruise results (Figure 13-10). With even larger amounts of extravasated blood, a hematoma *(hemal* = blood; *oma* = tumor) will develop (Figure 13-11). 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 platclets/ mrn"). massive bleeding from the gastrointestinal or urinary tract may be fatal. Epistaxis is often present in these patients. and hemoptosis indicates significant pulmonary hemorrhage. Intracranial hemorrhage is also a potentially fatal complication of severe thrombocytopenia.

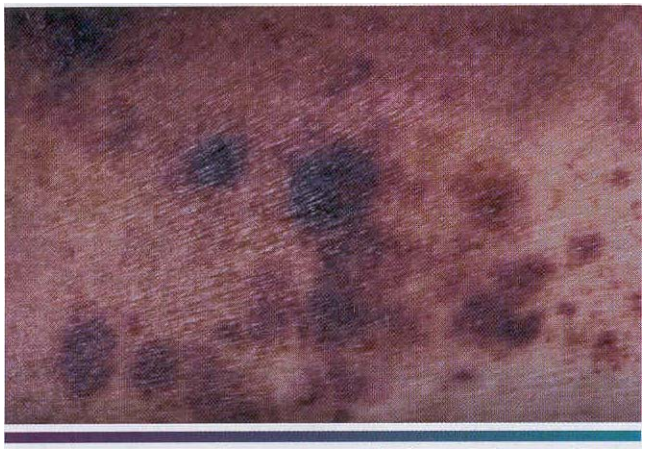

Figure 13-10 . Thrombocytopenia. The bruising (purpura) seen on this patient's forearm is a result of reduced platelet count secondary to myelodysplasia, a preleukemic bone marrow disorder.

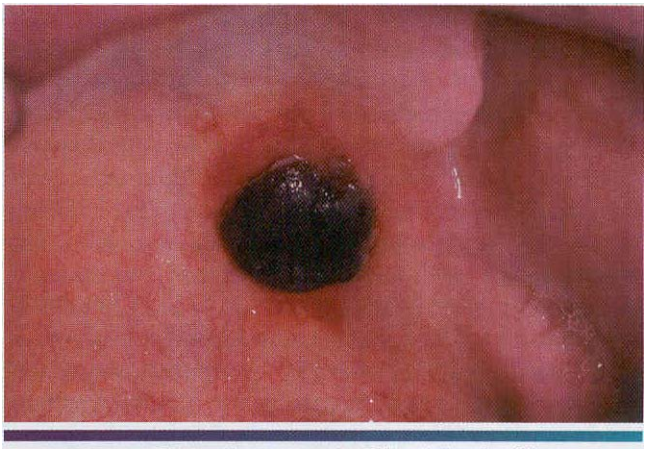

Figure 13-11 • Thrombocytopenia. This dark palatal lesion represents a hematoma caused by a lack of normal coagulation, characteristic of thrombocytopenia.

Special types of thrombocytopenia include idiopathic (immune) thrombocytopenic purpura (iTP) and TTP. [TP 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.

TTP is a serious disorder of coagulation. It is thought to be caused by some form of endothelial damage that appears to trigger the formation of numerous thrombi within the small blood vessels of the body.

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 thrombocytopenia is thought 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, [TP often resolves spontaneously, **but those cases that are more severe may require corti**costeroid therapy or intravenous immunoglobulin therapy. 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 improved since therapy with plasmapheresis or exchange transfusions became available. More than 50% **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. Uncontrolled production of platelets and granulocytes, however, is often seen concurrently, and **most authorities feel that this condition represents a relatively nonaggressive myeloproliferative disorder. The** overproduction is thought to be 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 gener**ally 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 predilec**tion is seen, and the prevalence of the condition is esti**mated to be 4 to 16 cases per million population.

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) 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 often 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 red blood cell mass. The first treatment is usually phlebotomy, with as much as 500 ml of blood removed daily. If thrombotic events are an immediate problem, treatment with 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. Each has disadvantages. An increased risk of thrombosis is associated with phlebotomy, and 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 2.5% of all cancers are leukemia, and 3.5% of deaths from cancer can be attributed to this disease.

Leukemias are usually classified according to their histogenesis and clinical behavior. Thus, 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 caused by 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**
- Schwachman syndrome
- **Ataxia-telangiectasia syndrome**
- Klinefelter syndrome
- **Fanconi's anemia**
- Wiskott-Aldrich syndrome

In addition, certain types of leukemia show specific chromosomal abnormalities. One of these, chronic myeloid leukemia, has a genetic alteration called the Philadelphia chromosome, which represents a translocation of the chromosomal material between the long arms of chromosomes 22 and 9. This rearrangement of the genetic material may occur in such a fashion as to activate a specific oncogene, which results in the uncontrolled proliferation of the leukemic cell. A variety of other genetic alterations in the bone marrow stem cells have 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 benzenelike 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 'l-cell leukemia/lymphoma virus type I (HTLV-II. 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's lymphoma (see page 517). Most cases have been identified in parts of the Caribbean, central Africa, and southwestern Japan.

As our knowledge about this group of diseases increases. the fact that the leukemias are diverse and complex cannot be overlooked. For example. 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 a peak incidence during the third and fourth decades of life. Acute lymphoblastic leukemia. in contrast, almost always occurs in children and represents one of the more common childhood malignancies. Chronic lymphocytic leukemia. the most common type of leukemia. primarily affects elderly 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 *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 megakaryocytcs 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^J 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 central nervous system 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 grayish-white necrotic base. Oral candidiasis is often a complication of leukemia. involvlng 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 mayor may not be ulcerated. This occurs most frequently with the myelomonocytic types of leukemia. and it may result in diffuse gingival enlargement (Figure 13-12) or a prominent tumorlike growth (Figure 13-13l. The tumorlike collection of leukemic cells is known as granulocytic sarcoma or extramedullary myeloid tumor. *and* historically the term chloroma has been used because it is oflen greenish *tchlor* = green; *orna* = tumor) on fresh cut sections. Other oral manifestations include infiltration of the periapical tissues. simulating periapical inflammatory disease both clinically and radiographically.

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.

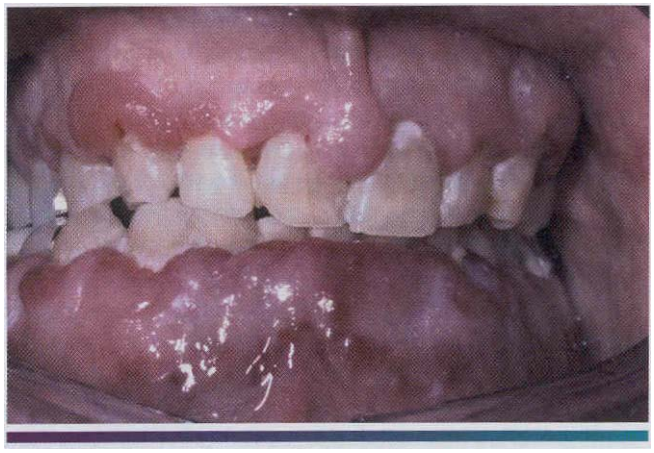

Figure 13-12 • leukemia. Diffuse gingival enlargement. as depicted in this photograph, may occur in leukemic patients, particularly in those with monocytic leukemia. This elderly man had a history of myelodysplasia for several years before the development of leukemia.

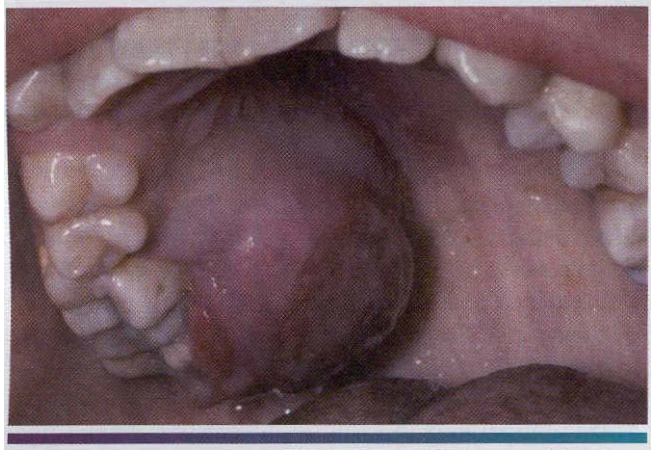

Figure 13-13 • Leukemia. The ulcerated soft tissue nodule of the hard palate represents leukemic cells that have proliferated in this area.

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 biood 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 on the tumor cells. Immunohistochemical confirmation of certain characteristic enzymes (such as** myeloperoxidase and lysozyme) is necessary to identify and classify the myeloid leukemias. In addition, cytogenetic evaluation of the lesional cells is often necessary. In many cases. the results of these various studies will be significant because the patient's prognosis is directly impacted.

Treatment and Prognosis

The treatment of a patient with leukemia consists of *various* forms of chemotherapy; the type of leukemia dictates the chemotherapeutic regimen. 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.

Drug therapy may be combined with radiation therapy to the CNS because the chemotherapeutic drugs often do not cross the blood and 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. a bone mar**row transplant may be considered as a therapeutic option. particularly for the types of ieukemia 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 red blood cells may be required. Infections, of course, should be evaluated with respect to the causative organism, and appropriate **antibiotics must be prescribed. Support must be main**tained 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 lympho**blastic leukemia. over 70% 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 S-year survival** rate is generally much lower in most reported series.

Patients under 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 *over* the age of 60 years, however, has a much poorer prognosis, with less than a 10% chance of survival seen in that pop-

ulation. 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 this malignancy was in the 20% range. Today, most centers are reporting a 50% to 60% 5-year survival rate, not only because treatment strategies have improved, but also because the disease is diagnosed at an early stage and there is better supportive care available. 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.

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)

The term *histiocytosis* X was introduced as a collective designation for a spectrum of 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 many believe that the condition is best designated as Langerhans cell histiocytosis. 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, it has been 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.

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-Schuller-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-Schuller-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-Schuller-Christian and Lettercr-Siwe disease serve no useful purpose and should be discontinued. Many cases reported as lettercr-Siwe disease in the older literature probably included obscure infections, immunodeficiency syndromes, and malignant histiocytic lesions.

Although Langerhans cell histiocytosis may be encountered in patients over a wide age range, more than 50% of all cases are seen in patients under age 10. There is a definite male predilection. 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 over 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 (Figure 13-14). Extensive alveolar involvement causes the teeth to appear as if they are "floating in air" (Figure 13-15).

Ulcerative or proliferative mucosal lesions or a proliferative gingival mass may develop if the disease breaks out of bone (Figure 13-16). 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.

Histopathologic Features

The bone lesions of patients with Langerhans cell histiocytosis show a diffuse infiltration of large, pale-staining

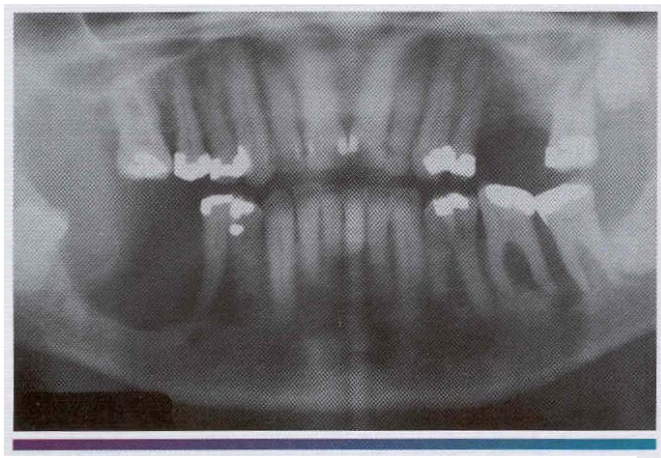

Figure 13-14 • Ilangerhans cell histiocytosis. Severe bone loss in the mandibular molar regions that resembles advanced periodontitis. **(Courtesy of Dr. James White.)**

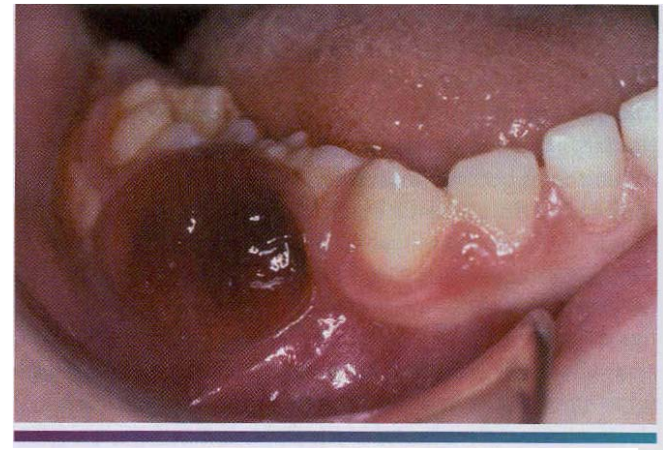

Figure 13-16 • Langerhans cell histiocytosis. Clinical photograph **of the same patient shown in Figure 13-15. The lesion has broken out of bone and produced this soft tissue mass.**

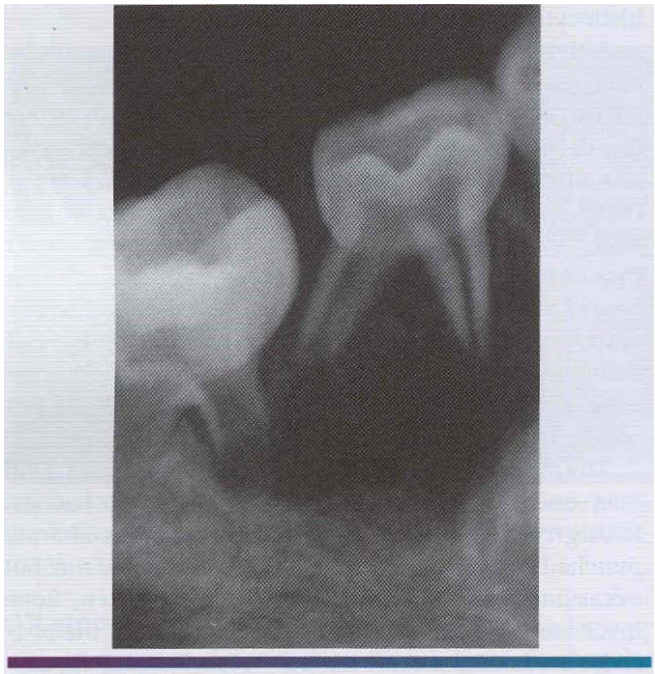

Figure 13-15 • Ilangerhans cell histiocytosis. Periapical radiograph **showing marked bone loss involving the mandibular teeth in a young girl. resulting in a "floating-in-air" appearance of the teeth.**

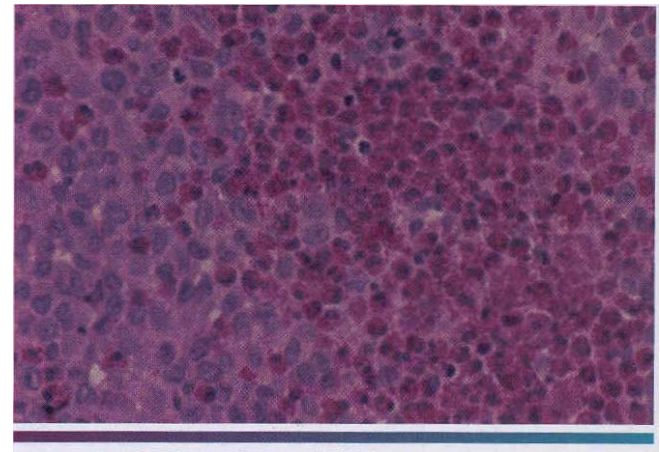

Figure 13-17 • Ilangerhans cell histiocytosis. There is a diffuse infiltrate of pale-staining Langerhans cells intermixed with numerous red granular eosinophils.

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 (Figure 13-17). 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 has been 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 (Figure 13-18). Most laboratories now rely on immunohistochemical procedures to identify the lesional Langerhans cells because of their immunoreactivity with antibodies directed against CD-1a. To a lesser extent, the lesional cells have S-100 protein immunoreactivity, and they also may show affinity for peanut agglutinin (PNA).

Treatment and Prognosis

Accessible bone lesions. such as those in the maxilla and mandible. are usually treated by curettage. Low doses of

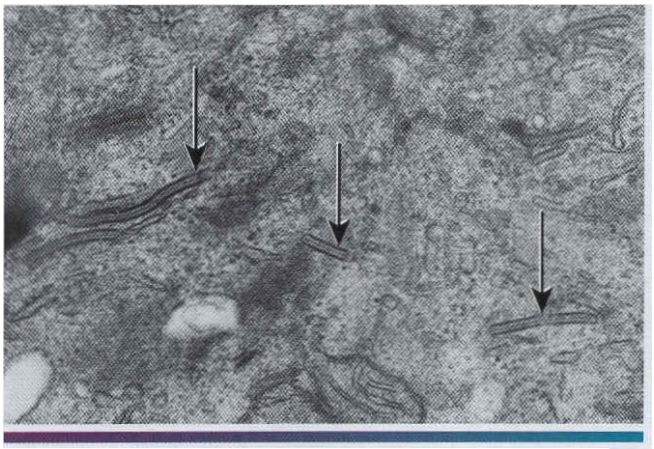

Figure 13-18. Langerhans cell histiocytosis. Electron micrograph showing rod-shaped Birbeck bodies *(black arrows)* in the cytoplasm of a Langerhans cell. (Courtesy of Richard Geissler.)

radiation may be employed 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 corticosteroids 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 3 or more bones affected.

Chronic disseminated disease is often associated with considerable morbidity. but few patients die as a result of the disease. 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. The acute disseminated form of the disease seen in infants and young children may not respond to this approach. and multiple chemotherapeutic agents are given in that situation. Diffuse involvement with compromise of multiple organs is associated with a poor prognosis and is often fatal. 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'S LYMPHOMA (HODGKIN'S DISEASE)

Most authorities classify Hodgkin's lymphoma as a malignant lymphoproliferative disorder, although the exact nature of the process is poorly understood. The difficulty in comprehending the character of the condition is reflected in the relatively noncommittal term "Hodgkin's disease," which was used for decades and still may be heard today. Perhaps one reason why Hodgkin's lymphoma is not easily understood is that. unlike most malignancies. the neoplastic cells (Reed-Sternberg cells) make up only about 1% to 3% of the cells in the enlarged lymph nodes that characterize this condition. Recent 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 20 years. In the United States. Hodgkin's lymphoma is about one sixth as common as non-Hodgkin's lymphoma: approximately 8000 cases are diagnosed annually. Although the cause of this disease is unknown. recent epidemiologic and molecular studies have linked Epstein-Barr virus infection to a significant percentage of these lesions.

Clinical Features

Hodgkin's 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 (Figure 13-19). 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. 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. 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's 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 com-

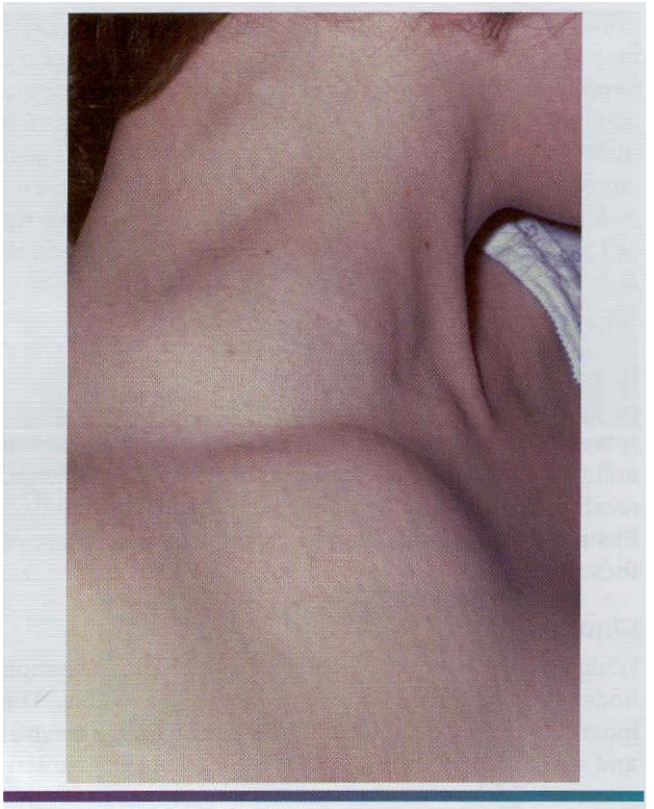

Figure 13-19 • **Hodgkin's lymphoma. The prominent supraclavicular and cervical masses represent Hodgkin's lymphoma.**

puted tomography (CT) scans or magnetic resonance imaging (MRil studies, chest radiographs, and routine hematologic studies (e.g., complete blood count, Serum chemistries, eryth rocyte sedimentation rate). Lymphangiography, gallium scan, bone marrow biopsy, exploratory laparotomy, and splenectomy may be necessary if the information that they would provide might have an impact **on staging or treatment. A summary of the staging system** for Hodgkin's lymphoma is presented in Table 13-2.

Table 13-2 *Alii' Arbor System for Classifimtioll of tiodgkln's Lymphoma*

STAGE	DEFINING FEATURES
	Involvement of a single lymph node region (I) or a single extralymphatic **organ or site (IE)**
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,)
III	**Involvement of lymph node regions on both sides of the diaphragm (III), possibly with an** extralymphatic organ or site (III,), the spleen (IIIs), 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** s-mcnth **period before diagnosis**

Adapted from DeVita VT, Hubbard SM: Hodgkin's disease, N *El7gl l Mad* 328:560-565, 1993.

Histopathologic Features

Hodgkin's lymphoma has recently been recognized to comprise two main forms, (I) nodular lymphocyte-predominant Hodgkin's lymphoma and (2) classical Hodgkin 'Slymphoma, which is divided into five subtypes. Although this group of diseases has certain features in **common, current immunohistochemical and molecular** biologic techniques have allowed distinctions to be made among the various types. The common features include effacement of the normal nodai 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's lymphoma, this atypical cell is known as a Reed-Sternberg cell (Figure 13-20J. The Reed-Sternberg cell is typically binucleated (vowl eye nuclei"), although it may be multinucleated ("pennies on a plate"), with prominent nucleoli. The malignant cell in nodular lymphocyte-predominant Hodgkin'S 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'S lymphoma, although their presence does not automatically imply that diagnosis, because similar cells may be seen **in certain viral infections, especially infectious mono**nucleosis. To summarize, Hodgkin 'S lymphoma is currently classified in the following manner:

- Nodular lymphocyte-predominant Hodgkin 'Slymphoma, or
- Classical Hodgkin'S 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 epidemio**logic and prognostic characteristics are associated with** each type.

Nodular lymphocyte- predominant Hodgkin's lymphoma constitutes 4% to 5% of all cases of Hodgkin'S

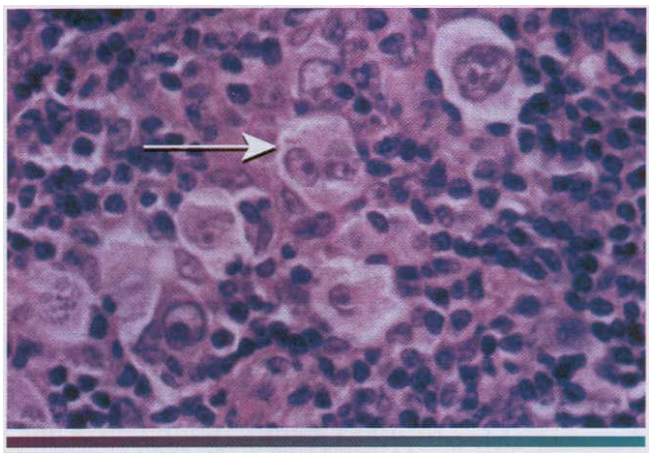

Figure 13-20 • **Hodgkin's lymphoma. This high-power photomicrograph shows the characteristic Reed-Sternberg cell *(arrow)* of Hodgkin's lymphoma, identified by its "owl-eye" nucleus.**

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's lymphoma represents about 6% of all cases. Sheets of small lymphocyteswith 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 leslonal 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, eosinophtls. and histiocytes with abundant Reed-Sternberg cells.

The lymphocyte depletion subtype, the most aggressive type, makes up less than I% 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'S lymphoma. numerous bizarre giant Reed-Sternberg cells are present with few lymphocytes.

Occasionally, examples of Hodgkin'S 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'S lymphoma depends on the stage of involvement. Patients who have limited disease (stages I and II) often are 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. A widely used regimen to treat Hodgkin'SIymphoma is known as MOPP **(mechlorethamine, Oncovin. procarbazine, prednisone).** Because significant long-term side effects can be associated with this chemotherapy, another regimen known as ABVO (Adriarnyctn. bleomycin, vinblastine, OTIC) is often **used because it has fewer complications.**

Before modern cancer therapy was developed for Hodgkin's 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 also influences the response to therapy. Patients with the lymphocyte-predominant and nodular sclerosis forms have the best prognosis, whereas those with the mixed cellularity form have a less favorable prognosis. Inthe past, the lymphocyte depletion form was thought to have a poor prognosis, **but with newer immunohistochemical studies, clinicians now realize that many of these cases were misdiagnosed;** therefore, the available data arc probably not reliable. In **most instances. however, 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 sec**ondary malignancy or cardiovascular disease. Currently,** research is focused on the development of treatment reg**imens that continue to have a superior cure rate. while** simultaneously decreasing the risk of treatment-related complications.

NON-HODGKIN'S LYMPHOMA

The non-Hodgkin's lymphomas include a diverse and complex group of malignancies of lymphoreticular histo**genesis. In most instances. they initially arise within** lymph nodes and tend to grow as solid masses. This is in contrast to lymphocytic leukemias (sec page 5101. 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's 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 arc 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 comprised 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," that is still often referred to in the United States. Based on this classification. lymphomas can be broadly grouped into three categories:

1. Low grade
2. Intermediate grade
3. High grade

These categories arc correlated with increasing degrees of aggressiveness. which correspond with their increasingly poor prognosis (Table 13-3). Of patients who are newly diagnosed with lymphoma. 35% to 40% will have a low-grade lesion, typically with widely disseminated involvement at the time of diagnosis; 55% to 60% wi ll have an intermediate-grade lymphoma; only 5% have a high-grade lymphoma.

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 (Box 13-2). With this system, a combination of histopathologic features, immunologic cell surface markers. and gene rearrangement studies arc used to organize this group of neoplasms. Recently, the World Health Organization (WHO) revised its lymphoma classification system to conform to a slightly modified version of the REAL classification. While the latter two classifications appear to be more precise than the Working Formulation, currently their use is primarily restricted to large academic medical centers because of the relative sophistication of some of the molecular studies. The REAL/WHO systems will probably require several years of additional use with clinical correlation to become widely accepted in the United States.

Over 54.000 cases of non-Hodgkin 's lymphoma are diagnosed in the United States annually; approximately one half of this number will die of the disease each year. The prevalence of lymphoma is increased in patients who have immunologic problems. such as congenital immunodeficiencies (e.g.. Bloom syndrome. Wiskolt-Aldrich syndrome, common variable immunodeficiency), AIDS. organ transplantation. and autoimmune disease (e.g.. Sjögren syndrome. systemic lupus erythematosus ISLE], 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 etioparhogenic agent in Burkitt's lymphoma (see page 523), a type of high-grade, small, noncleaved B-celilym-

Table 13-3 *Classificalion of the Non-Hodgkin's Lymphomas by tlu: Working Formulation*

SUBTYPE	FREQUENCY (%)	GROWTH PATTERN	MEDIAN AGE	POTENTIALLY CURABLE WITH CHEMOTHERAPY?
Low Grade				
A. Small lymphocytic	4	Diffuse	61	Unproved
B. Follicular small cleaved cell	23	Follicular	S4	Unproved
C. Follicular mixed cell	8	Follicular	56	Controversial
Intermediate Grade				
D. Follicular large cell	4	Follicular	55	Controversial
E. Diffuse small cleaved cell	7	Diffuse	58	Controversial
F. Diffuse mixed cell	7	Diffuse	58	Yes
G. Diffuse large cell	20	Diffuse	57	Yes
High Grade				
H. Immunoblastic	8	Diffuse	51	Yes
I. lymphoblastic	4	Diffuse	17	Yes
J. Small noncleaved cell	5	Diffuse	30	Yes

From Armitage 10: Treatment of non-Hodgktn's lymphoma. N *£/lgl I Med* 328:1023-1030.1993.

phoma. In addition. EBV may be related to lymphomas developing in the setting of immunosuppression after solid organ or bone marrow transplant (resulting in the condition known as posttransplant lymphoproliferative disorder) or in association with AIDS (see page 247). Human herpesvirus (HHV) type 8, has not only been associated with Kaposi's sarcoma. but also the recently described primary body *cavity* lymphoma. A blood-borne human retrovirus called HTIV-I has been shown to cause an aggressive form of peripheral T-cell lymphoma among certain populations in the Caribbean. central Africa, and southwest lapan,

Clinical and Radiographic Features

Non-Hodgkin's 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 25% of lymphomas *develop* in an extranodal site, but in countries of the Far East, such as Korea and tapan, nearly half of all lymphomas are extranodal.

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 (Figure 13-21). 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 dis**ease, 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**

Box 13-2 *Revised European-American Lymphoma (REAL) Classification*

B-CHl NEOPLASMS

I. Precursor ***B-cell neoplasms***
   Precursor a-lymphoblastic leukemia/ lymphoma
II. Peripheral B-cell neoplasms
   1. B-cell chronic lymphocytic leukemia/prolymphocytic leukemia/ small lymphocytic lymphoma
   2. lymphoplasmacytoid lymphoma/immunocytoma
   3. Mantle cell lymphoma
   4. Follicle center lymphoma. follicular
   5. Marginal zone B-celllymphoma
   6. Provisional entity: splenic marginal zone lymphoma
   Z Hairy cell leukemia
   8. Plasmacytoma/plasma cell myeloma
   9. Diffuse large B-ceillymphoma
   10. Burkitt's lymphoma
   11. Provisional entity: diffuse large Bvcell lymphoma, Burkittlike

T-CEll AND PUTATIVE NK CEll NEOPLASMS

I. Precursor T-cell neoplasm
II. Peripheral T-cell neoplasms
   1. T-cell chronic lymphocytic leukemia
   2. large granular lymphocytic leukemia
   3. Mycosis fungcides/Seaery syndrome
   4. Peripheral Tecelllymphoma unspecified
   5. Angioimmunoblastic T-cell lymphoma
   6. Angiocentric lymphoma
   Z Intestinal 'r-eef! lymphoma
   8. Adult T-cell lymphoma/ leukemia
   9. Anaplastic large cell lymphoma
   10. Provisional entity: anaplastic large-cell lymphoma, Hodgkins-like

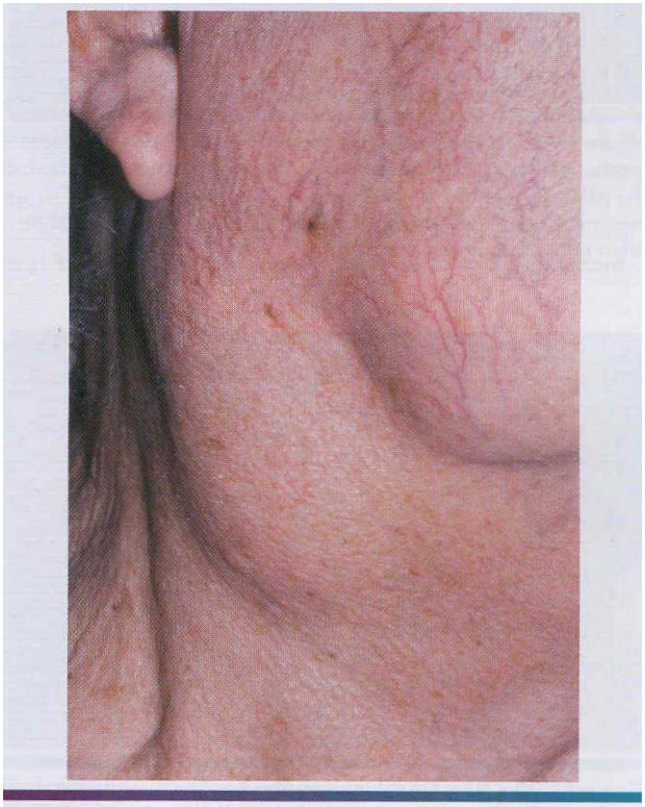

Figure 13-21 • Non-Hodgkin's lymphoma. The matted, nontender lymph node enlargement in the lateral cervical region represents a common presentation of lymphoma.

swellings; they most commonly affect the buccal vestibule. posterior hard palate. or gingiva (Figures 13-22 and 13-23l. 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 complain of paresthesia. particularly with a mandibular lesion. Radiographs usually show an ill-defined or ragged radiolucency. although in the early stages. the radiographic changes may be subtle or non-existent. If untreated. 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. routine chest radiographs. CT scans of the pelvic and abdominal regions. lymphangiography. and bone marrow biopsy. The staging system for Hodgkin's disease (see Table 13-2) has been widely adopted for use with the non-Hodgkin's lymphomas.

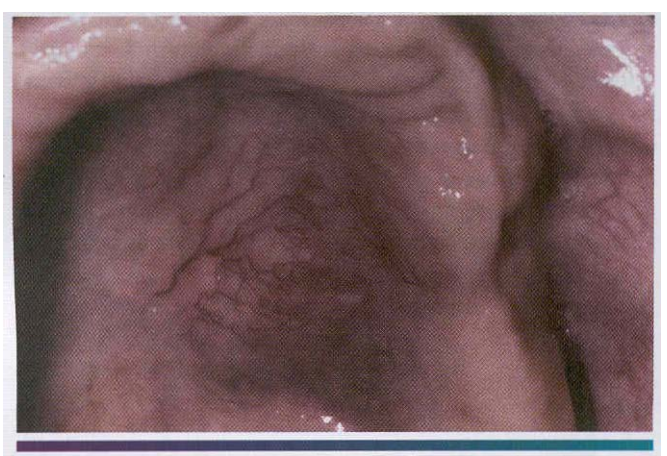

Figure 13-22 • Non-Hodgkin's lymphoma. One of the frequent locations of extranodal lymphoma **in the head and neck area is the palate. where the tumor appears as a nontender, boggy swelling. Note the overlying telangiectatic blood vessels. a feature often noted with malignancy.**

Histopathologic Features

Non-Hodgkin's 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 iymphomas grow as infiltrative. broad sheets of relatively uniform neoplastic cells that usually show little or no evidence of lesional tissue necrosis (Figures 13-24 and 13-25). 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 *diffuse.* If the lymphoma arises in a lymph node. the tumor destroys the normal architecture of the node.

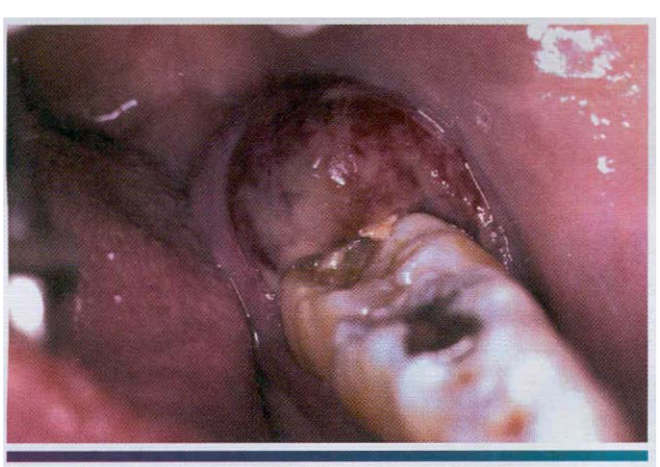

Figure 13-23 • Non-Hodgkin's lymphoma. The ulcerated mass of the retromolar region represents extranodal lymphoma, **which originated in bone and now involves the oral soft tissue.**

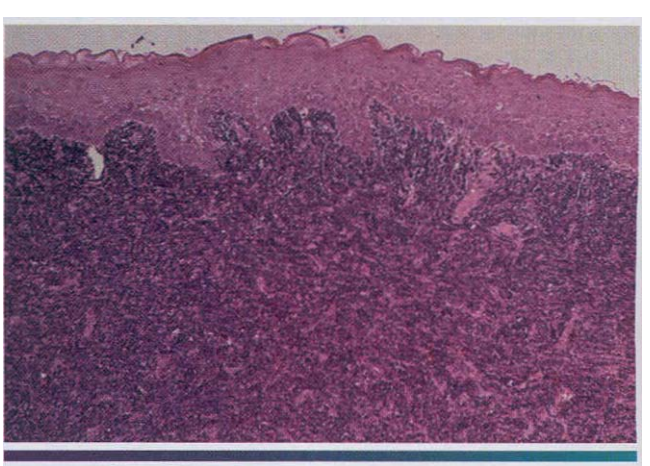

Figure 13-24 . Non-Hodgkin's lymphoma. This low-power photomicrograph shows a diffuse infiltration of the subepithelial connective tissue by lymphoma.

An extranodal lymphoma destroys the normal adjacent host tissue by infiltrating throughout the area.

Treatment and Prognosis

The treatment of a patient with non-Hodgkin's lymphoma consists of radiation therapy and/or chemotherapy. Using the Working Formulation, the appropriate therapy and the extent of therapy depends on the stage and grade of the lymphoma. For the REAL/WHO system, treatment is based on the specific diagnostic category and the stage and grade of the lymphoma. Surgical management is not usually indicated.

Low-grade 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 clinicians opt for a "watch and wait" strategy, treating the patient only if symptoms develop.

For the intermediate-grade and high-grade lymphomas, the treatment depends not only on the grade of the lesion but also on the stage of the disease. If the tumor Is localized, radiation therapy alone may be used. If the tumor is in a more advanced stage, then radiation plus chemotherapy or 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. For intermediate-grade lesions, a failure rate of 30% to 50% can be expected. 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. Mycosis fungoides is a relatively rare malignancy; only about 400 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 mean age at diagnosis of 55 to 60 years. 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 (Figure 13-26). Visceral involvement is also seen at this point.

Approximately 25 cases of mycosis fungoides with oral involvement have been reported. The most com-

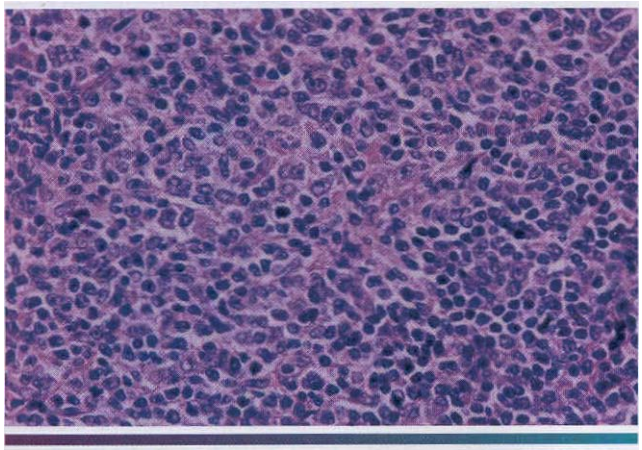

Figure 13-25 . Non-Hodgkin's lymphoma. This high-power photomicrograph shows lesional cells of lymphoma, consisting of population of poorly differentiated cells of the lymphocytic series with minimal cytoplasm.

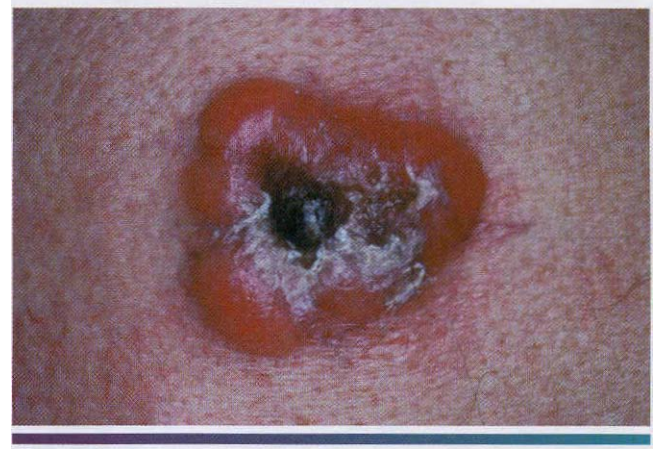

Figure 13-26 • Mycosis fungoides. In the tumor stage of the disease, patients with mycosis fungoides have ulcerated nodules of the skin. (From Oamm DO, White OK, Cibull ML, et al: Mycosis fungoides: initial diagnosis via palatal biopsy with discussion of diagnostic advantages of plastic embedding, *Oral Surg Oral Med Oral Pathol* 58:413-419, 1984.)

monly affected sites are the gingiva. hard and soft palates, and tongue (Figure 13-27). 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.

Sezary 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 eNS 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.

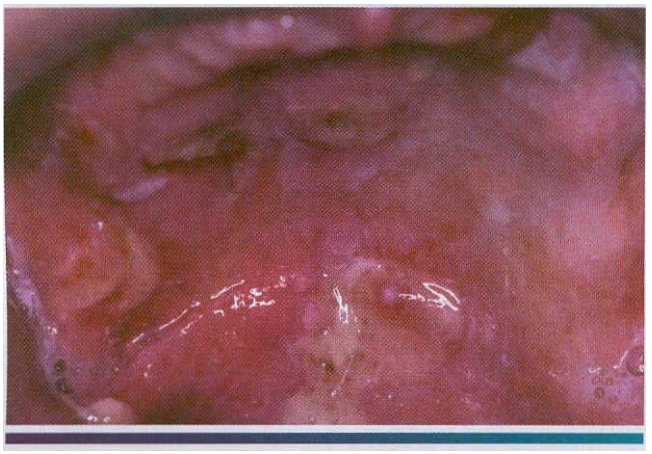

Figure 13-27 • Mycosis fungoides. The ulcerated palatal lesions represent a rare example of oral mucosal involvement by mycosis fungoides.

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 *Sezaty cells.* These atypical lymphocytes classically form small intraepithelial aggregates termed *Pauttler's* ***microabscesses*** (Figure 13-28). 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 (Figure 13-29). A mixed infiltrate of cosinophils, histiocytcs. and plasma cells may be observed in the subepithelial connective tissue.

n,morstage. 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.

Electron microscopic studies showing convoluted nuclei and immunohistochemical studies demonstrating a T-helper phenotype would help to establish the diagnosis of mycosis fungoides. Examination of the periph-

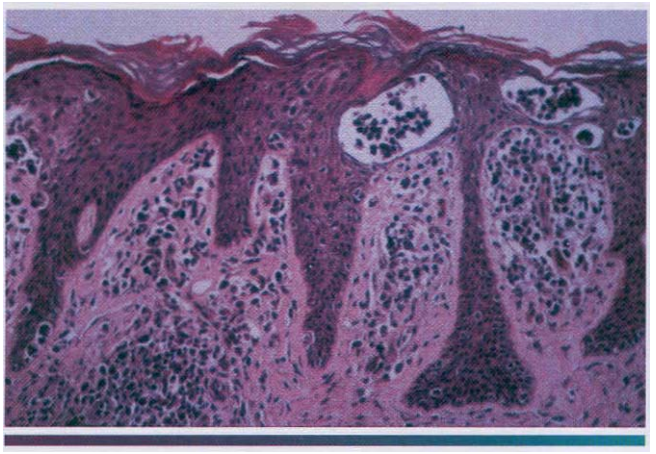

Figure 13-28 • Mycosis fungoides. This medium-power photomicrograph of a cutaneous lesion of mycosis fungoides shows infiltration of the epithelium by the malignant infiltrate that forms Pautrier's microabscesses.

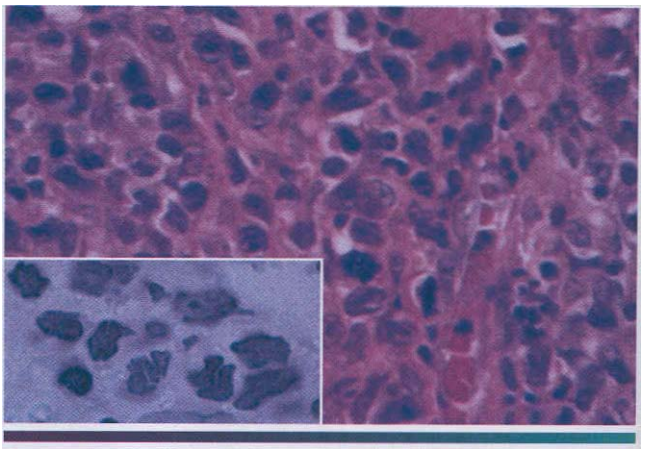

Figure 13-29. Mycosis fungoides. This high-power photomicrograph of an oral biopsy specimen reveals the atypical, malignant lymphoid cells of mycosis fungoides that exhibit a cerebriform morphology *(inset)*.

eral blood of a patient with Sczary syndrome shows circulating atypical lymphoid cells.

Treatment and Prognosis

Topical nitrogen mustard, electron beam therapy, or photochemotherapy (PUVA [8-methoxyPsoralen + Ultra-*Violet* 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. If Sezary syndrome develops, extracorporeal photopheresis or chemotherapy is used as a treatment modality. Extracorporeal photophcrcsls involves the ingestion of the photoactive drug 8-methoxypsoralen, followed by the *removal* of a portion of the patient's blood and a separation of red and white blood cells. The red blood cells are returned to the patient immediately. The white blood cells are irradiated outside the body (cxtracorporcal) with *UV-A*. These altered white cells are then infused back into the patient. Their altered state 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 expire 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'S LYMPHOMA

Burkitt's 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 proeess. 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's lymphoma has been applied to the disease. In addition, there is increased prevalence in other areas of the world, such as northeastern Brazil. and some investigators now refer to such tumors arising in these areas of increased prevalence as endemic Burkitt's lymphoma. This malignancy is thought to be related pathogenetically to Epstein-Barr virus (EBV) because more than 90% of the tumor cells, particularly in the African type, show expression of EBV nuclear antigen and the affected patients have elevated antibody titers to EBV. 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's lymphoma, have been observed in other countries where the neoplasm is usually first detected as an abdominal mass. Some HIV-related lymphomas may also have the microscopic features of Burkitt's lymphoma.

Clinical and Radiographic Features

As many as 50% to 70% of the cases of African Burkitt's lymphoma present in the jaws. The malignancy usually 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 commonly than the mandible fa 2:I 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. American Burkitt's 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 American Burkitt's lymphoma (Figure 13-30).

The growth of the tumor mass may produce facial swelling and proptosts. 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 (Figure 13-31). This process may begin as *several* smaller sites, which evcntu-

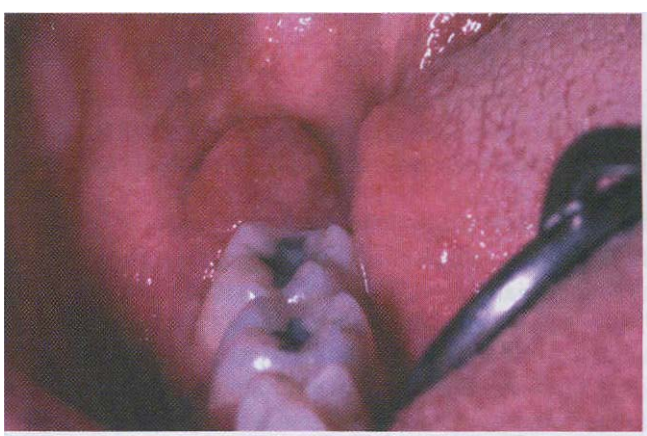

Figure 13-30 . Burkitt's lymphoma. This patient had documented American Burkitts lymphoma involving the abdominal region. The retromolar swelling represents oral involvement with the malignancy.

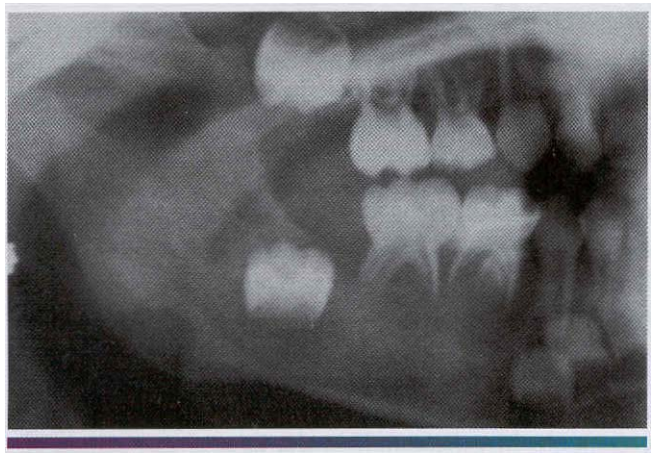

Figure 13-31 • Burkitt's lymphoma. This a-year-old child had evidence of bone destruction with tooth mobility in all four quadrants of his jaws. Note the patchy, ill-defined loss of bone. (Courtesy of Dr. Gregory Anderson)

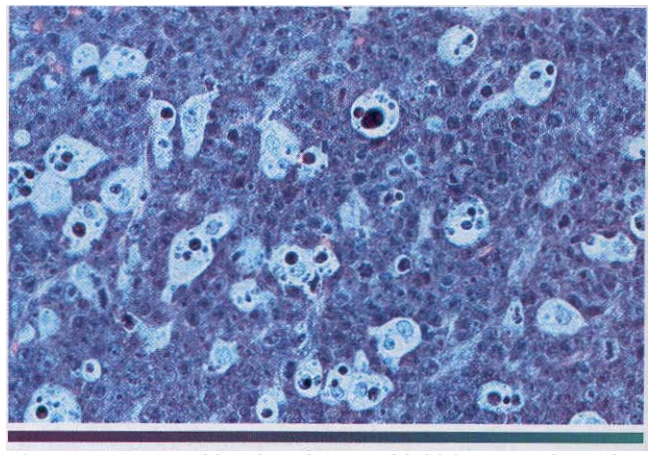

Figure 13-33 • Burkitt's lymphoma. This high-power photomicrograph demonstrates the undifferentiated, small, dark lesicnal cells with numerous histiocytes.

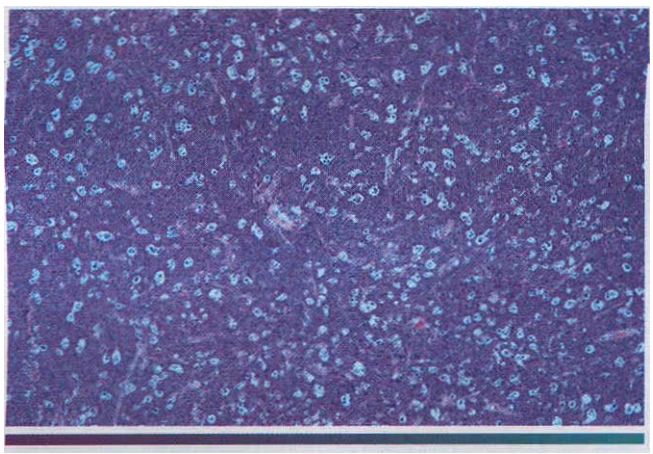

Figure 13-32 • Burkitt's lymphoma. This low-power photomicrograph shows the classic "starry-sky" appearance, a pattern caused by interspersed histiocytic cells with abundant cytoplasm [tstars") set against a background of malignant. darkly staining lymphoma cells ("night sky").

ally enlarge and coalesce. Patchy loss of the lamina dura has been mentioned asan early sign of Burkitt's lymphoma.

Histopathologic Features

Burkitt's lymphoma histopathologically represents an undifferentiated, smaii, noncleaved B-cell lymphoma. The lesion invades as broad sheets of tumor cells that exhibit round nuclei with minimai cytoplasm. Each tumor **nucleus often has several prominent nucleoli, and numerous mitoses are** seen, **A classic *starry-sky* pattern** is associated with the lesional tissue, a phenomenon that is caused by the presence of macrophages within the tumor tissue (Figure 13-32). 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 (Figure *)3-33).*

Treatment and Prognosis

Burkitt's 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's lymphoma in the past was poor, with a median survival time of only $10^1/_2$ months. **More recent trials with more intensive, multiagent chemo**therapeutic 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's lymphoma, the event-free survival has improved to 75% to 85%.

ANGIOCENTRIC T-CELL LYMPHOMA (MIDLINE LETHAL GRANULOMA; IDIOPATHIC MIDLINE DESTRUCTIVE DISEASE; POLYMORPHIC RETICULOSIS; MIDLINE MALIGNANT RETICULOSIS; LYMPHOMATOID GRANULOMATOSIS; ANGIOCENTRIC IMMUNOPROLIFERATIVE LESION)

Angiocentric T-cell lymphoma is a rare process that is characterized clinically by aggressive, nonrelenting destruction of the midline structures of the palate and nasal fossa. For many decades. the nature of this process has been 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

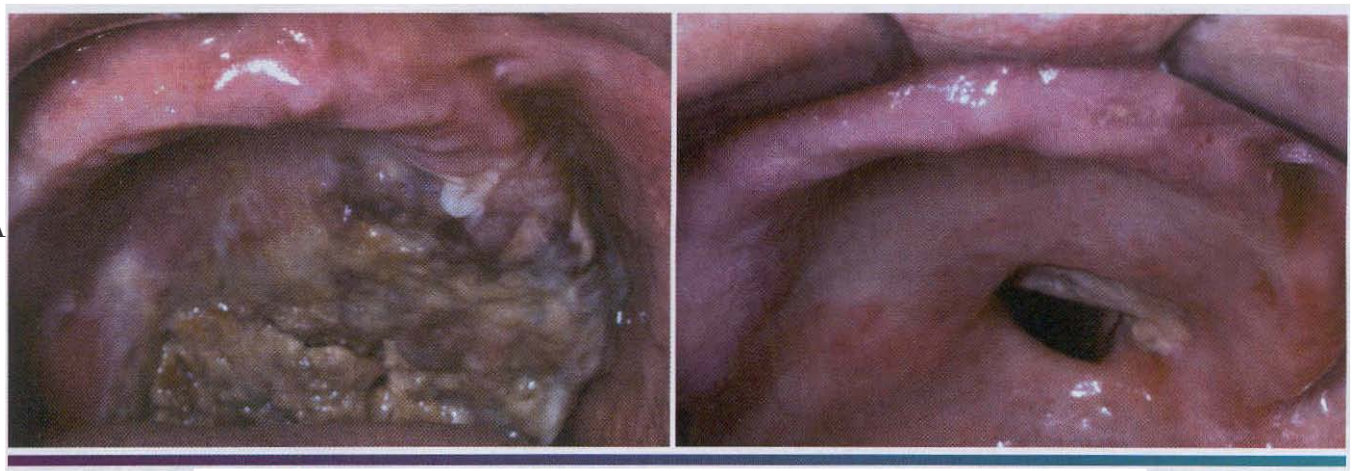

Figure 13-34 • **Angiocentric** T-cell lymphoma. **A. This** 62-year-old **man had a destructive palatal lesion that proved to be a** "l-celllymphoma. **and evaluation showed** cervical lymph **node** involvement **as well. B. Resolution of the lesion 1 month later. after multiagent chemotherapy.**

variety of immunologic (e.g.. Wegener's 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, the consensus among most investigators** is that this disorder should be classified as a T-cell lymphoma, based on modern cytogenetic, immunologic, and molecular studies.

Eventhough angiocentric 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 iymphomas respond. For reasons that are unclear, this con**dition is seen with greater frequency in Asian, Guate**malan, and Peruvian popuiations.

Clinical Features

Angiocentric T-cell lymphoma is typically observed in adults. 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 eniarges and destroys the palatal tissues, which typically creates an oronasal fistula (Figure 13-34). 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,

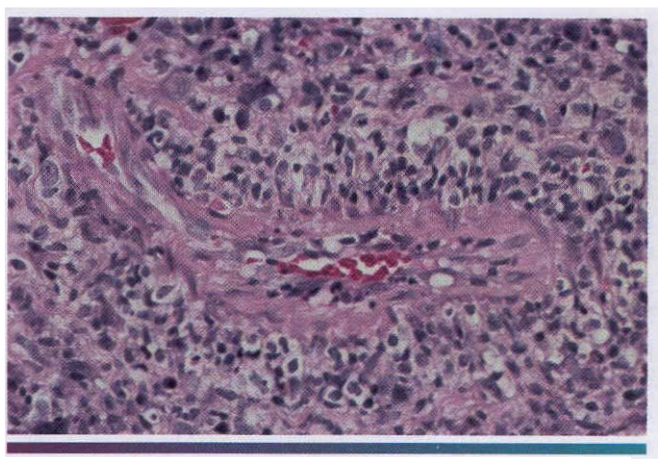

Figure 13-35 • **Angiocentric** T-cell lymphoma. **This medium-power photomicrograph shows** atypical lymphoid **cells infiltrating the wall and filling the lumen of a blood vessel. Such a pattern is termed** *angiocentric* **(meaning "around blood vessels").**

often arranged around blood vessels *(angiocentric)* (Figure 13-35), 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. Large, angular, lymphocytic cells with an atypical appearance are usually identified as a component of the cellular infiltrate. Immunohistochemical evaluation of this Infiltrate often shows a monoclonal T-lymphocyte proliferation. Molecular genetic studies typically show gene rearrangements of the T-lymphocyte receptor consistent with a lymphoreticular malignancy.

Treatment and Prognosis

Without treatment, angiocentric 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 thai are localized usuaily respond 10 radiation therapy, a feature that is similar 10 that of T-ceil lymphomas of other sites, Approximately 4500 cGy is required to control the disease, and many of these patients show no evidence of recurrence or dissemination of the lesion, 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 generaily reported,

MULTIPLE MYELOMA

Multiple myeloma is a relatively uncommon malignancy of plasma ceil origin that often appears to have a multicentric origin within bone. The cause of the condition is unknown, although sometimes a plasmacytoma (see page 527) may evolve into multiple myeloma, This disease -nakcs up about I% of ail malignancies and 10% to 15% of hematologic malignancies, If metastatic disease is excluded, multipie myeloma accounts for nearly 50% of ail malignancies that involve the bone, More than 13,000 cases are diagnosed annually in the United States,

The abnormal plasma ceils that compose this tumor are typieaily 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 neopiasm develops from a single cell. ail the daughter ceils that compose the lesional tissue have the same genetic makeup and produce the same proteins. These proteins arc the immunoglobulin components that the plasma ceil 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 is the most characteristic presenting symptom. Some patients experience pathologic fractures caused by tumor destruction of 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 calcifieations may involve the soft tissues and are thought to be caused by hypercalcemia secondary to tumor-related osteolysis.

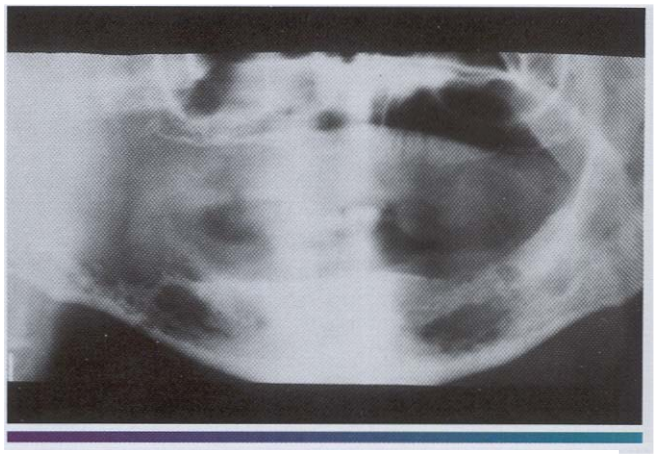

Figure 13-36 • **Multiple** myeloma. Multiple myeloma affecting the mandible. The disease produced several radiolucencies with ragged. ill-defined margins. (Courtesy of Dr. Joseph Finelli.)

Radiographicaily, multiple well-defined. "punched out" radiolucencies or ragged radiolucent lesions may be seen in multiple myeloma (Figure i3-36). 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.

Some patients with multiple myeloma show deposition of amyloid (see page 710) 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.

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 (Figure 13-37).

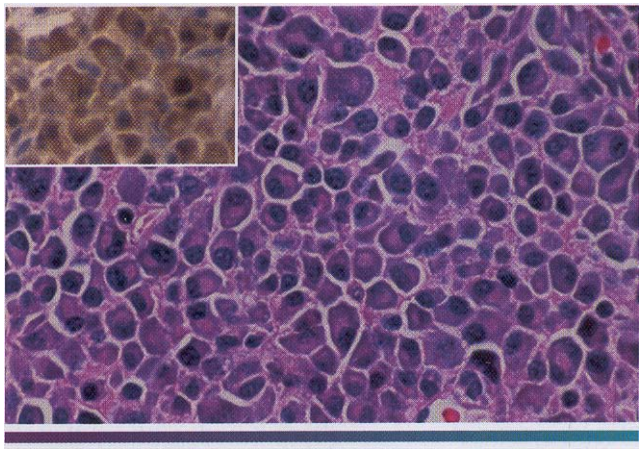

Figure 13-37 • Multiple myeloma. This high-power photomicrograph reveals sheets of malignant plasma cells with eccentric nuclei and stippled nuclear chromatin. Immunohistochemical studies *(inset)* show a uniform reaction of the lesional cells for antibodies directed against *kappa* light chains, indicating a monoclonal neoplastic proliferation.

Mitotic activity may be seen with some frequency. Occasionally, deposition of amyloid may be observed in association with the neoplastic cells. Like other types of amylold, this materiai 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.

Although the histopathologic and radiographic findings strongly suggest a diagnosis of multiple myeloma, screening of the serum or urine by protein electrophoresis should be performed. If an abnormality is detected, 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 (JgA, IgG, IgM, IgO, or IgE) and one of two light chain polypeptides of the same class *(kappa* or *lambda).* Occasionally, only the light chain component is produced by the neoplastic cells.

Treatment and Prognosis

The treatment of multiple myeloma consists of chemotherapy. An alkylating agent, such as melphalan or cyclophosphamide, is often used in conjunction with prednlsone, and approximately 60% of patients will respond initially to this regimen. More aggressive chemotherapeutic regimens and 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.

The prognosis is considered poor, but younger patients tend to fare better than older ones. A median survival time of about 30 to 36 months can be expected after the onset of symptoms. In the past, a 10% 5-year *survival* rate was typical; the prognosis today has not improved dramatically. Most hematology and oncology centers report a 5-year survival rate of 25%. Even with aggressive chemotherapy and bone marrow transplantation, the 5-year survival rate is only marginally improved; nevertheless, this approach seems to hold the most promise for control of this aggressive disease.

PLASMACYTOMA

The plasmacytoma is a untfocal, 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 3:1. 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. Approximatcly 90% 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 (Figure 13-38). No other lesions should be identifiable by a skeletal *survey* or careful physical examination, however.

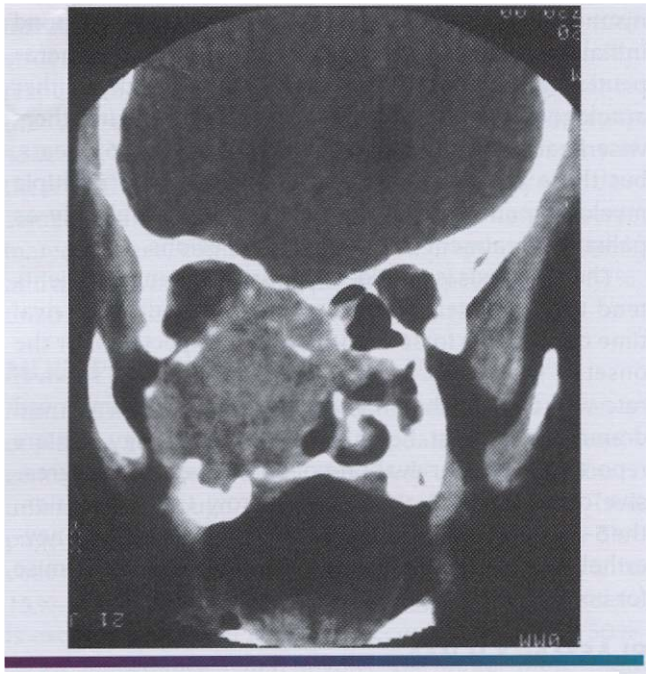

Figure 13-38 • Plasmacytoma. This CT scan depicts a solitary plasmacytoma involving the left maxillary sinus and nasal cavity.

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.

Treatment and Prognosis

Plasmacytomas are usually treated with radiation therapy, and typically a dose of at least 4000 cGy 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 only 30% of these patients showing progression to multiple myeloma and 70% having a 10-year disease-free period after treatment.

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CHAPTER 14

Bone Pathology*

CHAPTER OUTLINE

*Dr. Charles A. Waldron wrote the original version of this chapter in the first edition of this book.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta comprises a heterogeneous group of heritable disorders characterized by impairment **of collagen maturation. Except on rare occasions, the dis-**order arises from heterozygosity for mutations in one of two genes that guide the formation of type I collagen: the COLI A I gene on chromosome 17 and the COLI A2 gene on chromosome 7. Collagen forms a major portion of bone, dentin, sclerae, ligaments, and skin: osteogenesis imperfecta demonstrates a variety of changes that involve these sites. Several different forms of osteogenesis imperfecta are seen, and they represent the most common type of inherited bone disease. Abnormal col**lagenous maturation results in bone with a thin cortex,** fine trabeculation, and diffuse osteoporosis. Upon fracture, healing will occur but may be associated with exu**berant callus formation.**

Clinical and Radiographic Features

Osteogenesis imperfecta is a rare disorder that affects one in 8000 individuals, with many being stillborn or dying shortly after birth. Both autosomal dominant and **recessive hereditary patterns occur, and many cases are sporadic. The severity of the disease varies widely, even** in affected members of a single family. In addition to bone fragility, some affected individuals also have blue sclera, altered teeth, hypoacusis (hearing loss), long bone and spine deformities, and joint hyperextensibility.

The radiographic hallmarks of osteogenesis imperfecta include osteopenia, bowing, angulation or deformity of the long bones, multiple fractures, and worrnian bones in the skull. Wormian bones consist of ten or more **sutural bones that are 6 X 4 mm in diameter or larger and arranged in a mosaic pattern. \Vormian bones are not specific and can be seen in other processes,** such as cleidocranial dysplasia.

Several distinctive findings are noted in the oral cavity. Dental alterations that appear clinically and radiographically identical to dentinogenesis imperfecta (see page 94) are occasionally noted (Figure 14-1, *A).* In affected patients, both dentitions are involved and demonstrate blue to brown translucence. Radiographs typically reveal premature pulpal obliteration, although shell teeth rarely may be seen (Figure 14-1, *B).* Although the altered teeth closely resemble dentinogenesis irnperrecta, the two diseases are the result of different mutations and should be considered as separate processes. Such dental defects in association with the systemic bone disease should be termed opalescent teeth, reserving the **diagnosis of dentinogenesis imperfccta for those patients** with alterations isolated to the teeth.

In addition, patients with osteogenesis imperfecta demonstrate an increased prevalence of class III malocclusion that is caused by maxillary hypoplasia, with or without mandibular hyperplasia. On rare occasions, panoramic radiographs may reveal multifocal radiolucen**cies, mixed radiolucencies, or radiopacities that resemble** those seen in florid cernento-osseous dysplasia. When predominantly radiopaque, these areas are sensitive to inflammation and undergo sequestration easily. In these **patients, marked coarseness also is noted in the remainder** of the skeleton.

Four major types of osteogenesis imperfecta arc rec-ognized, each having several subtypes.

Type I osteogenesis imperfecta. Type I is the most common and mildest form. Affected patients have mild

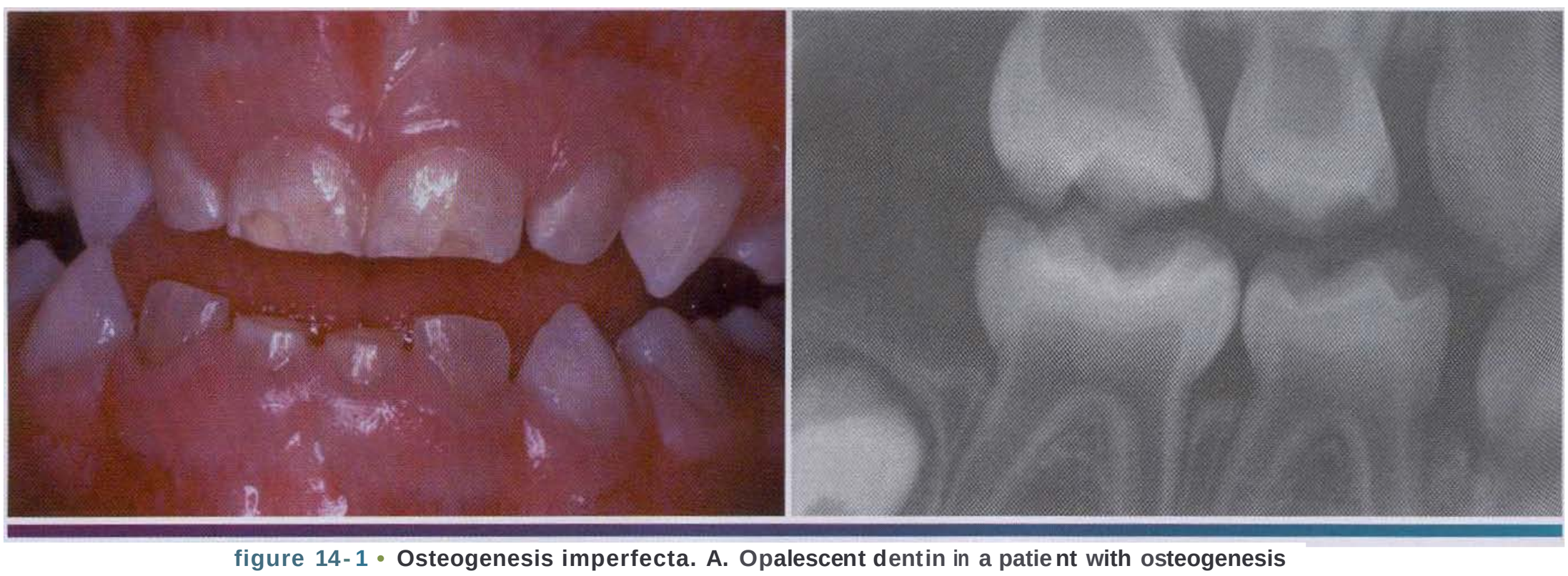

figure 14-1 • **Osteogenesis imperfecta. A. Opalescent dentin in a patient with osteogenesis imperfecta. B. Bite-wing radiograph of the same patient showing shell teeth with thin dentin and enamel of normal thickness. (Courtesy of Dr. Tom Ison.)**

to moderately severe bone fragility. Fractures are present at birth in about 10% of cases, but there is great variability in frequency and age of onset of fractures, with **10% of patients not demonstrating fractures. Most fractures** occur during the preschool years and are less common after puberty. Hearing loss commonly develops before age 30. and most older patients have hearing deficits. Hypermobile joints and easy bruising because of capillary fragility are not rare. Some affected patients have normal teeth, but others show opalescent dentin. The sclerae are distinctly blue at all ages and aid in classification. **Osteogenesis imperfecta type I is inherited as an autosomal dominant trait.**

***Type** /I osteogenesis imperfecta*. Osteogenesis imperfecta type II is the most severe form and exhibits extreme bone fragility and frequent fractures, which may occur during delivery. Many patients are stillborn. and 90% die before 4 weeks of age. Blue sclerae are present (Figure 14-2). opalescent teeth may be present. Both autosomal **recessive and dominant patterns may occur, and many** cases appear to be sporadic.

***Type** 11/ osteogenesis imperfecta*, Type III is the most severe form noted in individuals beyond the perinatal **period and demonstrates moderately severe to severe** bone fragility. The sclerae are normal or pale blue or gray at birth; if discoloration is present, it fades as the child grows older. Ligamentous laxity and hearing loss are **common. Fractures may be present at birth, but there is** a low mortality In Infancy. Although one third survives into adulthood, the majority of affected individuals die during childhood, usually from cardiopulmonary complications caused by kyphoscoliosis. Some patients have **opalescent dentin. whereas others *have* normal teeth.**

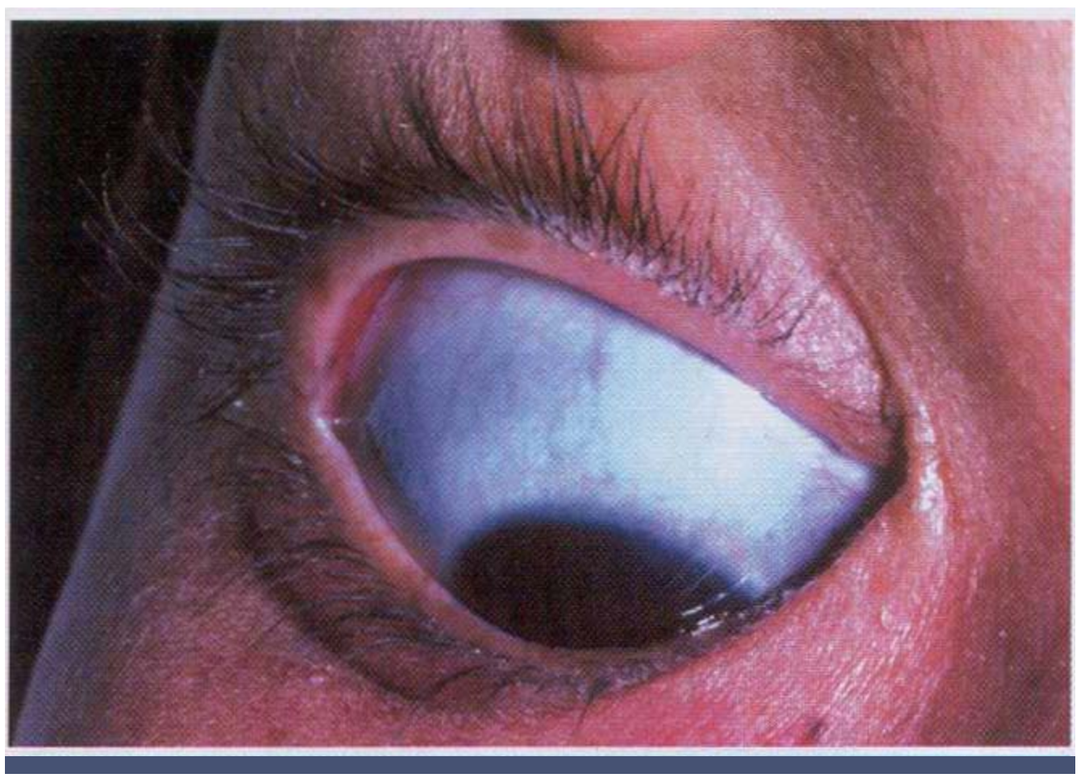

Figure 14-2 • Osteogenesis imperfecta. Blue sclera in a patient with osteogenesis imperfecta.

Both autosomal dominant and recessive hereditary pat**terns arc noted.**

***Type** IV osteogenesis imperfecta*. Type IV is associated with mild to moderately severe bone fragility. The sclerae may be pale blue in early childhood. but the blue color fades later in life. Fractures are present at birth in about 50% of these patients. The frequency of fractures **decreases after puberty. and some individuals never experience bone fracture at any time. Some of these patients have opalescent dentin: others have normal** teeth. This variant appears to be inherited as an autosomal dominant trait.

Histopathologic Features

Upon histopathologic examination, cortical bone appears attenuated. Osteoblasts are present, but bone matrix production is reduced markedly. The bone architecture remains immature throughout life. and there is a failure of woven bone to become transformed to lamellar bone.

Treatment and Prognosis

There is no treatment for osteogenesis irnperfecta. **Management** of the fractures may be a major problem. **Patients with opalescent dentin usually show** severe attrition of their teeth, leading to tooth loss. Treatment of the dentition is similar to that employed for dentinogenesis imperfecta (see page 96), but use of implants is questionable because of the deficient quality of the supporting bone.

In patients with significant malocclusion, orthognathic surgery may be performed. but associated medical problems make presurgical planning paramount. Although highly variable. occasional patients have associated bleeding disorders. cardiac malformations, and an increased risk of hyperthermia. Intubation may be difficult because of kyphoscoliosis and ease of fracture of the **mandible and cervical vertebrae.**

The prognosis varies from relatively good to very poor. Some patients have little to no disability, whereas others have severe crippling as a result of the fractures. In severe forms. death occurs *ill utero,* during delivery. or early in childhood.

OSTEOPETROSIS (ALBERS-SCHONBERG DISEASE; MARBLE BONE DISEASE)

Osteopetrosis is a group of rare hereditary skeletal disorders characterized by a marked increase in bone density resulting from a defect in remodeling caused by failure of normal osteoclast function. The number of **osteoclasts** present **is often increased; however, because** of their failure to function normally, bone is not resorbed.

Defective osteoclastic bone resorption, combined with continued bone formation and endochondral ossification, results in thickening of cortical bone and sclerosis of the cancellous bone.

Although a number ot types have been identified, these pathoses group into two major clinical patterns: (1) infantile and (2) adult osteopetrosis. Although the exact prevalence has not been determined, it is estimated to be I in 100,000 to I in 500,000. The clinical severity of the disease varies widely, even within the same pattern of osteopetrosis.

Clinical and Radiographic Features

II/fal/lile osteopetrosis. Patients discovered with osteopetrosis at birth or in early infancy usually have severe disease that is termed malignant osteopetrosis.

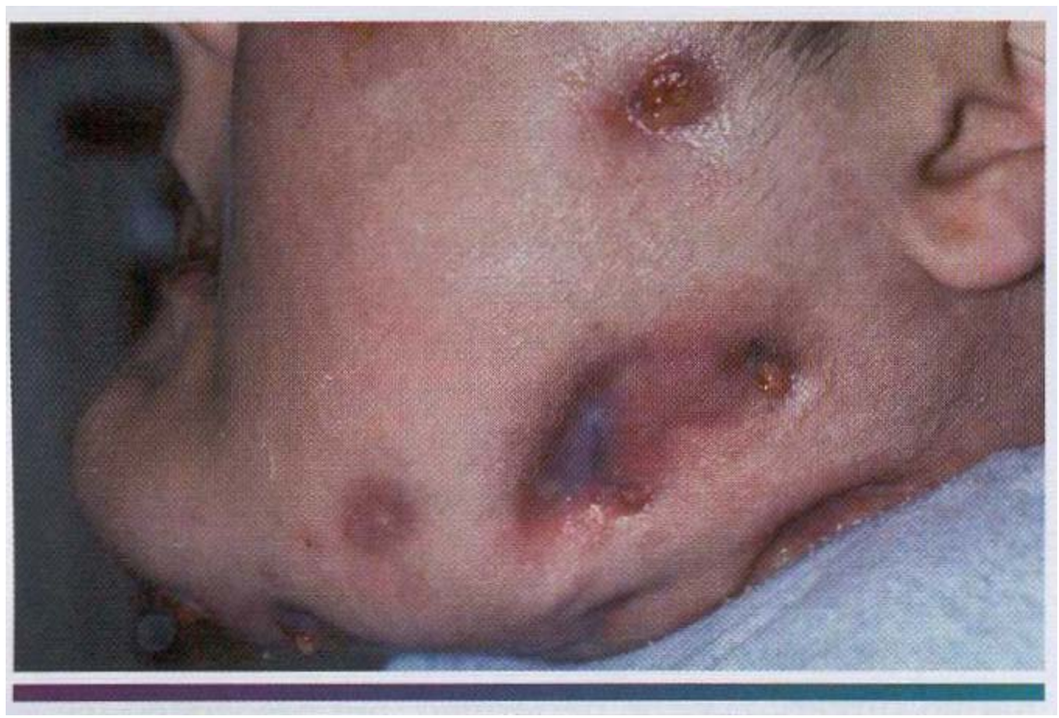

Figure 14-3 • Osteopetrosis. This 24-year-old white man has the infantile form of osteopetrosis. He has suffered from mandibular osteomyelitis. and multiple draining fistulae are present on his face. (Courtesy of Dr. Dan Sarasin.)

In most cases, infantile osteopetrosis is inherited as an autosomal recessive trait and leads to a diffusely sclerotic skeleton. Marrow failure, frequent fractures, and evidence of cranial nerve compression are common.

The initial signs of infantile osteopetrosis often are normocytic anemia with hepatosplenomegaly resulting from compensatory extramedullary hematopoiesis. Increased susceptibility to infection is common as a result of granulocytopenia. Facial deformity develops In many of the children, manifesting as a broad face, hypertelorism, snub nose, and frontal bossing. Tooth eruption almost always is delayed. Failure of resorption and remodeling of the skull bones produces narrowlngs of the skull foramina that press on the various cranial nerves and result in optic nerve atrophy and blindness, deafness, and facial paralysis. In spite of the dense bone, pathologic fractures are common. Osteomyelitis of the jaws is a common complication of tooth extraction (Figure 14-3).

Radiographically, there is a widespread increase in skeletal density with detects in metaphyseal remodeling. The radiographic distinction between cortical and cancellous bone is lost (Figure 14-4). In dental radiographs, the roots of the teeth often are difficult to visualize because of the density of the surrounding bone.

Less severe variants of infantile osteopetrosis exist and have been termed intermediate osteopetrosis. Affected patients oflen are asymptomatic at birth but frequently exhibit fractures by the end of the first decade. Marrow failure and hepatosplenomegaly are rare.

In some cases, patients show radiographic evidence of diffuse sclerosis and associated marrow failure bUl resolve without specific therapy. This pattern has been termed transient osteopetrosis, and most affected patients return to normalcy with no known sequelae.

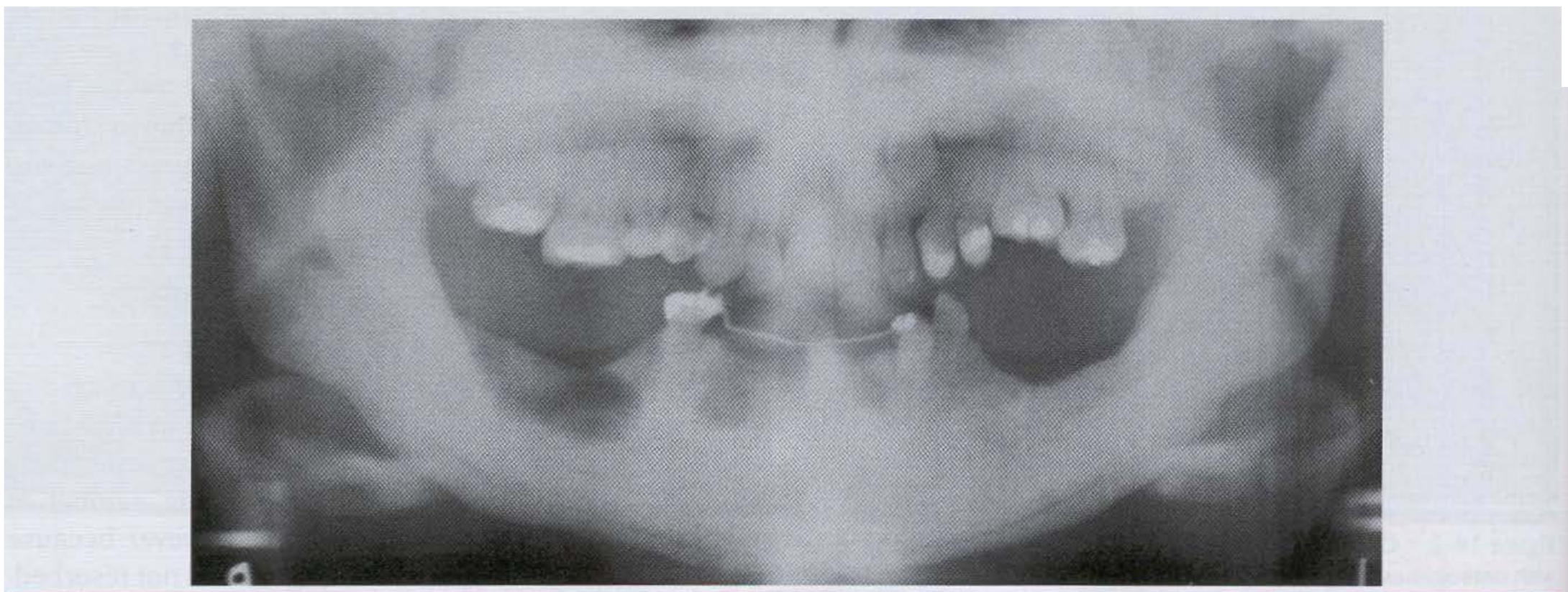

Figure 14-4 • Osteopetrosis. Extensive mandibular involvement is apparent in this radiograph of a 31-year-old woman. She had been diagnosed as having osteopetrosis as a child. There is a history of multiple fractures and osteomyelitis of the jaws. (Courtesy of Dr. Dan Sarasin.)

***Adult** osteopetrosis.* Adult osteopetrosis is usually discovered later in life and exhibits less severe manifestations. **In most patients, this pattern is inherited as an autosomal** dominant trait **and has been termed benign osteopetrosis.** The axial skeleton usually reveals significant sclerosis whereas the long bones demonstrate little or no defects. Approximately 40% are asymptomatic, and marrow failure is rare. Occasionally. the diagnosis is discovered initially on review of dental radiographs that reveal a diffuse increased radiopacity of the medullary portions of the bone. In symptomatic patients, bone pain is frequent.

Two **major variants of adult osteopetrosis are seen. In one form, cranial *nerve* compression is common,** although fractures occur rarely. In contrast, the second **pattern demonstrates frequent fractures, but nerve compression** is uncommon. When the mandible is Involved, **fracture and osteomyelitis after tooth extraction are significant complications.**

Although distinctly uncommon, other causes of widespread osteosclerosis exist and should be considered during evaluation of patients with osteopetrosis. Such **diseases include autosomal dominant osteosclerosis** (endosteal hyperostosis, Worth type), sclercsteosls. 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 (Figure 14-5)
- Osteophytic bone formation

Numerous osteoclasts **may be seen, but there is no evidence that they function because Howship's lacunae are not visible.**

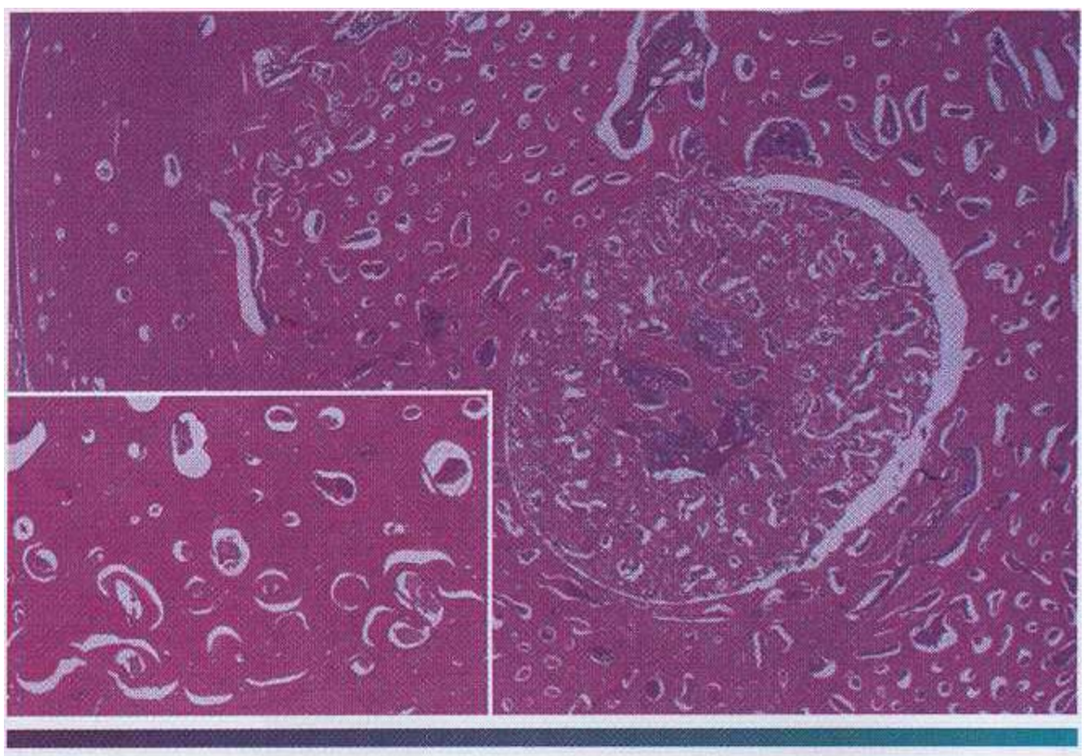

Figure 14·5 • Osteopetrosis. Low-power **photomicrograph showing sclerotic bone that is replacing the normal cancellous bone. The inset shows a nodular pattern of the dense bone obliterating the marrow spaces.**

Treatment and Prognosis

Because of the mild severity of the disease, adult **osteopetrosis is usually associated with long-term survival. In contrast, the prognosis of infantile osteopetrosis** without therapy is typically poor, with most affected patients dying during the first decade of life. Bone marrow transplantation is the only hope for permanent **cure. However, an appropriately matched donor is available** for only about half of affected patients, and successful engraftment occurs in only approximately 45% **of those receiving bone marrow transplantation.**

Because of the unavailability or risk of bone marrow transplantation, search for other therapies is ongoing. **Interferon gamma-Ib, often in combination with calcitriol, has been shown to reduce bone mass, decrease** the prevalence of infections, and lower the frequency of **nerve compression. Other therapeutic avenues include administration of corticosteroids (to increase circulating** red blood cells and platelets), parathormone, macrophage colony stimulating factor, and erythropoietin. Limiting calcium intake also has been suggested.

Additional therapy consists of supportive measures. **such as transfusions and antibiotics for the complications. Osteomyelitis of the jaws requires rapid intervention to minimize osseous destruction. Affected patients** should receive early diagnosis, appropriate drainage and surgical debridement, bacterial culture with sensitivity, **appropriate antibiotic therapy, and reconstruction if necessary.** The infection often requires prolonged antibiotic therapy, with fluoroquinolones and lincomycin often being most effective. Hyperbaric oxygen is useful in promoting healing of recalcitrant cases.

CLEIDOCRANIAL DYSPLASIA

Best known for its dental and clavicular abnormalities, cleidocranial dysplasia is a disorder of bone caused by a defect in the CBFAI gene of chromosome 6p21. This gene normally guides osteoblastic differentiation and appropriate bone formation. The process was initially thought to involve only membranous bones (e.g., clavicles, skull, flat bones) but now is known also to affect **endochondral ossification and to represent a generalized** disorder of skeletal structures. The disease shows an **autosomal dominant inheritance pattern, but as many as 40% of cases appear to represent spontaneous mutations. This condition formerly was known as *cleidocranial dysostosis*.**

Clinical and Radiographic Features

The bone defects in patients with cleidocranial dysplasia chiefly involve the clavicles and skull, although a wide variety of anomalies may be found in other bones. The clavicles are absent, either unilaterally or bilaterally, in about 10% of all cases. More commonly, the clavicles show varying degrees of hypoplasia and malformation.

The muscles associated with the abnormal clavicles are underdeveloped. The patient'S neck appears long: the shoulders are narrow and show marked drooping. The absence or hypoplasia of the clavicles leads to an unusual mobility of the patient's shoulders. In some instances, the patient can approximate the shoulders in front of the chest (Figure 14-6). Although the clavicular defects result **in variations of the associated muscles. function is** remarkably good.

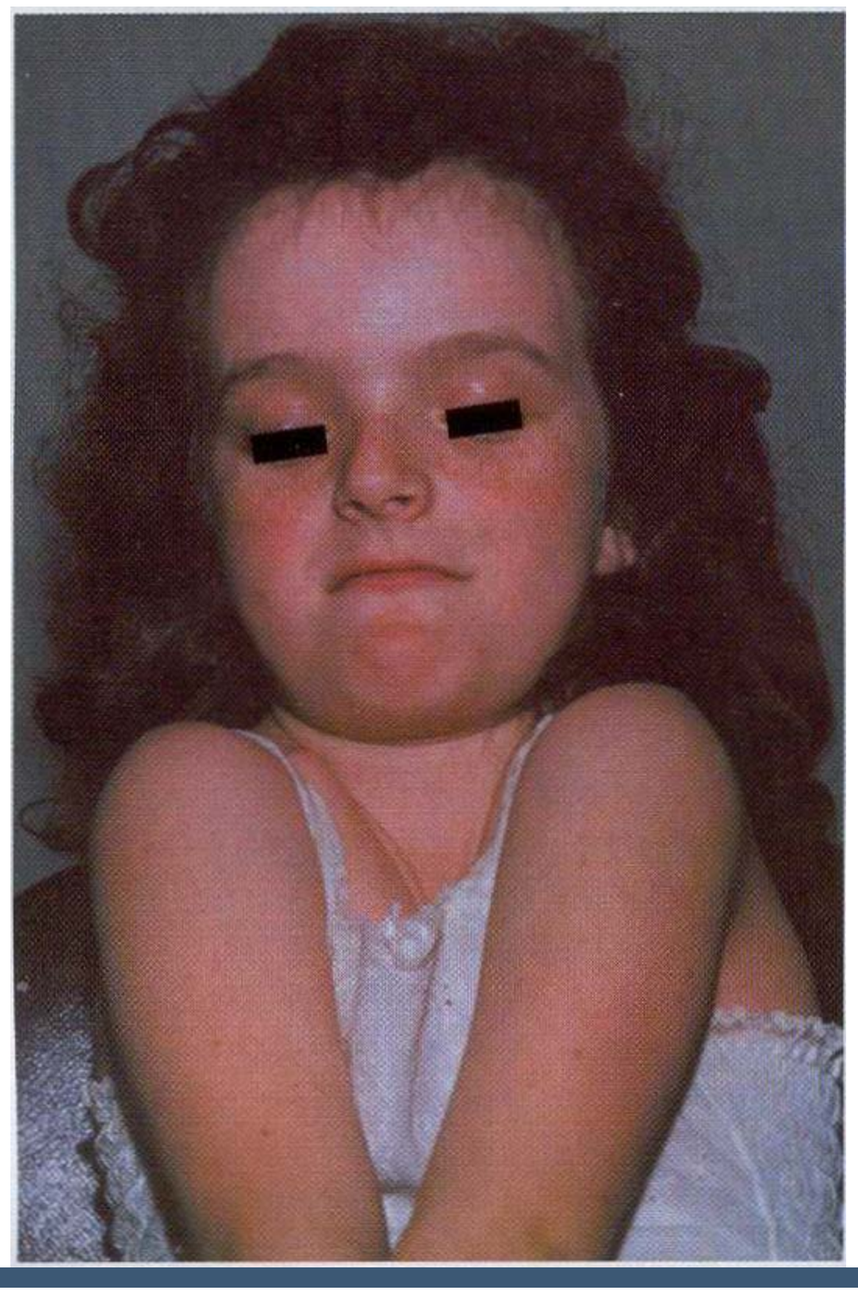

Figure 14-6 • Cleidocranial dysplasia. The patient can almost approximate her shoulders in front of her chest. (Courtesy of Dr. William Bruce.)

The appearance of the patient affected by cleidocranial dysplasia often is diagnostic, The patients tend to be of short stature and have large heads with pronounced frontal and parietal bossing. Ocular hypertelorism and a broad base of the nose with a depressed nasal bridge often are noted. On skull radiographs, the sutures and fontanels show delayed closure or may remain open throughout the patient'S life, Secondary centers of ossi**fication appear in the suture lines, and many wormian** bones may be seen.

The gnathic and dental manifestations are distinctive and may lead to the initial diagnosis. The patients often have a narrow, high-arched palate, and there is an increased prevalence of cleft palate. Prolonged retention of deciduous teeth and delay or complete failure of eruption of permanent teeth are characteristic features. Upon review of dental radiographs, the most dramatic finding **is the presence of numerous unerupted permanent and** supernumerary teeth, many of which frequently exhibit distorted crown and root shapes (Figure 14-7). The **number of supernumerary teeth can be impressive, with** reports of some patients demonstrating greater than 60 such teeth.

In addition to the dental alterations, review of pano**ramic radiographs also reveals an increased prevalence** of a number of additional osseous malformations. The **mandible often demonstrates coarse trabeculation with areas of increased density, narrow ascending rami, and**

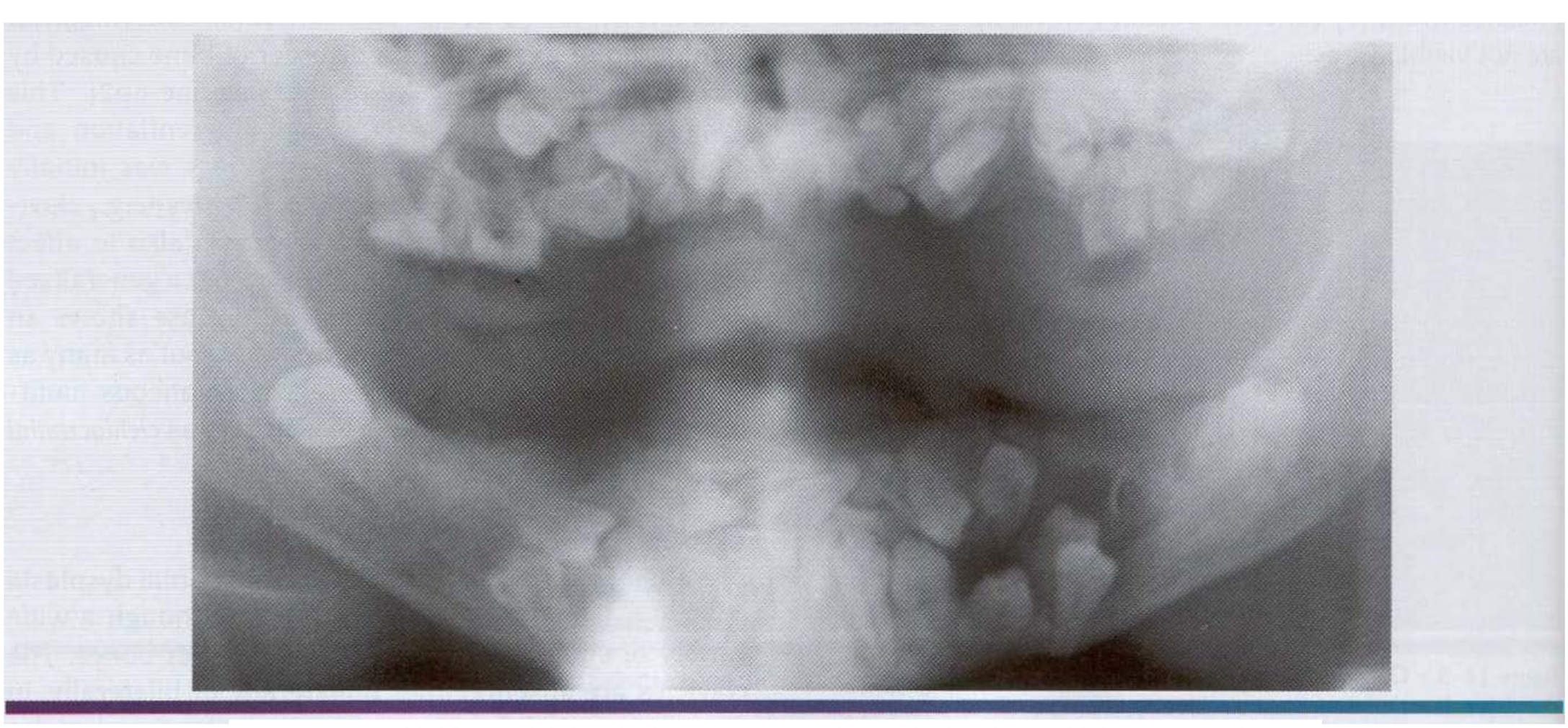

Figure 14-7 • Cleidocranial dysplasia. Panoramic radiograph showing multiple unerupted teeth. (Courtesy of Dr. John R. Cramer.)

slender, pointed coronoid processes. The maxilla often is associated with a thin zygomatic arch and small or **absent maxillary sinuses.**

Although young patients typicaily exhibit a relativeiy normai jaw relationship, as the individuals age, a short lower face height, acute gonial angie, anterior inclination of the mandible, and mandibular prognathism deveiop. Clinicians believe that these changes may be from inadequate verticai growth of the maxiila and hypopiastic alveolar ridge development caused by deiay or iack of eruption of the permanent teeth.

Histopathologic Features

The reason for failure of permanent tooth eruption in patients with cleidocranial dysplasia is not understood well. Microscopic study of unerupted permanent teeth **shows that these teeth lack secondary cementum.**

Treatment and Prognosis

No treatment exists for the skull, clavicular, and other bone anomaiies associated with cleidocranial dysplasia. Most patients function well without any significant problems. It is not unusual for an affected individual to be **unaware of the disease until some professional calls it to his or her attention.**

Treatment of the dental problems associated with the disease, however, may be a major problem. Therapeutic **options include full-mouth extractions with denture construction, autotransplantation of selected impacted teeth** followed by prosthetic restoration, or removal of primary and supernumerary teeth followed by exposure of permanent teeth that are subsequently extruded orthodontically. The latter mode of therapy appears to be the treatment of choice; if performed before adulthood, it can prevent the short lower face height and mandibular prognathism.

FOCAL OSTEOPOROTIC MARROW DEFECT

The focal osteoporotic marrow defect is an area of **hematopoietic marrow that is sufficient in size to produce** an area of radiolucency that may be confused with **an intraosseous neoplasm. The area does not represent** a pathologic process, but its radiographic features may be confused with a variety of pathoses. The pathogen**esis of this condition is unknown. Various theories** include the following:

- **Aberrant bone regeneration after tooth extraction**
- Persistence of fetal marrow
- **Marrow hyperplasia in response to increased** demand for erythrocytes

Clinical and Radiographic Features

The focal osteoporotic marrow defect is invariably asymptomatic and is detected as an incidental finding on **a radiographic examination. The area appears as a radiolucent lesion, varying in size from several millimeters to several centimeters in** diameter. In **many instances, when** discovered in panoramic radiographs, the area appears **radiolucent and somewhat circumscribed; however,** upon review of higher detailed periapical radiographs, the defect typically exhibits ill-defined borders and fine central trabeculations (Figure 14-8). More than 75% of ail cases are discovered in adult women. About 70% **occur in the posterior mandible, most often in edentulous** areas. No expansion of the jaw is noted clinically,

Histopathologic Features

Microscopically, the defects contain cellular hematopoietic marrow, Lymphoid aggregates may be present. Bone trabeculae included in the biopsy specimen show no evi**dence of abnormal osteoblastic or osteoclastic activity** (Figure 14-9),

Treatment and Prognosis

The radiographic findings, although often suggestive of the diagnosis, are not specific and may simulate those

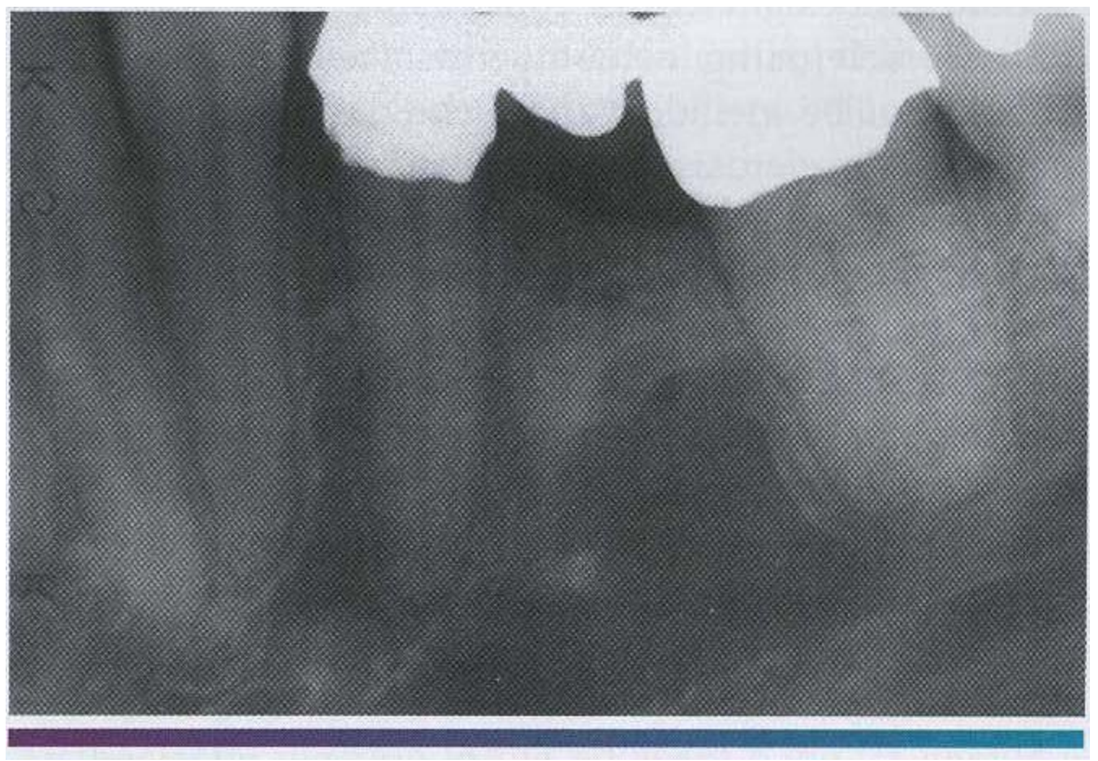

Figure 14-8 • Focal osteoporotic marrow defect. The periapical film shows a radiolucent area containing fine trabeculatlons. (Courtesy of Dr; Ed McGaha.)

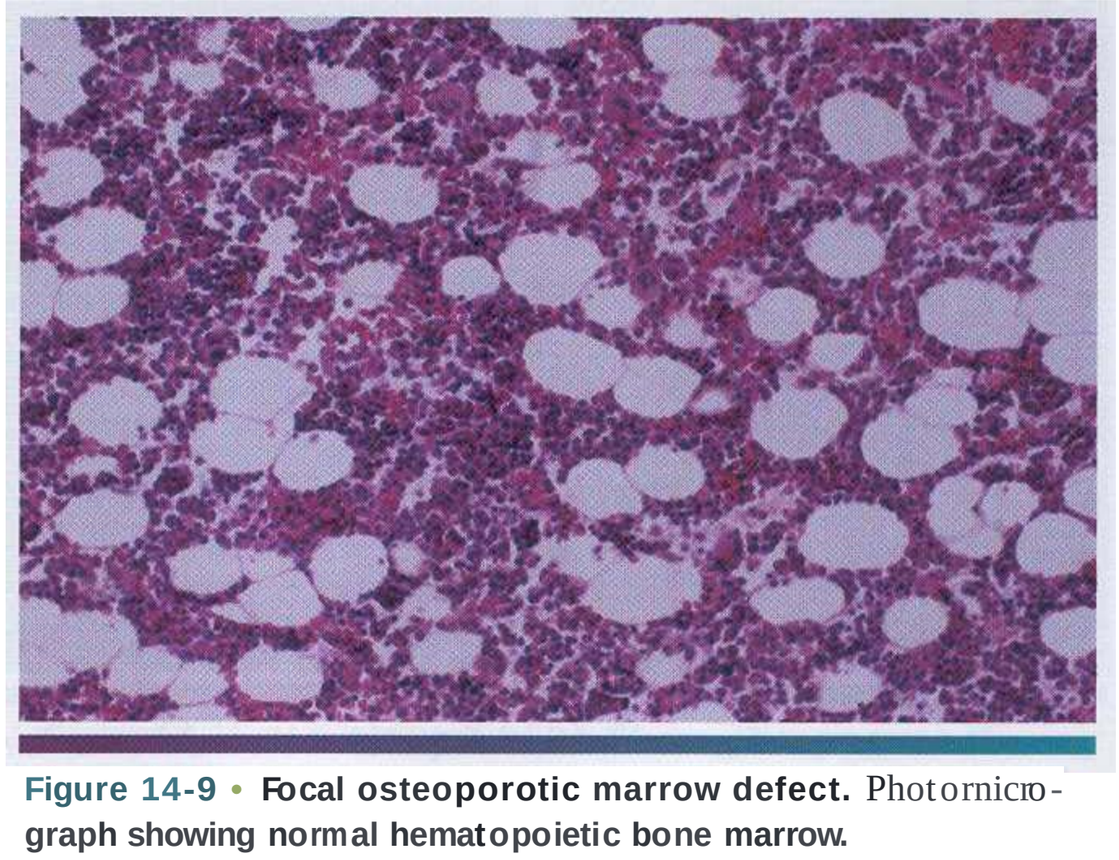

Figure 14-9 • Focal osteoporotic marrow defect. Photornicro**graph showing normal hematopoietic bone marrow.**

of a variety of other diseases. Incisional biopsy, therefore, often is necessary to establish the diagnosis.

Once the diagnosis is established, no further treatment is needed. The prognosis is excellent, and no association between focal osteoporotic marrow defects and anemia or other hematologic disorders has been established.

IDIOPATHIC OSTEOSCLEROSIS

Idiopathic osteosclerosis refers to a focal area of increased radiodensity that is of unknown cause and 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*. These sclerotic areas are not restricted to the jaws, and radiographically similar lesions may be found in other bones.

Similar radiopaque foci may develop in the periapical areas of teeth with nonvital or significantly inflamed pulps; these lesions most likely represent a response to a low-grade inflammatory stimulus. Such reactive foci should be designated as condensing osteitis or focal chronic sclerosing osteomyelitis (see page 131) and should not be included under the designation of idiopathic osteosclerosis. Because past studies did not distinguish the idiopathic lesions from those of inflammatory origin, confusion in terminology has resulted.

Clinical and Radiographic Features

Although previous studies often are difficult to interpret because of differences in diagnostic criteria, the prevalence appears to be approximately 5%, with some investigators suggesting a slightly increased frequency in blacks and Asians. No significant sex predilection is seen.

Upon review of several studies with long-term follow-up, a pattern has emerged. Although exceptions can be seen, most areas of idiopathic osteosclerosis arise in the late first or early second decade. Once noted, the lesions may remain static, but many reveal a slow increase in size. In almost all cases, once the patient reaches full maturity, all enlargement ceases and the sclerotic area stabilizes. In a smaller percentage, the lesion diminishes or undergoes complete regression. The peak prevalence of osteosclerosis occurs in the third decade, with the attainment of peak bone mass seen in the fourth decade.

Idiopathic osteosclerosis is invariably asymptomatic, not associated with detectable cortical expansion, and is typically detected during a routine radiographic examination. About 90% of examples are seen in the mandible, most often in the first molar area. The second premolar and second molar areas also are common sites. In most cases, only one focus of sclerotic bone is present. A small number of patients have two or even three separate areas of involvement.

Radiographically, the lesions are characterized by a well-defined, rounded, or elliptic radiodense mass. Although the majority is uniformly radiopaque, occasional large lesions demonstrate a nonhomogeneous mixture of increased and reduced radiopacity. This is most likely due to variation in the three-dimensional shape of the lesion and is unrelated to differences in the mineral content of the mass. The lesions vary from 3 mm to more than 2.0 em in greatest extent. A radiolucent rim does not surround the radiodense area. Most examples of idiopathic osteosclerosis are associated with a root apex. In a lesser number of cases, the sclerotic area may extend into or be located only in the interradicular area (Figure 14-IO). In about 20% of cases, the sclerotic area

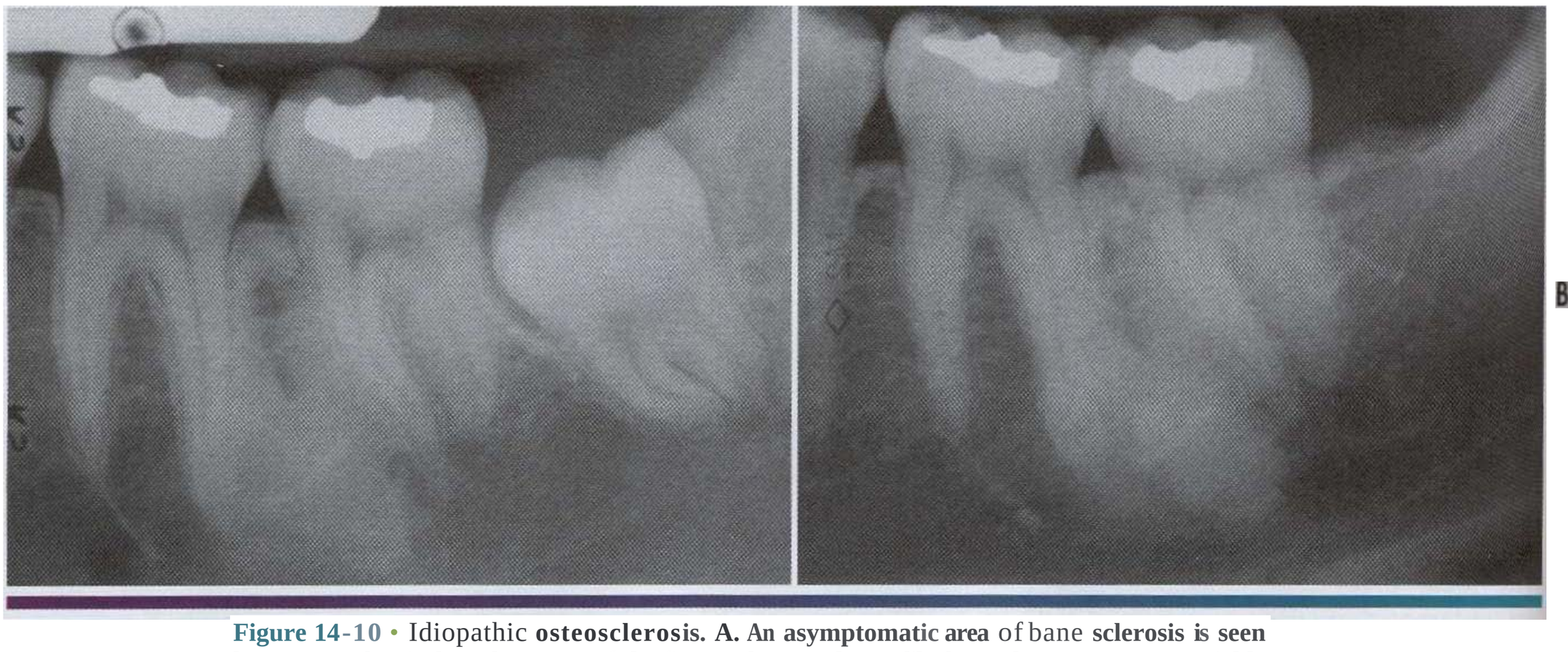

Figure 14-10 • Idiopathic osteosclerosis. A. An asymptomatic area of bane sclerosis is seen between and apical to the roots of the first and second mandibular molars. B, No appreciable change can be seen on this radiograph taken 10 years later. (Courtesy of Dr. Michael Quinn.)

is located in the jaw, with no apparent relationship to a tooth. Rarely, the sclerotic bone may surround all or portions of an impacted tooth. Root resorption and movement of teeth have been noted but are uncommon.

Histopathologic Features

In the few microscopic studies that have been reported, the lesion consists of 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 considered only if associated symptoms or significant cortical expansion is present. Although idiopathic osteosclerosis demonstrates radiographic and histopathologic similarities with a compact osteoma (see page 566), the lack of cortical expansion and failure of continued growth rule against a neoplastic process. Differentiation from condensing osteitis may be difficult; but in the absence of a deep restoration or caries, a periapical radiodense area associated with a vital tooth is likely to represent idiopathic osteosclerosis.

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 for idiopathic osteosclerosis, because there is little or no tendency for the lesions to progress or change in adulthood.

MASSIVE OSTEOLYSIS (GORHAM DISEASE; GORHAM-STOUT SYNDROME; VANISHING BONE DISEASE; PHANTOM BONE DISEASE)

Massive osteolysis is a rare disease that is characterized by spontaneous and usually progressive destruction of one or more bones. The destroyed bone initially is replaced by a vascular proliferation. The affected area does not regenerate or repair itself; eventually, the site of destruction fills with dense fibrous tissue.

The cause of massive osteolysis is unknown. There is no evidence of any underlying metabolic or endocrine imbalance. Many investigators believe that massive osteolysis is related to a vascular proliferation that is occasionally multicentric and has been termed hemangiomatosis of bone.

Clinical and Radiographic Features

Although massive osteolysis has been documented in patients up to 70 years of age, most affected patients are children and young adults. About 50% of all patients report an episode of trauma before the diagnosis, but this is often trivial in nature. Lesions have occurred in almost any bone or combination of bones. The most commonly involved sites are the pelvis, humeral head, humeral shaft, and axial skeleton. Generally, the results of laboratory studies are completely within normal limits.

In approximately 30% of affected patients, maxillofacial involvement is noted, with the mandible being affected most frequently. Simultaneous involvement of the maxilla and mandible may occur. Signs and symptoms include mobile teeth, pain, malocclusion, deviation of the mandible, and clinically obvious deformity. Obstructive sleep apnea syndrome has been noted secondary to posterior mandibular displacement after extensive osteolysis. Pathologic fracture of the mandible may occur.

Radiographically, the earliest changes consist of intramedullary radiolucent foci of varying size with indistinct margins (Figure i4-il). These coalesce to become larger and involve the cortical bone. Eventually, large portions of the involved bone disappear (Figure i4-i2). As the process proceeds, newly involved areas often demonstrate loss of the lamina dura and thinning of the cortical plates before development of obvious radiolucency.

Histopathologic Features

The microscopic findings in massive osteolysis contrast sharply with the striking clinical and radiographic findings. In the early stages of disease, specimens removed from the radiolucent defects consist of a nonspecific vascular proliferation intermixed with fibrous connective and a chronic Inflammatory Infiltrate of lymphocytes and plasma cells. The vascular proliferation varies in intensity and is characterized by thin-wailed channels that may be capillary or cavernous in nature (Figure i4-i3). Osteoclastic reaction in the adjacent bone fragments is usually not conspicuous.

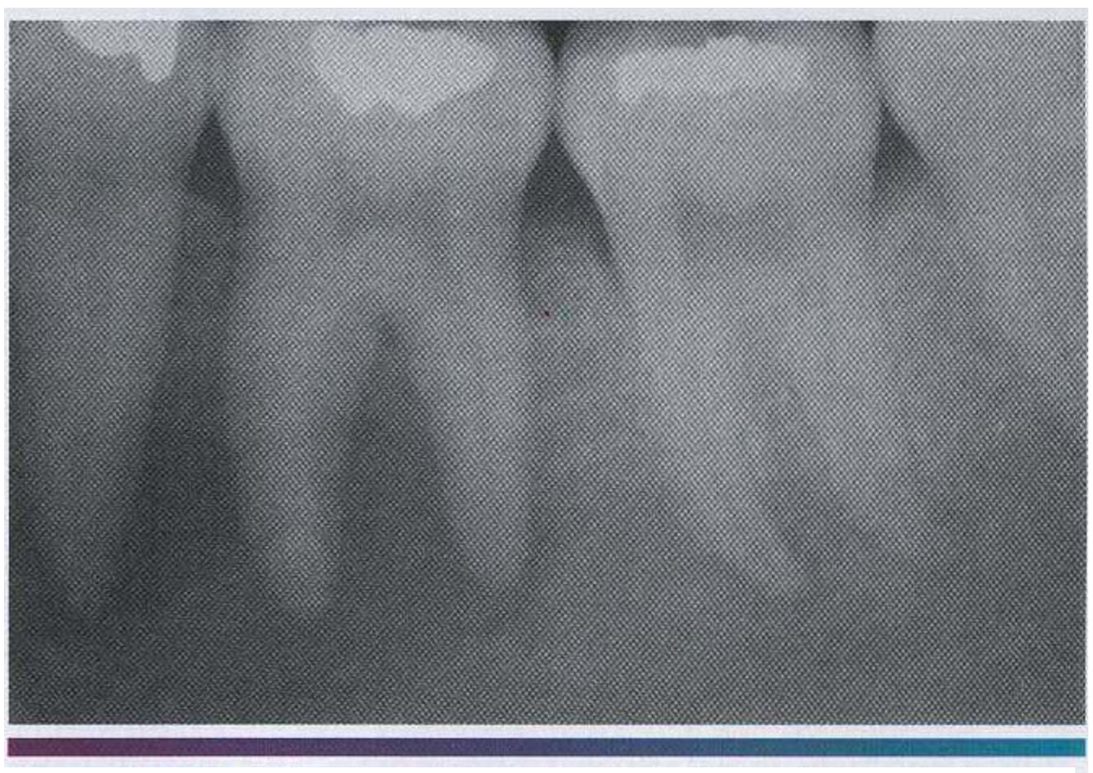

Figure 14-11 • Massive osteolysis. Periapical radiograph showing an ill-defined radiolucency associated with vital mandibular teeth. Note the loss of lamina dura. (Courtesy of Dr. John R. Cramer.)

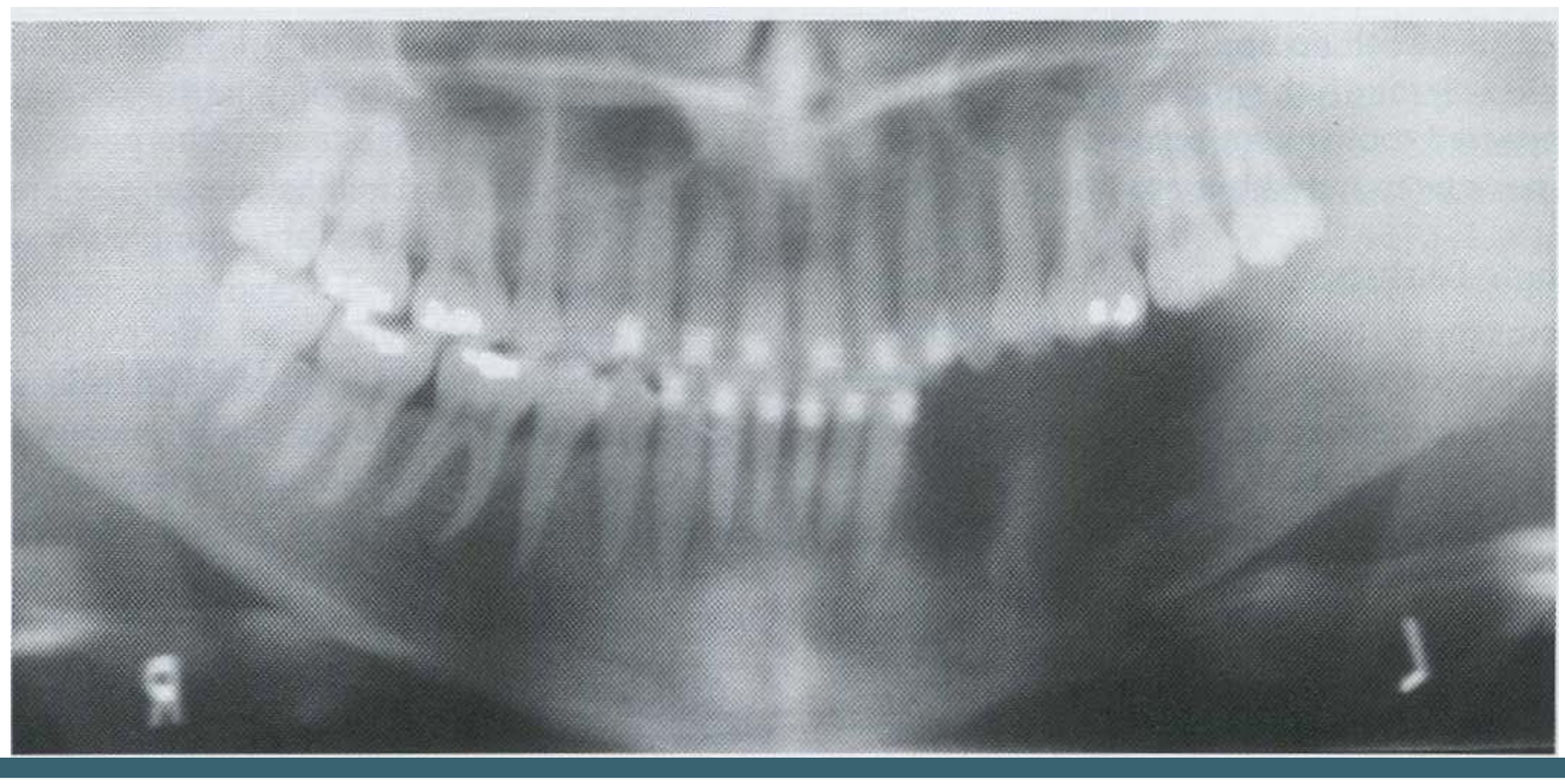

Figure 14-12 • Massive osteolysis. Panoramic radiograph of the same patient shown in Figure 14-11, showing extensive bone loss and a pathologic fracture of the left mandible. This destruction occurred over an 8-month period. (Courtesy of Dr. John R. Cramer.)

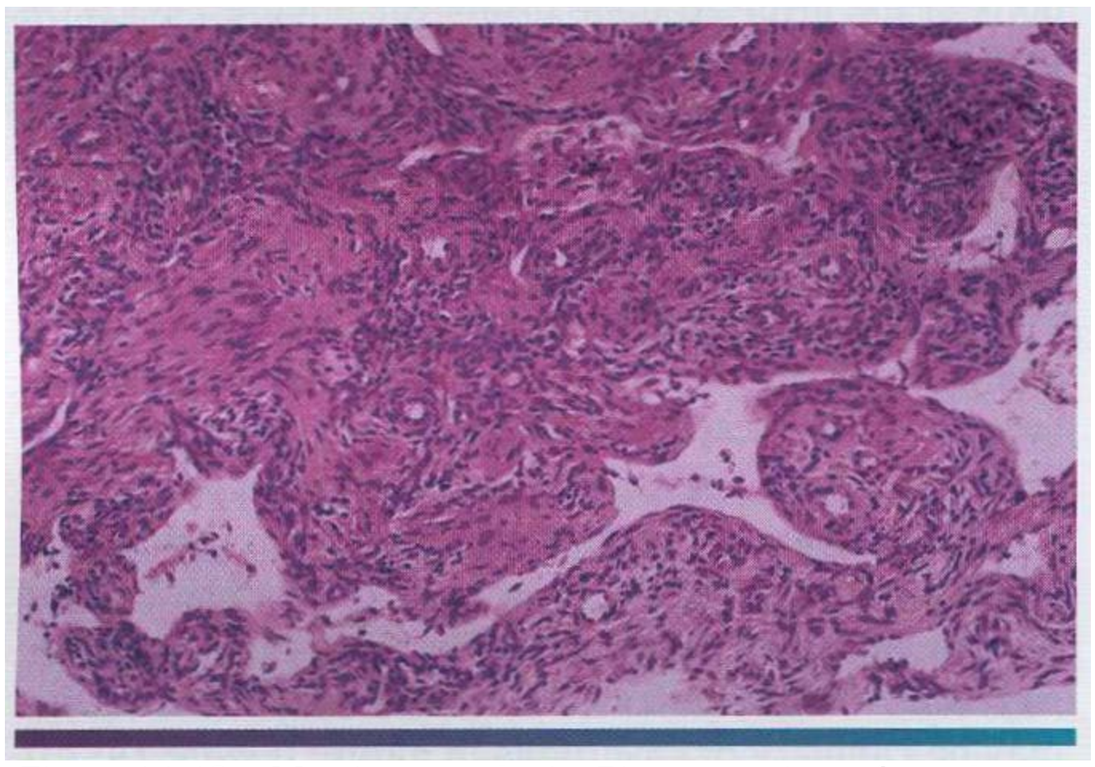

Figure 14-13 • Massive osteolysis. Biopsy specimen from the same patient shown in Figures 14-11 and 14-12. The loose, highly vascular connective tissue shows a diffuse chronic inflammatory cell infiltrate.

In the later stages, tissue from the area of bone loss is more collagenized. Evidence of repair by new bone formation is not seen.

Treatment and Prognosis

The clinical course of massive osteolysis is variable and impossible to predict. In most cases, bone destruction progresses over months to a few years and results in the total loss of the affected bone or bones. Some patients, however, experience a spontaneous arrest of the process without complete loss of the affected bone. The prognosis varies from slight to severe disability. Mortality from massive osteolysis is relatively uncommon and usually the result of severe chest cage involvement or destruction of vertebral bodies with spinal cord compression.

Treatment is not particularly satisfactory. Previous reported therapies include estrogens, magnesium, calcium, vitamin D, fluoride, calcitonin, and chemotherapeutic agents (e.g., cisplatin, actinomycin D, etoposide). Surgical intervention has met with limited success. When surgical removal is combined with bone grafting, the newly placed bone often undergoes osteolysis. Radiation therapy is the most successful and widely accepted mode of therapy, but failures may occur. In addition, this therapy places the patient at risk for postradiation sarcoma. All therapeutic interventions are difficult to evaluate, because the disease may arrest spontaneously in some patients.

PAGET'S DISEASE OF BONE (OSTEITIS DEFORMANS)

Paget's disease of bone is a disease characterized by abnormal and anarchic resorption and deposition of bone, resulting in distortion and weakening of the affected bones. The cause of Paget's disease is unknown, but inflammatory, genetic, and endocrine factors may be contributing agents. In some studies, 15% to 30% of affected patients have a positive family history of the disease. The possibility that the disease is the result of a slow virus infection has received considerable attention in recent years, but a viral cause remains unproven. Inclusion bodies identified as nucleocapsids from a paramyxovirus have been detected in osteoclasts in patients with Paget's disease, but a cause-and-effect relationship has not been established.

Clinical and Radiographic Features

Paget's disease is relatively common, although there is a **marked geographic variance in its prevalence. It is more common in Britain than in the United States, whereas it** is rare in Africa and Asia. The disease principally affects older people and is rarely encountered in patients younger than 40 years of age. Men are affected more often than women, and whites are affected more than blacks. Reviews have estimated that i in 100 to 150 individuals greater than 45 years of age have Paget's disease. Sub**clinical disease is not rare, and an increased number of** cases are being seen as the population ages. Asymptomatic disease often is discovered in radiographs taken **for unrelated reasons or from an unexpected elevation in** serum alkaline phosphatase. The frequency increases with age and the true prevalence (Including undiscovered subclinical disease) probably ranges from I% in the fifth decade to 10% in the tenth decade.

Although the disease may be monostotic (limited to one bone), most cases of Paget's disease are polyostotic (more than one bone is affected). Symptoms vary, and **some patients may remain relatively asymptomatic. Bone pain, which may be quite severe, is a common complaint. In addition. pagetic bone often forms near joints and promotes osteoarthritic changes. with associated joint** pain and limited mobility.

The iumbar vertebrae, pelvis, skull, and femur are the most commonly affected bones. Affected bones become thickened, enlarged, and weakened. Involvement of weight-bearing bones often leads to a bowing deformity, resulting in what is described as a simian (rnonkcylikc) stance. Paget's disease affecting the skull generally leads **to a progressive increase in the circumference of the** head.

Jaw involvement is present in approximately 17% of patients diagnosed with Paget's disease. Maxillary dis**ease, which is far more common than mandibular** involvement, results in enlargement of the middle third **of the face. In extreme cases, the alteration results in a** lionlike facial deformity (leontiasis ossea). Nasal **obstruction, enlarged turbinates, obliterated sinuses,** and deviated septum may develop secondary to maxil**lary involvement. The alveolar ridges tend to remain** symmetric but become grossly enlarged. If the patient is dentulous, the enlargement causes spacing of the teeth. Edentulous patients may complain that their dentures no longer fit because of the increased alveolar size.

Radiographically, the early stages of Paget's disease reveal a decreased radiodensity of the bone and alteration of the trabecular pattern. Particularly in the skull, large circumscribed areas of radiolucency may be present (osteoporosis clrcumscrtpta). During the osteoblastic phase of the disease, patchy areas of sclerotic bone are formed, which tend to become confluent. The patchy sclerotic areas often are described as having a "cotton wool" appearance (Figures i4-14 and 14-15). On radiographic examination, the teeth often demon**strate extensive hypercementosis.**

On initial discovery of Paget's disease, bone scintigraphy should be performed to evaluate fully the extent of involvement. When the mandible is affected, the bone scan may demonstrate marked uptake throughout the entire mandible from condyle to condyle, a feature that has been termed *black beard* or *Lincoln's Sign.*

Radiographic findings of Paget's disease may resemble those of cementa-osseous dysplasia (see page 557). Patients with presumed cementa-osseous dysplasia who demonstrate clinicai expansion of the jaws should be evaluated further to rule out Paget's disease.

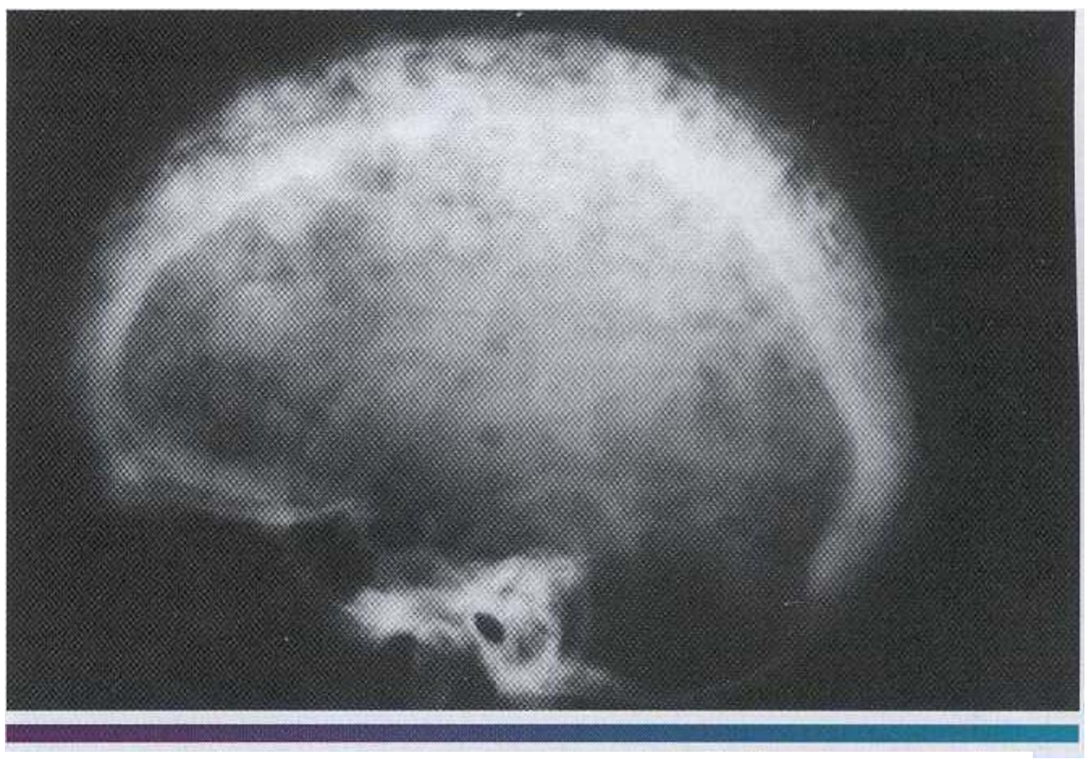

Figure 14-14 . Paget's disease. Lateral skull film shows marked enlargement of the cranium with new bone formation above the outer table ofthe skull and a patchy, dense, "cotton wool" appearance. (Courtesy of Dr. Reg Munden.)

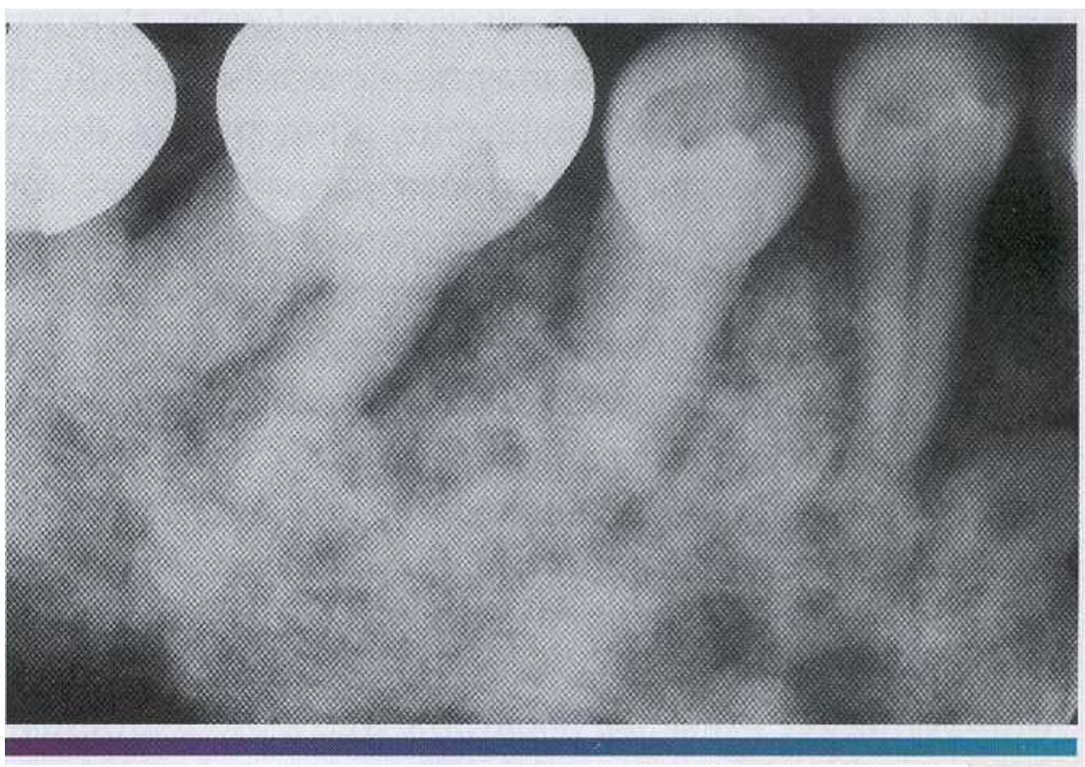

Figure 14-15 • Paget's disease. Periapical film showing the "cotton wool" appearance of the bone.

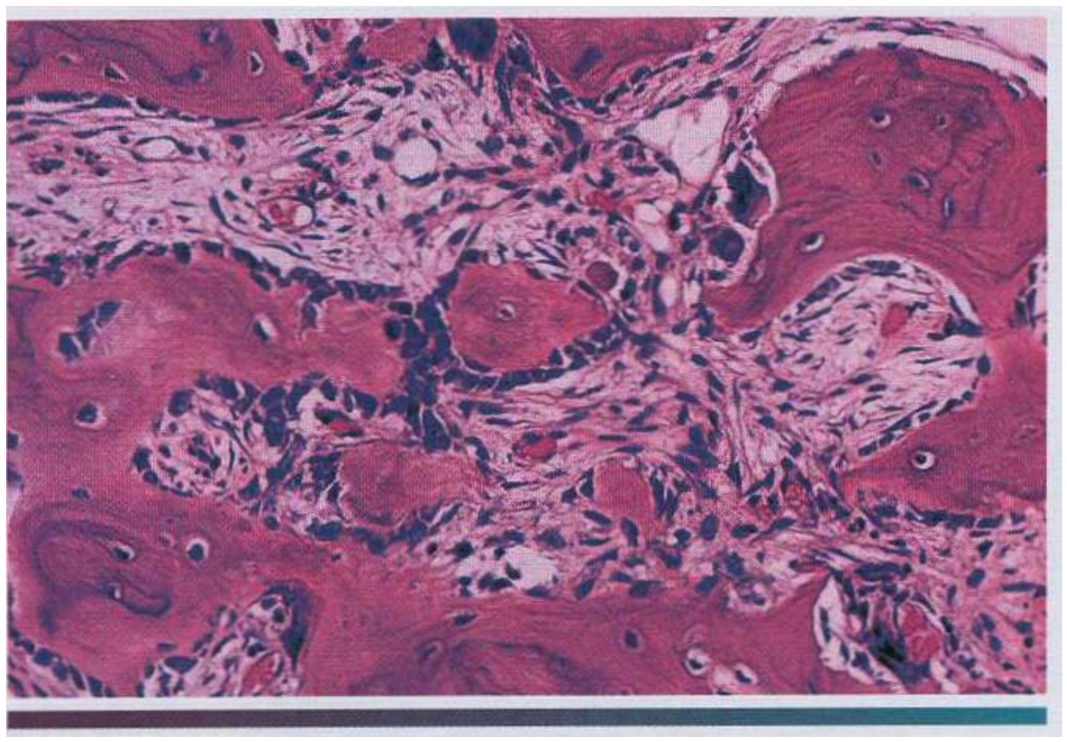

Figure 14-16 • Paget's disease. Prominent osteoblastic and osteoclastic activity surround the bone trabeculae. Note the resting and reversal lines.

Histopathologic Features

Microscopic examination shows an apparent uncontrolled alternating resorption and formation of bone. In the active resorptive stages. numerous osteoclasts surround bone trabeculae and show evidence of resorptive activity. Simultaneously, osteoblastic activity is seen with formation of osteoid rims around bone trabeculae. A highly vascular fibrous connective tissue replaces the marrow. A characteristic microscopic feature is the presence of basophilic reversal lines in the bone. These lines indicate the junction between alternating resorptive and formative phases of the bone and result in a "jigsaw puzzle." or "mosaic." appearance of the bone (Figure 14-1 6). In the less active phases, large masses of dense bone showing prominent reversal lines are present.

Diagnosis

Patients with Paget's disease show high elevations in serum alkaline phosphatase levels but usually have normal blood calcium and phosphorus levels. Urinary hydroxyproline levels also may be elevated markedly. It is recognized that hydroxyproline often breaks down before excretion, making it a less precise method for measurement of bone resorption. Newer and more sensitive markers of bone resorption are N-telopeptides and pyridinoline cross-link assays. The clinical and radiographic features, combined with supportive laboratory findings, are typically sufficient for diagnosis. Histopathologic examination can be confirmatory but often is unnecessary for a strong presumptive diagnosis.

Treatment and Prognosis

Although Paget's disease is chronic and slowly progressive, it is seldom the cause of death. In patients with more limited involvement and no symptoms. treatment often is not required. In asymptomatic patients, systemic therapy is usually not initiated unless the alkaline phosphatase is more than 25% to 50% above normal. When svmptornatlc, bone pain is noted most frequently and often may be controlled by aspirin or other analgesics. Neurologic complications, such as deafness or visual disturbances. may result from bony encroachment on cranial nerves passing through skull foramina.

Use of parathyroid hormone antagonists, such as calcitonin and biphosphonates, can reduce bone turnover and improve the biochemical abnormalities. In many instances, acceptable control has been obtained with the newer biphosphonates. such as etidronate, pamidronate. alendronate, tiludronate, or risedronate. In mild cases, a single infusion of a biphosphonate often is associated with yearlong remissions. Patients with more severe disease usually receive weekly or biweekly treatments for a few weeks. The goal of therapy is to achieve midrange normal levels of serum alkaline phosphatase, with retreatment occurring when values rise 25% above normal. Plicamycin, a cytotoxic antibiotic, is known to inhibit osteoclastic activity. but its use is restricted to patients with severe disease that is refractory to calcitonin and biphosphonates.

Edentulous patients may require new and larger dentures periodically to compensate for progressive enlargement of the alveolar processes. Dental complications include difficulties in extraction of teeth exhibiting significant hypercementosis. During active disease, pagetoid bone is extremely vascular with multiple arteriovenous shunts. Oral surgical procedures during this time can result in extensive hemorrhage. During the later sclerotic phase, the bone is hypersensitive to inflammation and can develop osteomyelitis with minimal provocation.

Development of a malignant bone tumor, usually an osteosarcoma, is a recognized complication of Paget's disease. Osteosarcoma in adults over the age of 40 is quite uncommon in individuals who do not have Paget's disease. The frequency of bone sarcoma complicating Paget's disease ranges from 0.9% to 13% in various studies. The true frequency is probably in the range of I% or less. Most of the osteosarcomas develop in the pelvis and long bones of the lower extremities. The skull and jaws are very rare sites for sarcomas associated with Paget's disease. Osteosarcoma in Paget's disease is very aggressive and associated with a poor prognosis. Benign and malignant giant cell tumors (see page 5471 also may develop in bones affected by Paget's disease. Most of these occur in the craniofacial skeleton.

CENTRAL GIANT CELL GRANULOMA (GIANT CELL LESION; GIANT CELL TUMOR)

The giant cell granuloma is considered widely to be a nonneoplastic lesion. Although formerly designated as "giant cell reparative granuloma," there is little evidence

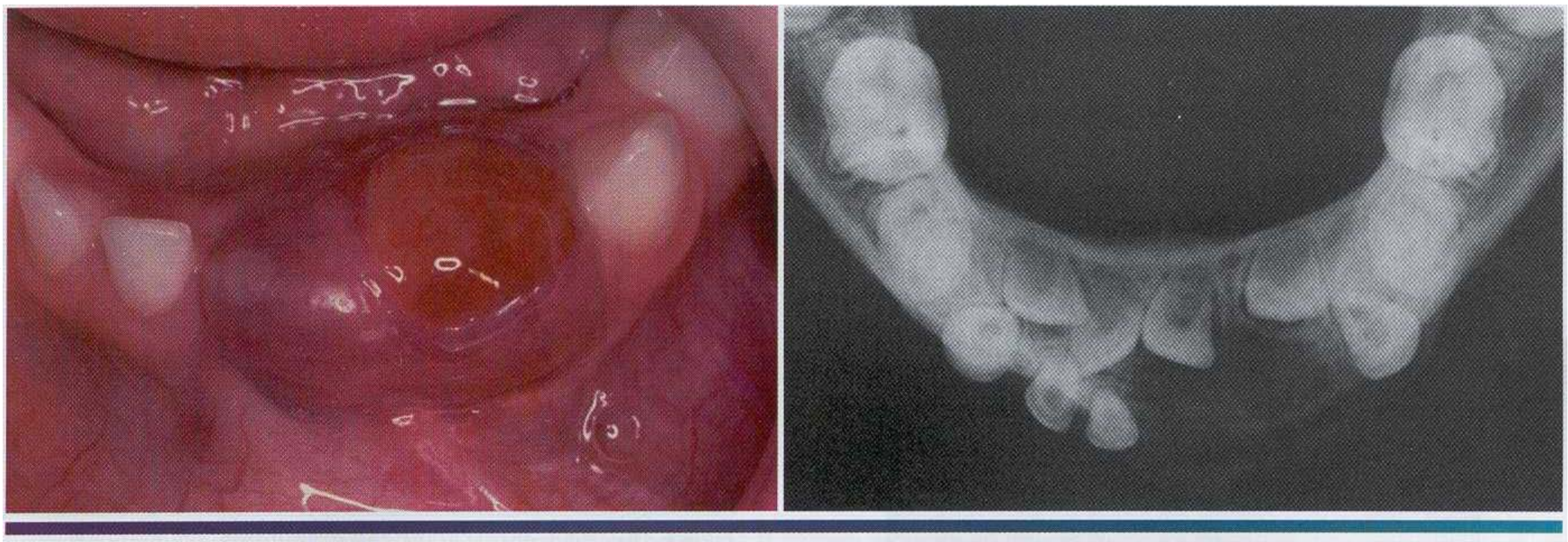

Figure 14-17 . Central giant cell granuloma. A, A bluish-purple mass is present on the anterior alveolar ridge of this 4-year-old white boy. B, The occlusal radiograph shows a radiolucent lesion with cortical expansion.

that the lesion represents a reparative response. Some **lesions demonstrate aggressive behavior similar to that** of a neoplasm. Most oral and maxillofacial pathologists *have* dropped the term *"reparative";* today, these lesions are designated as giant cell granuloma or by the more noncommittal term, giant cell lesion. Whether or not **true giant cell tumors occur in the jaws is uncertain and** controversial. (This topic is discussed later in the chapter.)

Clinical and Radiographic Features

Giant cell granulomas may be encountered in patients ranging from 2 to 80 years of age, although more than 60% of all cases occur before age 30. Although the sex **ratio varies in different reviews, a majority of giant cell** granulomas are noted in females, and approximately **70% arise in the mandible. Lesions are more common in** the anterior portions of the jaws, and mandibular lesions frequently cross the midline.

Most giant cell granulomas of the jaws are asymptomatic **and first come to attention during a routine radiographic examination or as a result of painless expansion** of the affected bone. A minority of cases, *however,* may be associated with pain, paresthesia, or perforation of the cortical bone plate, occasionally resulting in ulceration of the mucosal surface by the underlying lesion (Figure 14-i7).

Based on the clinical and radiographic features, *several* groups of investigators *have* suggested that central giant cell lesions of the jaws may be *divided* into two **categories:**

1. **Nonaggressive lesions make up most cases, exhibit** few or no symptoms, demonstrate slow growth, and **do not show cortical perforation or root resorption** of teeth *involved* in the lesion.

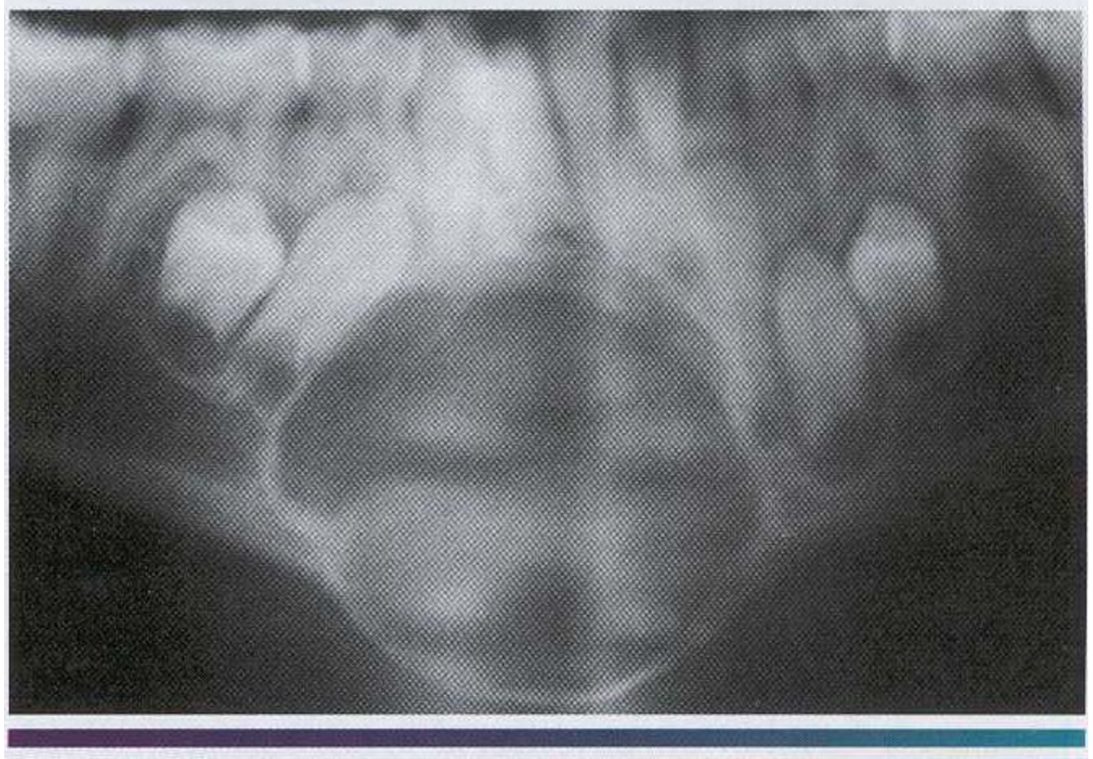

Figure 14-18 • Central giant cell granuloma. Panoramic radiograph showing a large, expansile radiolucent lesion in the anterior mandible. (Courtesy of Dr. Gregory R. Erena.]

2. Aggressive lesions are characterized by pain, **rapid growth. cortical perforation. and root resorption.** They show a marked tendency to recur after treatment, compared with the nonaggressive types.

Radiographically, central giant cell lesions appear as radiolucent defects, which may be unilocular or multilocular. The defect is usually well delineated, but the margins are generally noncorticated. The lesion may *vary* from a 5 X 5 mm incidental radiographic finding to **a destructive lesion greater than 10 em in size (Figure** 14-18). The radiographic findings are not specifically diagnostic. Small unilocular lesions may be confused with periapical granulomas or cysts (Figure 14-19). Multilocular giant celi lesions cannot be distinguished radiographically from ameloblastomas or other multilocular lesions.

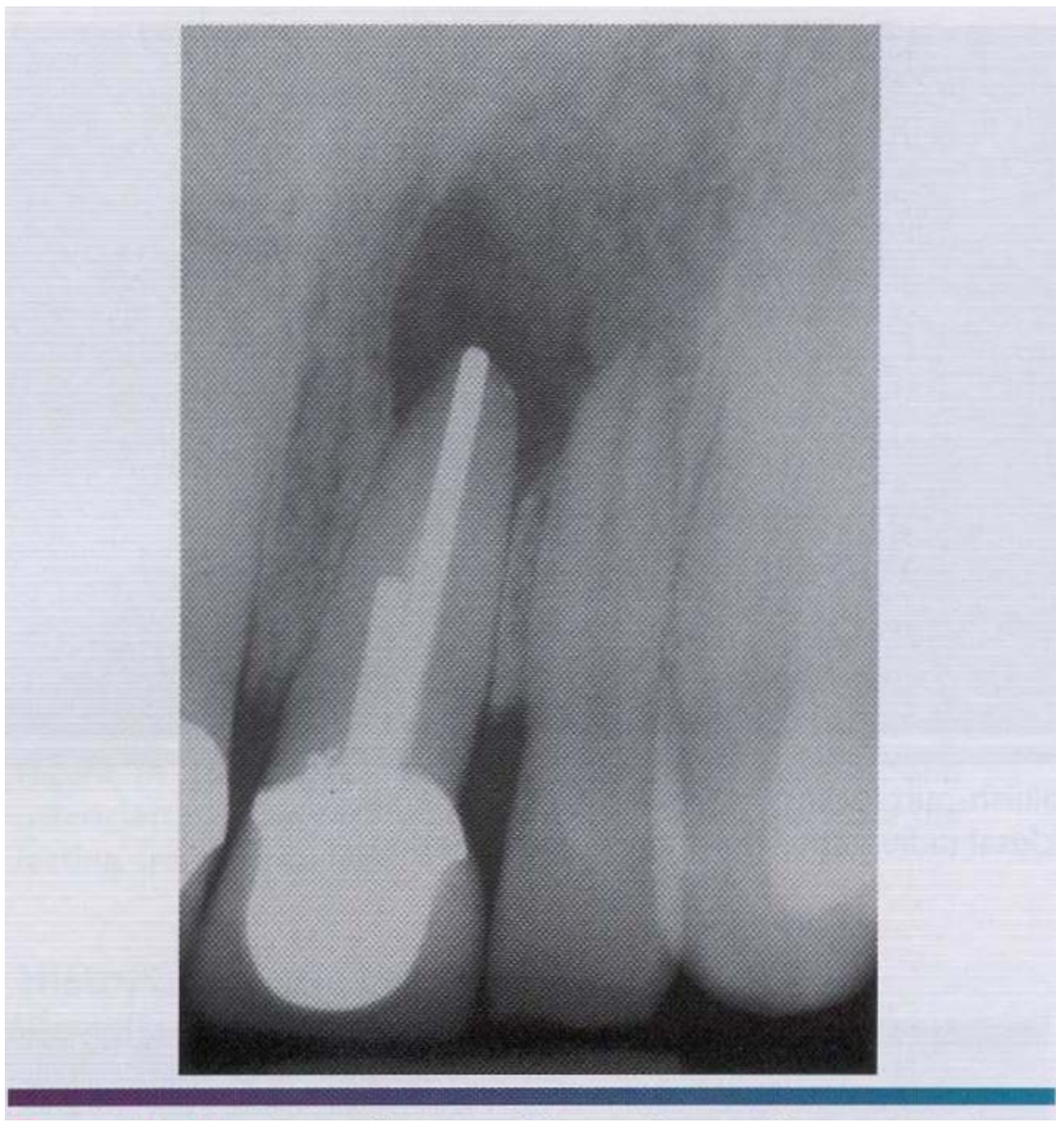

Figure 14-19 • **Central giant cell granuloma. The periapical radiograph shows a radiolucent area involving the apex of an endodontically treated tooth. This was considered preoperatively to represent a periapical granuloma or periapical cyst.**

Areas histopathologically identical to giant cell granuloma have been noted aneurysmal bone cysts (see page 551) and intermixed with central odontogenic fibromas (see page 633). Because giant cell granulomas are histopathologically identical to brown tumors, hyperparathyroidism (see page 724) should be ruled out in all instances. In addition. multifocal involvement in childhood suggests cherubism (see next section) and warrants further investigation. Most giant cell granulomas are single lesions: rarely. multifocal involvement is seen in patients who demonstrate no evidence of an associated disease, such as hyperparathyroidism or cherubisrn.

Histopathologic Features

Giant cell lesions of the jaw show a variety of features. Common to all is the presence of few to many multinucleated giant cells in a background of ovoid to spindle-shaped mesenchymal cells (Figure 14-20). There is evidence that these giant cells represent ostcoclasts, although others suggest the cells may be aligned more closely with macrophages. 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 and contain only a few nuclei. In other cases, the giant cells are large and round and contain 20 or more nuclei.

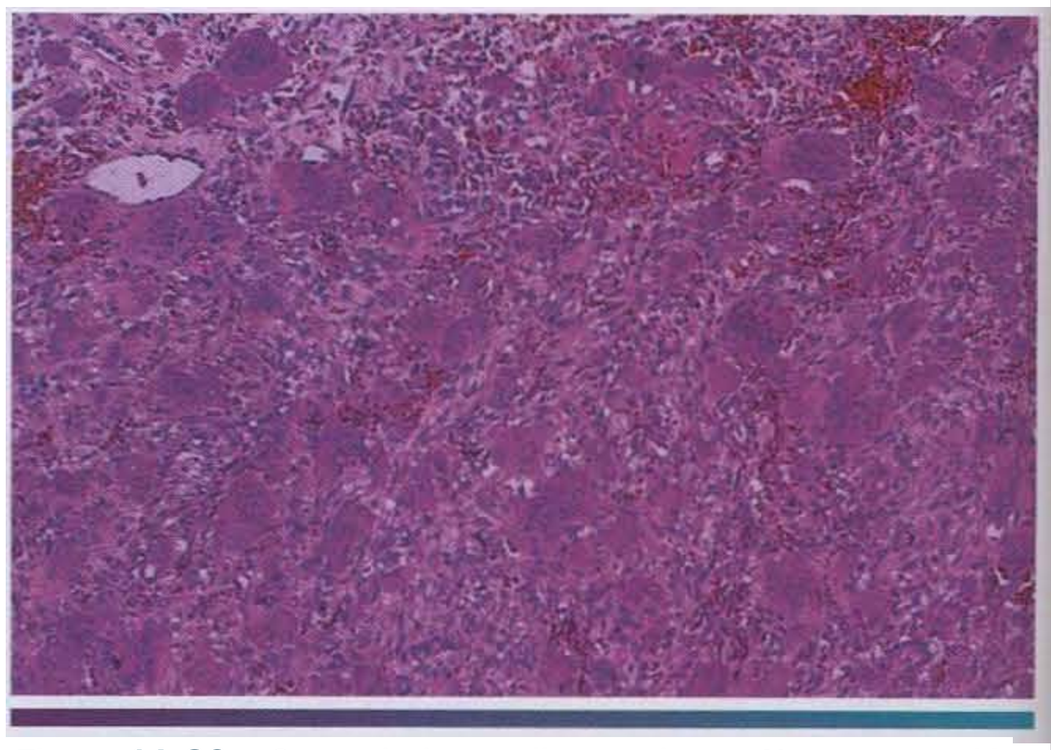

Figure 14-20 • **Central giant cell granuloma. Numerous multinucleated giant cells within a background of plump proliferating mesenchymal cells. Note extensive red blood cell extravasation.**

In some cases, the stroma is loosely arranged and edematous; In other cases, it may be quite cellular. Areas 01 **erythrocyte extravasation and hemosiderin deposition** often are prominent. Older lesions may show considerable fibrosis of the stroma. Foci of osteoid and newly formed **bone are occasionally present within the lesion. Correlation** of the histopathologic features with clinical behavior remains debatable, but lesions showing large, uniformly distributed giant cells and a predominantly cellular stroma appear more likely to be clinically aggressive with a greater **tendency to recur after** surgical **treatment.**

Treatment and Prognosis

Central giant cell lesions of the [aws are usually treated by thorough curettage. In reports of large series of cases, **recurrence rates range from II % to 50% or greater. Most studies indicate a recurrence rate of about 15% to 20%.** Those lesions considered on clinical and radiologic grounds to be potentially aggressive show a higher fre**quency of recurrence. Recurrent lesions often respond to** further curettage, although some aggressive lesions **require more radical surgery for cure.**

In patients with aggressive tumors. three alternatives\0 surgery–**(I)** corticosteroids, (2) calcitonin, and (3) interferon alfa-2a-are being investigated. Several investiga**tors have reported small numbers of patients. some of** which exhibited remarkable response to these interven**tions. Weekly injections directly into the tumor with tri**amcinolone acetonide for approximately 6 weeks have **been used successfully. Systemic administration of salmon calcitonin has resulted in resolution of large lesions. even some that were resistant to intralesional corticosteroids. Calcitonin is administered daily for** approximately 12 months as an intradermal injection or nasal spray. These therapeutic approaches provide pos-

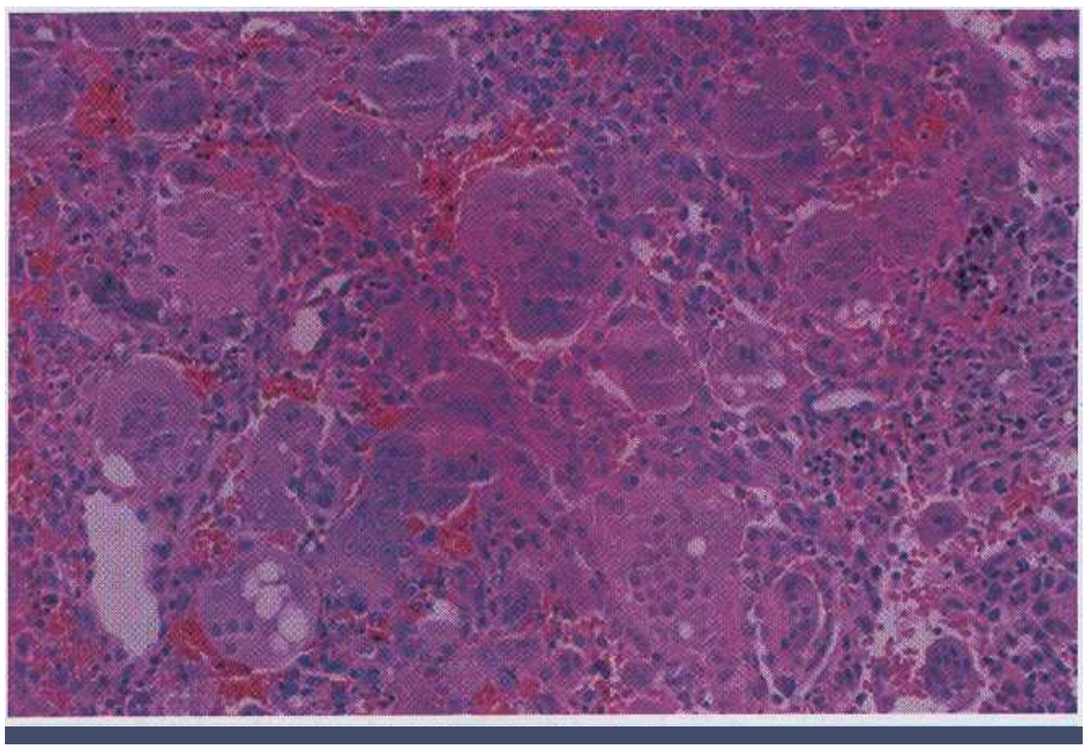

Figure 14-21 • **Giant cell tumor. This photomicrograph shows large giant cells that are distributed in a cellular mesenchymal tissue. This specimen was from an aggressive lesion that had destroyed most of the maxilla.**

sible alternatives for large lesions that if treated surgically would result in significant deformity. Evaluation of greater numbers of patients with appropriate controls is **necessary to compare these therapeutic approaches to** surgery adequately.

In spite of the reported recurrence rate, the long-term prognosis of giant cell granulomas is good and metastases do not develop.

GIANT CELL TUMOR

The question of whether true giant cell tumors, which most often occur in the epiphyses of long tubular bones, occur in the jaws has been argued for many years and still is unresolved. Although most central giant cell lesions can be distinguished histopathologically from the long **bone tumors. a number of jaw lesions are indistinguish**able microscopically from the typical giant cell tumor of long bone (Figure 14-21). In spite of the histopathologic similarity, these jaw lesions appear to have a biologically different behavior from long bone lesions, which have **higher recurrence rates after curettage and show malignant change in up to 10% of cases. One case of metastasis from a mandibular tumor, however, has been** reported. It has been suggested that giant cell granulomas of the jaws and giant cell tumors of the extragnathic skeleton are not distinct and separate entities: rather, they **represent a continuum of a single disease process mod**ified by the age of the patients, the locations of the lesions, and possibly other factors that are not yet understood.

CHERUBISM

Cherubism is a rare developmental jaw condition that is generally inherited as an autosomal dominant trait with high penetrance but variable expressivity. **In** two reports

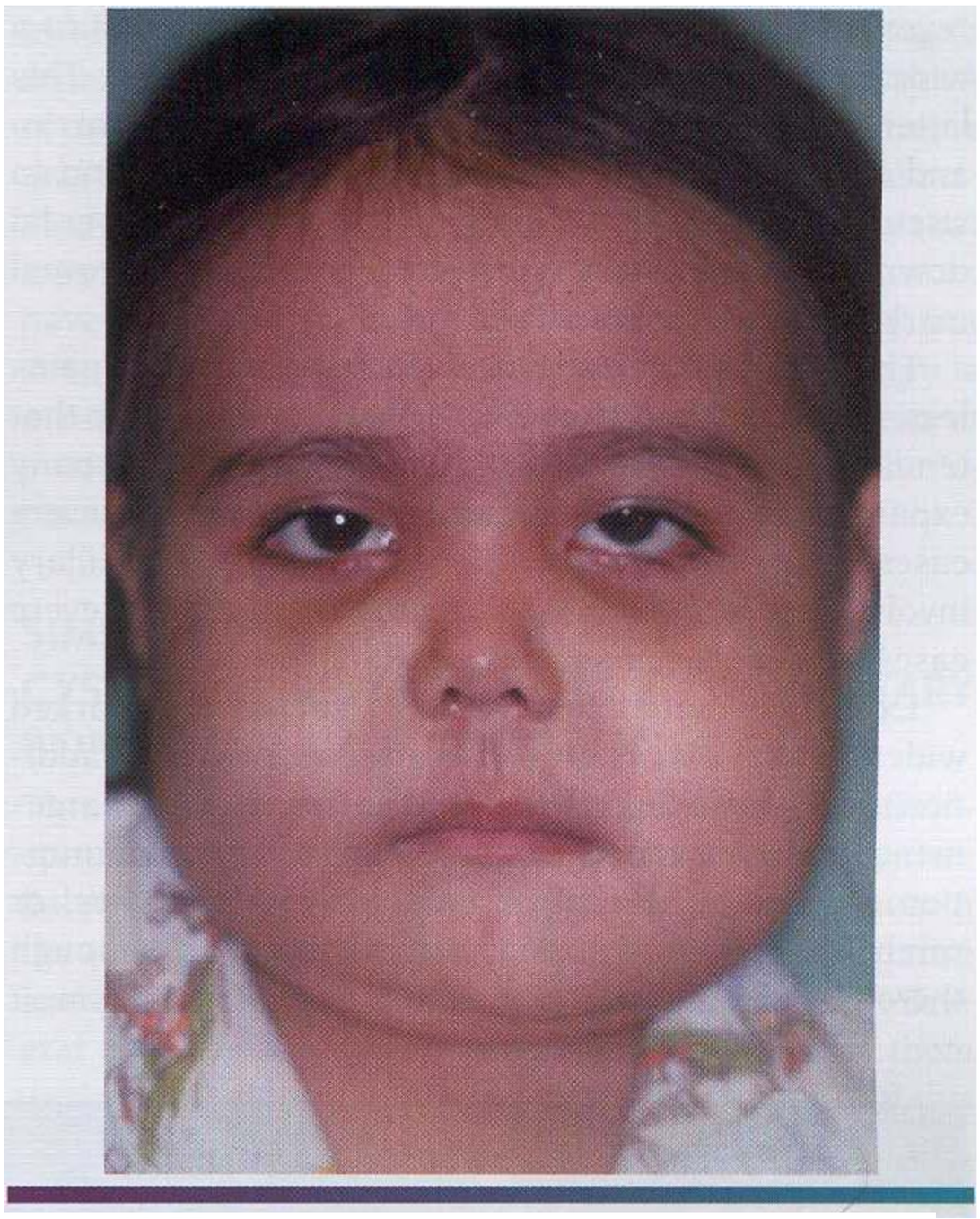

Figure 14-22 • **Cherubism. This young girl shows the typical cherubic facies resulting from bilateral expansile mandibular and maxillary lesions. (Courtesy of Dr. Román Carlos.)**

published simultaneously from authors on different continents, the gene for cherubism was mapped to chromosome 4p16. Although genetic heterogeneity is possible, these findings were discovered in widely separated **cohorts. Sporadic cases do occur and are thought to represent spontaneous mutations.**

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 553).

Clinical and Radiographic Features

Although some examples of cherubism may develop as early as I year of age, the disease usually occurs between the ages of 2 and 5 years. In mild cases, the diagnosis **may not be made until the patient reaches 10 to 12 years** of age. The clinical alterations typically progress until puberty, then stabilize and slowly regress.

The cherublike facies arises from bilateral involvement of the posterior mandible that produces angelic chubby checks (Figure 14-22). In addition, there is an

"eyes upturned to heaven" appearance that is due to a wide rim of exposed sclerae noted below the iris. This latter feature is due to involvement of the infraorbital rim and orbital floor that tilts the eyeballs upward, and to stretching of the upper facial skin that pulls the lower lid downward. On occasion, affected patients also reveal marked cervical lymphadenopathy.

The mandibular lesions typically appear as a painless, bilateral expansion of the posterior mandible that tends to involve the angles and ascending rami. The bony expansion is usually bilaterally symmetrical: in severe cases. most of the mandible is involved. Milder maxillary **involvement occurs in the tuberosity areas; in severe** cases, the entire maxilla can be affected.

Extensive bone involvement causes a marked widening and distortion of the alveolar ridges. In addition to the aesthetic and psychologic impact. the enlargements may cause tooth displacement or failure of eruption, **impair mastication, create speech difficulties, or** rarely lead to loss of normal vision or hearing. Although there have been rare reports of unilateral chcrublsrn, it is difficult to accept these as examples of this disease unless there is a strong family history.

Radiographically. the lesions are typically multilocular. expansile radiolucencies (Figure 14-23). The appearance is virtually diagnostic as a result of their bilateral location. Less commonly, the lesions appear as unilocular radiolucencies. Although cherubism typically involves only the jaws. involvement also has been reported rarely in other bones such as the ribs and humerus.

No unusual biochemical findings have been reported in patients with cherubism. If laboratory results do not suggest the diagnosis of hyperparathyroidism, most children with multiple symmetric giant cell granulomas represent examples of cherubism. However, multiple giant **cell lesions may be seen in association with other con**ditions, including Ramon syndrome. Iaffe-Carnpanacct syndrome. and a Noonan-like syndrome. It has been suggested that the bony lesions of cherubism represent a phenotypic picture common to a number of disease processes that arise from multiple. distinct. initiating **pathogenetic events.**

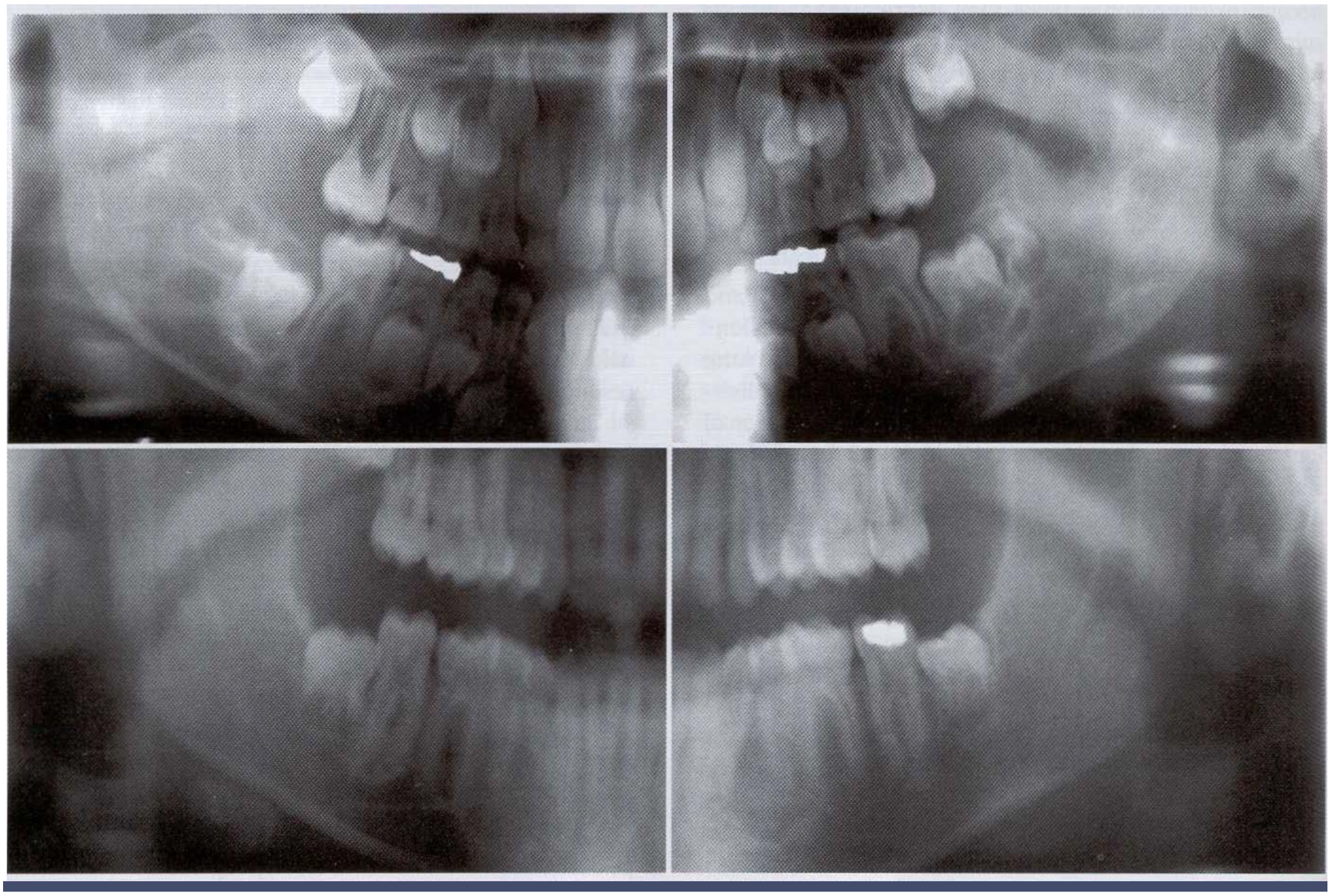

Figure 14-23 • Cherubism. A, Panoramic radiograph **of a 7-year-old white male. Bilateral multilocular radiolucencies can be seen in the posterior mandible. B, Same patient 6 years later. The lesions in the mandibular rami demonstrate significant resolution, but areas of involvement are still present in the body of the mandible. (Courtesy of Dr. John R. Cramer.)**

Histopathologic Features

The microscopic findings of cherubism are essentially similar to those of isolated giant cell granulomas, and they seldom permit a specific diagnosis of cherubism in the absence of clinical and radiologic information. The lesional tissue consists of vascular fibrous tissue containing variable numbers of multinucleated giant cells. The giant cells tend to be small and usually aggregated focally (Figure 14-24). Foci of extravasated blood are commonly present. The stroma in cherubism often tends to be more loosely arranged than that seen in giant cell granulomas; in some cases, cherubism reveals eosinophilic, cufflike deposits surrounding small blood vessels throughout the lesion. The eosinophilic cuffing appears to be specific for cherubisrn. However, these deposits are not present in many cases, and their absence does not exclude a diagnosis of cherubism. 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

The prognosis in any given case is unpredictable. In most instances, the lesions tend to show varying degrees of remission and involution after puberty (see Figure 14-23). By the fourth decade, the facial features of most patients approach normalcy. In spite of the typical scenario, some patients demonstrate very mild alterations, whereas others reveal grotesque changes that often are very slow to resolve. In occasional patients, the deformity can persist.

The question of whether to treat or simply observe a patient with cherubism is difficult. Excellent results have been obtained in some cases by early surgical intervention with curettage of the lesions. Conversely, early surgical intervention sometimes has been followed by rapid regrowth of the lesions and worsening deformity. A course limited only to observation may result in extreme and sometimes grotesque facial deformity, with associated psychologic problems and functional deformity that may necessitate extensive surgery_ Several investigators have suggested the use of calcitonin in severe cases, but such therapy awaits further study. Radiation therapy is contraindicated because of the risk of development of postirradiation sarcoma. The optimal therapy for cherubism has not been determined.

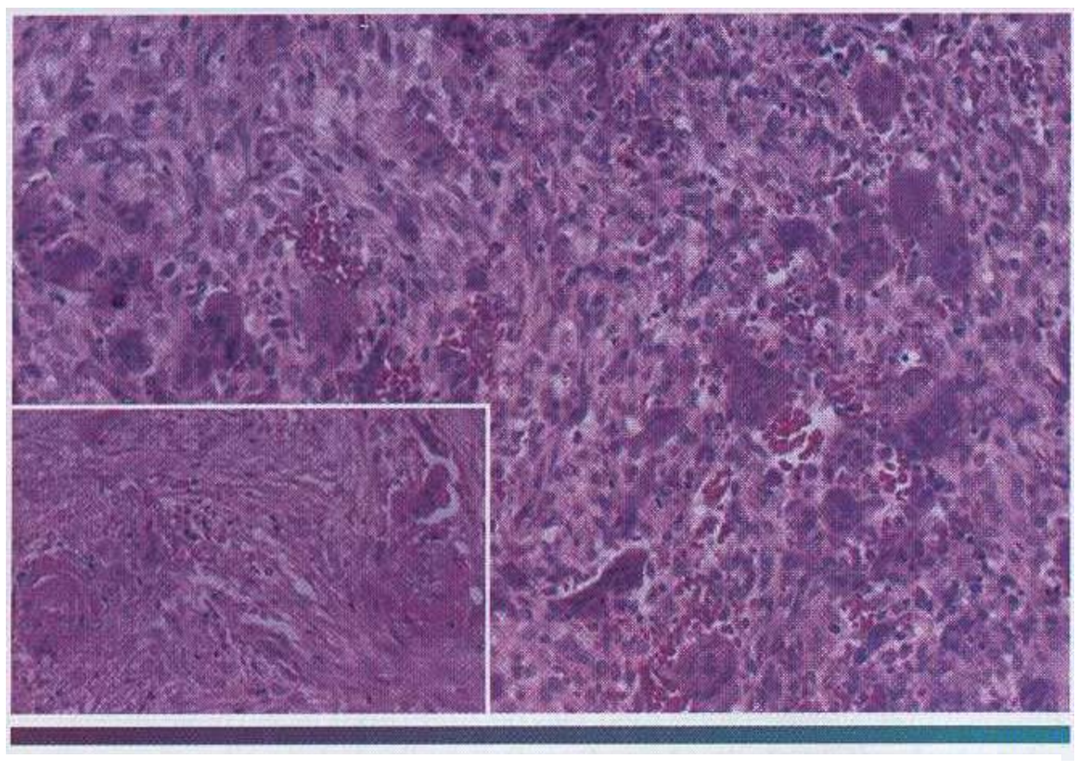

Figure 14-24 • Cherubism. Photomicrograph showing scattered giant cells within a background of cellular, hemorrhagic mesenchymal tissue. The inset demonstrates perivascular eosinophilic cuffing.

SIMPLE BONE CYST (TRAUMATIC BONE CYST; HEMORRHAGIC BONE CYST; SOLITARY BONE CYST; IDIOPATHIC BONE CAVITY)

The simple bone cyst is a benign, empty, or fluid-containing cavity within bone that is devoid of an epithelial lining. The lesion is undoubtedly more common in the jaws than the literature would indicate. The cause and pathogenesis are uncertain and controversial. Several theories have been proposed, but none of them explains all of the clinical and pathologic features of this disease.

The trauma-hemorrhage theory has many advocates, as evidenced by the Widely used designation traumatic bone cyst. This theory suggests that trauma to the bone that is insufficient to cause a fracture results in an intraosseous hematoma. If the hematoma does not undergo organization and repair, it may liquefy, resulting in a cystic defect. Some affected patients may recall an episode of trauma to the affected area, but this anecdotal information is of uncertain significance and has not been subjected to detailed, controlled analysis.

Although the trauma-hemorrhage theory appears to be accepted widely in the dental literature, it has little support in the orthopedic literature to explain similar cysts most commonly found in the proximal diaphysis of the femur and tibia in young patients. In addition, it cannot explain gnathic simple bone cysts that have demonstrated progressive enlargement over several years and, upon surgical investigation, fail to reveal any evidence of continued hemorrhage. Other etiologic theories include inability of interstitial fluid to exit the bone because of inadequate venous drainage, local disturbance in bone growth, ischemic marrow necrosis, and localized alteration in bone metabolism resulting in osteolysis.

Clinical and Radiographic Features

Simple bone cysts have been reported in almost every bone of the body, but the vast majority involves the long bones. Simple bone cysts within the jaws are common and most frequently encountered in patients between 10

and 20 years of age. The lesion is rare in children under age five and is seldom seen in patients over age 35. Simple bone cysts of the jaws are essentially restricted to the mandible. although there have been reports of the lesion in the maxilla. Bilateral simple bone cysts of the mandible arc occasionally encountered. About 60% of **cases occur in males.**

The simple bone cyst usually produces no symptoms and is discovered only when radiographs are taken for **some other reason. About 20% of patients, however,** have a painless swelling of the affected area. Pain and paresthesia may be noted in a few cases. Although any area of the mandible may be involved, simple bone cysts **are more common in the premolar and molar areas.**

Radiographically, the lesion most frequently appears as a well-delineated radiolucent defect. In some areas. the margins of the defect are sharply defined; in other areas, the margins are ill defined. The defect may range from I to 10 cm in diameter. When several teeth are involved in the lesion, the radiolucent defect often shows domelike projections that scallop upward between the roots. This feature is highly suggestive but not diagnostic of a simple bone cyst (Figures 14-25 and 14-26). Teeth that appear to be involved in the lesion are generally vital and do not show root resorption.

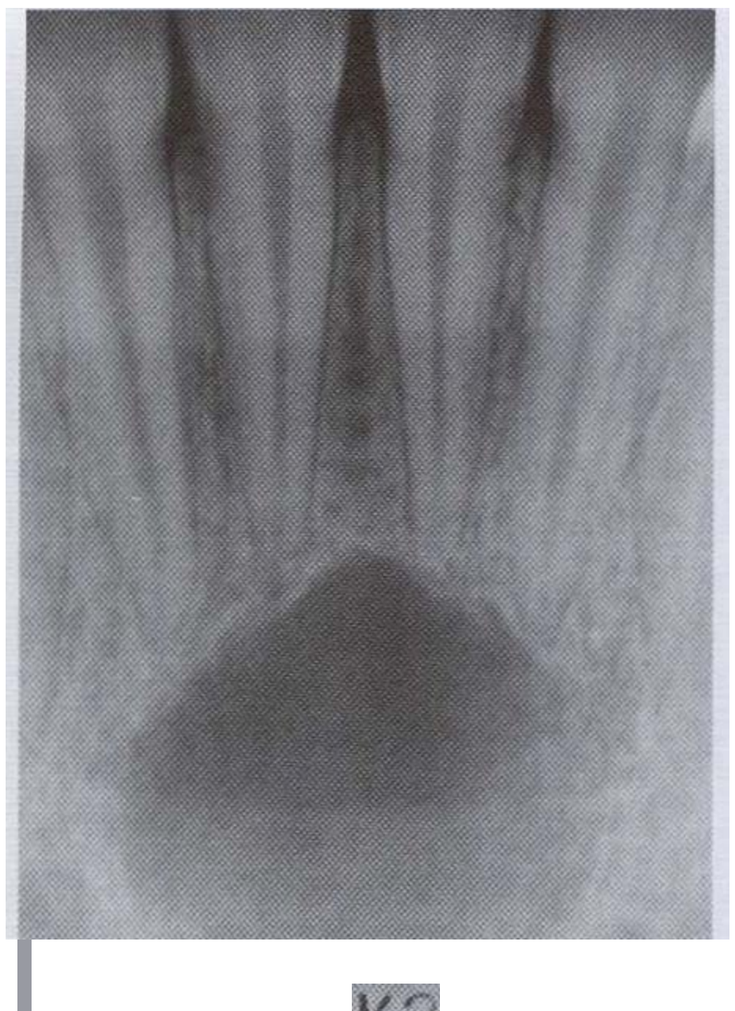

Figure 14-25 • **Simple bone cyst. Periapical radiograph showing a radiolucent area in the apical region** of the **anterior mandible. The incisor teeth responded normally to vitality testing, and no restorations are present.**

Although not characteristic. a simple bone cyst may rarely appear as a multilocular radiolucency associated **with cortical expansion and slow enlargement.** When expansion is present. an occlusal radiograph typically demonstrates a thin shell of cortical bone that exhibits **no further reactive changes. Extensive lesions involving** a substantial portion of the body and ascending ramus are occasionally encountered (Figure J4-27).

Similar simple cysts may be associated with lesions **of cemento-osseous dysplasia and** other fibre-osseous proliferations. These typically occur in older patients and are discussed later (sec page 557).

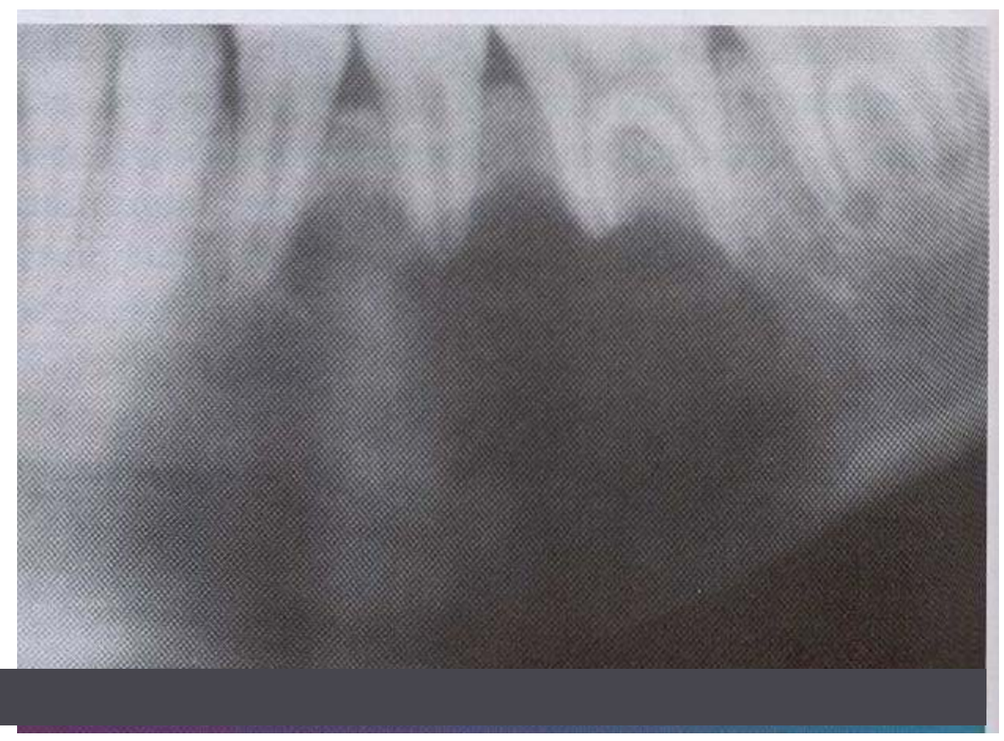

Figure 14-26 • **Simple bone cyst.** Panoramic film **showing a large simple bone cyst of the mandible in a 12-year-old girl. The scalloping superior aspect of the cyst between the roots of the** teeth **is highly suggestive of, but not diagnostic for, a simple bone cyst.** (Courtesy of Dr. Lon Doles.)

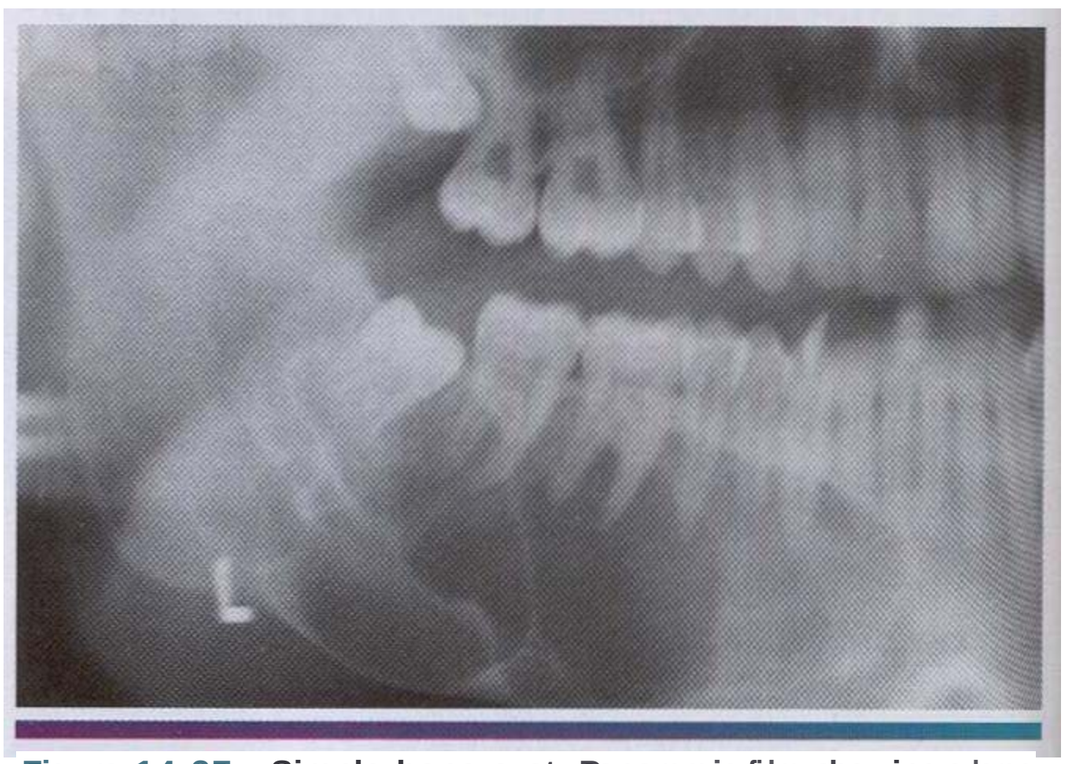

Figure 14-27 • **Simple bone cyst.** Panoramic film **showing a large multilocular simple bone cyst of** the **mandible in a 16-year-old white male. (Courtesy of Dr. Amy Bogardus.)**

Histopathologic Features

The walls of the defect may be lined by a thin band of **vascular fibrous connective tissue or demonstrate a** thickened myxofibromatous proliferation that often is intermixed with trabeculae of cellular and reactive bone. This lining may exhibit areas of vascularity, fibrin, erythrocytes, and occasional giant cells adjacent to the bone surface (Figure 14-28). There is never any evidence of an epithelial lining. The bony surface next to the cavity often **shows resorptive areas (Howship's lacunae) indicative of** past osteoclastic activity.

Diagnosis

The radiographic features of the simple bone cyst, although often suggestive of the diagnosis, are not diagnostic and may be confused with a wide variety of **odontogenic and nonodontogenic radiolucent jaw** lesions. Surgical exploration is necessary to establish the diagnosis.

Because little to no tissue often is obtained at the time of surgery. the diagnosis of simple bone cyst is primarily based on the clinical and radiographic features, together with the surgical findings. In about one third of cases, the lytic defect will be found to be an empty cavity with smooth, shiny bony walls. in about two thirds of cases. **the cavity will contain small amounts of serosanguineous** fluid. The mandibular neurovascular bundle may be seen lying free in the cavity.

Treatment and Prognosis

Although the treatment of simple bone cysts of the long bones often is more aggressive and includes intralesional steroid injections or thorough surgical curettage. simple surgical exploration to establish the diagnosis is usually sufficient therapy for gnathic lesions. Although the bony walls of the cavity at surgical exploration often appear smooth and shiny, it is wise to curette them and submit the small amount of tissue obtained for microscopic **examination to rule out more serious diseases. Rarely. on microscopic examination. a lesion considered to be a** simple bone cyst at surgical exploration will prove to be a thin-walled lesion. such as an odontogenic keratocyst or cystic ameloblastoma. When a thickened myxofibro**matous wall is encountered. curettage and submission** of this material appears prudent. After surgical exploration with or without curettage of the bony walls, obliteration of the defect by new bone formation is generally rapid. Even large defects may show normal radiographic **findings within 6 months after exploration. Recurrence** or persistence of the lesion is most unusual. but it has been reported. Periodic radiographic examination should be continued until complete resolution has been con**firmed. The prognosis is excellent. however.**

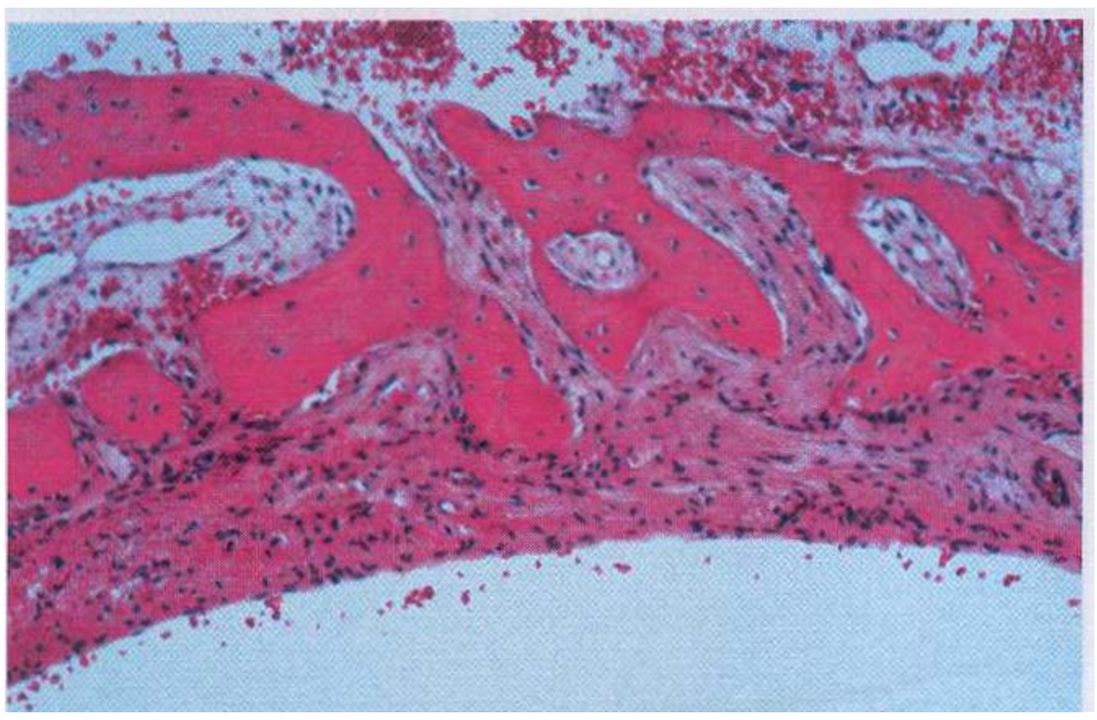

Figure 14-28 • **Simple bone cyst.** Photomicrograph of the bony wall of a simple bone cyst. A thin. vascular connective tissue membrane is adjacent to the bone and no epithelial lining is identified.

ANEURYSMAL BONE CYST

Aneurysmal bone cyst is an intraosseous **accumulation** of variable-sized. blood-filled spaces surrounded by cellular fibrous connective tissue that often is admixed with trabeculae of reactive woven bone. The cause and pathogenesis of the aneurysmal bone cyst are poorly understood. Several investigators have proposed that aneurys**mal bone cyst arises from a traumatic event. vascular** malformation. or neoplasm that disrupts the normal osseous hemodynamics and leads to an enlarging. hemorrhagic extravasation. As a corollary of this theory. others have suggested that aneurysmal bone cyst and giant cell granuloma are closely related. An aneurysmal bone cyst may form when an area of hemorrhage main**tains connection with the disrupted feeding vessels; sub-**sequently. giant cell granuloma-like areas can develop **after loss of connection with the original vascular source.**

Some authors have presented large series of cases involving the extragnathic skeleton and claim that none of their cases has shown evidence of a preexlstlng lesion. Others have reported similar large series and contend that a preextstlng lesion may be evident in one third of cases. It is likely that the aneurysmal bone cyst **may occur either as a primary lesion or as a result of** disrupted vascular dynamics in a preexisting intrabony lesion.

Clinical and Radiographic Features

Aneurysmal bone cysts are located most commonly in the shaft of a long bone or in the vertebral column in patients

younger than age 30. Gnathic aneurysmal bone cysts are uncommon, with approximately 2% reported from the jaws. Within the jaws, a wide age range is noted, but most cases arise in children and young adults with an approximate mean age of 20 years. No significant sex predilection is noted. A mandibular predominance is noted, and the vast majority arises in the posterior segments of the jaws.

The most common clinical manifestation is a swelling that has usually developed rapidly. Pain often is reported; paresthesia, compressibility, and crepitus are rarely seen. On occasion, malocclusion, mobility, migration, or resorption of involved teeth may be present. Maxillary lesions often bulge into the adjacent sinus; nasal obstruction, nasal bleeding, proptosis, and diplopia are noted uncommonly.

Radiographic study shows a unilocular or multilocular radiolucent lesion often associated with marked cortical expansion and thinning (Figure 14-29). The radiographic borders are variable and may be well defined or diffuse. Frequentiy, a ballooning or "blow-out" distention of the contour of the affected bone is described. Uncommonly, small radiopaque foci, thought to be small trabeculae of reactive bone, are noted within the radiolucency.

At the time of surgery, intact periosteum and a thin shell of bone are typically found covering the lesion. Cortical perforation may occur, but spread into the adjacent soft tissue has not been documented. When the periosteum and bony shell are removed, dark venous blood frequently wells up and venouslike bleeding may be encountered. The appearance at surgery has been likened to that of a "blood-soaked sponge."

Histopathologic Features

Microscopically, the aneurysmal bone cyst is characterized by spaces of varying size, filled with unclotted blood surrounded by cellular fibroblastic tissue containing multinucleated giant cells and trabeculae of osteoid and woven bone. On occasion, the wall contains an unusual lacelike pattern of calcification that is uncommon in other intraosseous lesions. The blood-filled spaces are not lined by endothelium (Figure 14-30). In approximately 20% of the cases, aneurysmal bone cyst is associated with another pathosis, most commonly a fibro-osseous lesion or giant cell granuloma.

Treatment and Prognosis

Aneurysmal bone cysts of the jaws are usually treated by curettage or enucleation, sometimes supplemented with cryosurgery. The vascularity of gnathic lesions is typically low flow, and removal of the bulk of the lesion is usually sufficient to control the bleeding. Rare cases require more extensive surgical resection. In most instances, the surgical defect heals within 6 months to I year and does not necessitate bone grafting. Irradiation is contraindicated.

The reported recurrence rates are variable and have been as low as 8% and as high as 60%. Most recurrent examples arise from inadequate or subtotal removal upon initial therapy. On occasion, recurrence may be related to incomplete removal of a coexisting lesion such as an osteoblastorna or ossifying fibroma. Overall, in spite of recurrences, the long-term prognosis appears favorable.

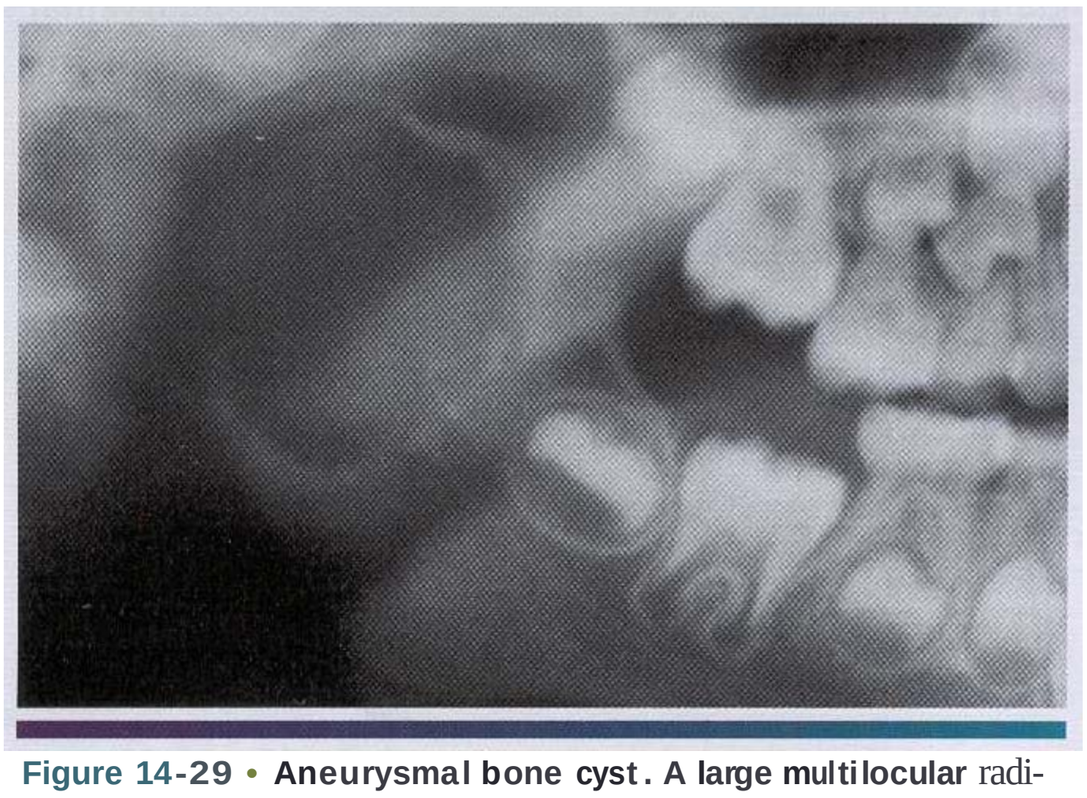

Figure 14-29 • Aneurysmal bone cyst. A large multilocular radiolucent lesion involves most of the ascending ramus in a 5-year-old white boy. (Courtesy of Dr. Samuel McKenna.)

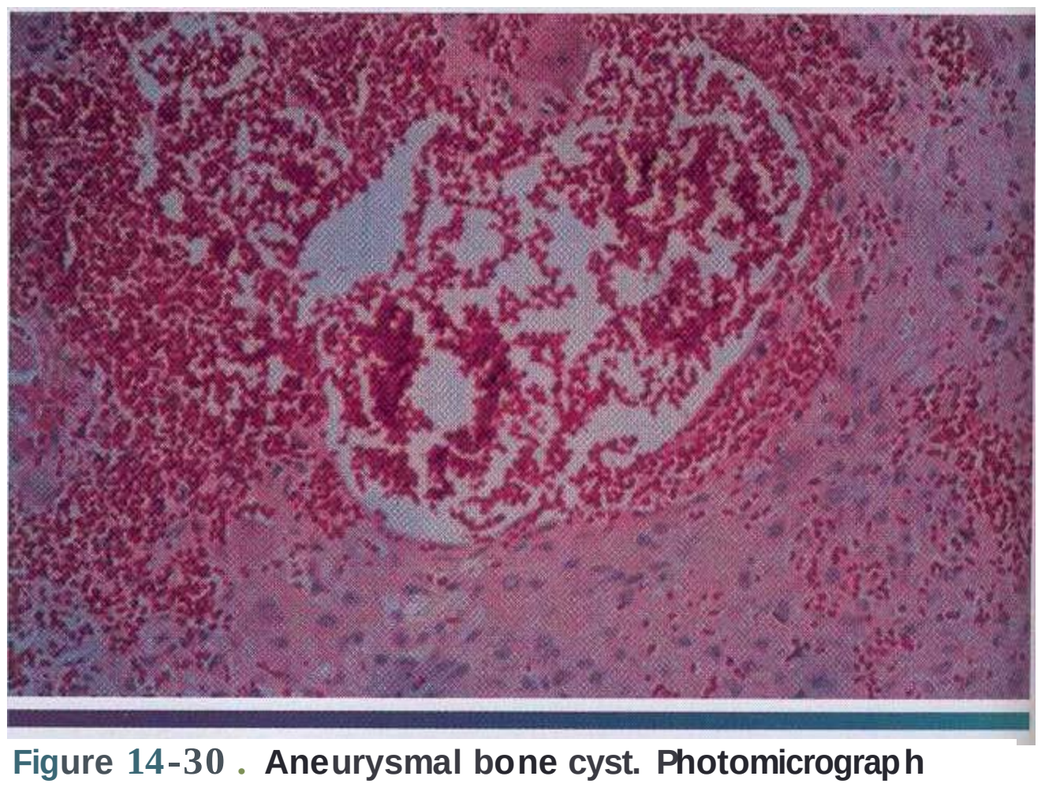

Figure 14-30. Aneurysmal bone cyst. Photomicrograph showing a blood-filled space surrounded by fibroblastic connective tissue. Scattered multinucleated giant cells are seen adjacent to the vascular space.

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 designation *{ibro-osseous lesion* is not a specific diagnosis and describes only a process. Fibro-osseous lesions of the jaws include developmental (hamartomatous) lesions. reactive or dysplastic proc-**esses, and neoplasms.**

The pathologic features on a biopsy specimen may be very **similar in lesions of diverse cause, behavior, and** prognosis. Clinical. radiographic. and histopathologic correlation is usually most beneficial in establishing a specific diagnosis. Commonly included among the fibro-**osseous lesions of the jaws are the following:**

1. Fibrous dysplasia
2. Cemento-osseous dysplasia
   - **a. Focal cementa-osseous dysplasia**
   - b. Periapical cemento-osseous dysplasia
   - c. Florid cemento-osseous dysplasia
3. Ossifying fibroma

Although these processes have been grouped under the encompassing heading of *benign {ibro-osseous lesions*. **a more specific diagnosis often is critical because the treatment of these pathoses varies from none to surgical** recontouring to complete removal. Although many examples can be diagnosed from the clinical and radiographic features, others require knowledge of the histopathologic, clinical, and radiographic features for an appropriate diagnosis.

FIBROUS DYSPLASIA

Fibrous dysplasia is a developmental tumorlike condition that is characterized by replacement of normal bone by an excessive proliferation of cellular fibrous connective **tissue intermixed with irregular bony trabeculae.** Although considerable confusion has existed regarding the nature of fibrous dysplasia, much has been learned about the genetics of this group of disorders, and this knowledge makes the wide variety of clinical patterns more understandable.

Fibrous dysplasia is a sporadic condition that results from a postzygotic mutation in the GNAS I (guanine nucleotide-binding protein, a-stimulating activity polypeptide I) gene. Clinically, fibrous dysplasia may manifest as a localized process involving only one bone, as a condition involving multiple bones, or as multiple **bone lesions in conjunction with cutaneous and endocrine abnormalities. The clinical severity of the con-**dition presumably depends on the polnt in time during fetal or postnatal life that the mutation of GNAS I occurs.

If the mutation occurs in one of the undifferentiated stem ceils during early embryologic life, the osteoblasts, melanocytes, and endocrine cells that represent the progeny of that mutated ceil all will carry that mutation and express the mutated gene. The clinical presentation of multiple bone lesions. cutaneous pigmentation, and endocrine disturbances would result. Skeletal progenitor ceils at later stages of embryonic development are assumed to migrate and differentiate as part of the process of normal skeletal formation. If the mutation occurs during this later period, the progeny of the mutated cell will disperse and **participate in the formation of the skeleton resulting in** multiple bone lesions of fibrous dysplasia. Finaily. if the mutation occurs during postnatal life. the progeny of that mutated cell are essentiaily confined to one site, resulting in fibrous dysplasia affecting a single bone.

Clinical and Radiographic Features

Monostotic fibrous dysplasia o{ the jaws. When the **disease is limited *to* a single bone, it is** termed **monostotic fibrous dysplasia**. This type accounts for about 80% to 85% of ail cases, with the jaws being among the most commonly affected sites. Although the postnatal mutation of GNASI may occur during infancy, childhood. or adulthood. most examples of monostotic fibrous dysplasia are diagnosed during the second decade of life. Males and females are affected with about equal frequency. A painless swelling of the affected area is the most common feature (Figure 14-3i). Growth is gener-

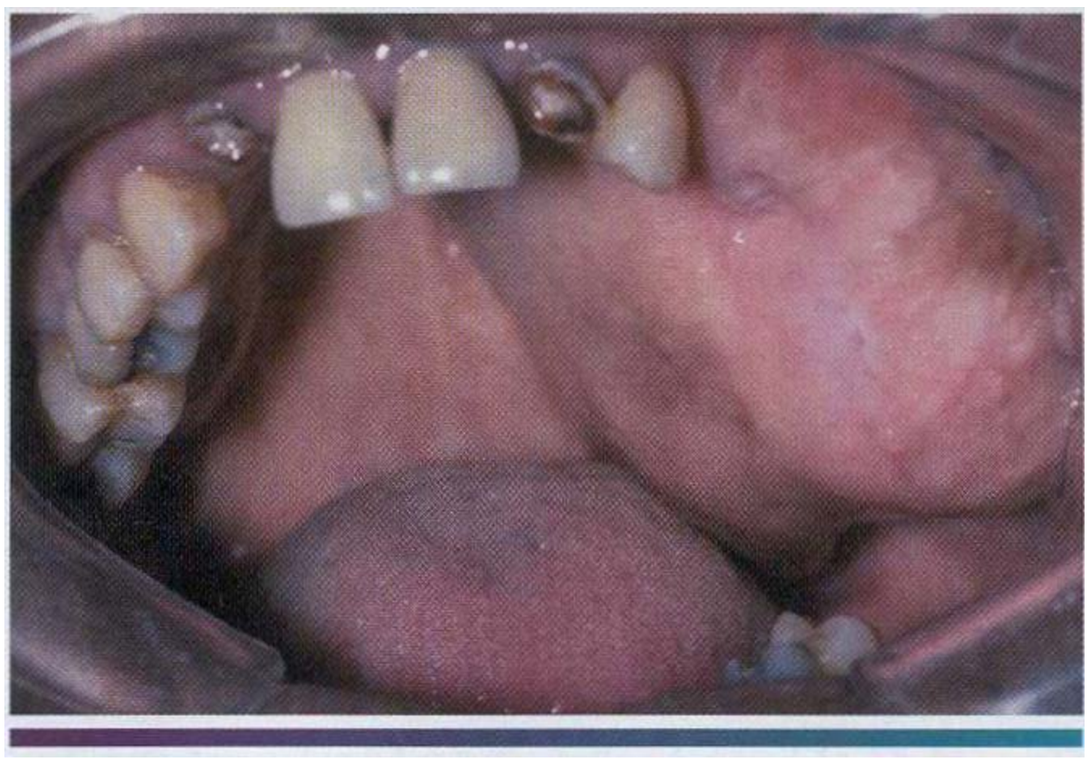

Figure 14-31 • Fibrous dysplasia. Expansile mass of the left maxilla in a 45-year-old woman. This lesion was known to have been present for at least 20 years.

ally slow, and the patient or parents are often unable to recall when the lesion was noted first. Occasionally, however, the growth may be fairly rapid. The maxilla is involved more often than the mandible.

Although mandibular lesions are truly monostotic, maxillary lesions often involve adjacent bones (such as the zygoma, sphenoid, and occiput) and are not strictly **monostotic. The designation of craniofacial fibrous dysplasia** is appropriate for these lesions. Teeth involved in the lesion usually remain firm but may be displaced by the bony mass.

The chief radiographic feature is a fine "ground-glass" opacification that results from superimposition of a myriad of poorly calcified bone trabeculae arranged in a disorganized pattern. Radiographically, the lesions of fibrous dysplasia are not well demarcated. The margins blend imperceptibly into the adjacent normal bone so that the limits of the lesion may be difficult to define (Figures 14-32 to 14-34). In the earlier stages, the lesion may be largely radiolucent or mottled.

Involvement of the mandible often results not only in expansion of the lingual and buccal plates but also bulging of the lower border. Superior displacement of the **inferior alveolar canal is not uncommon. Periapical** radiographs of the involved dentition often demonstrate narrowing of the periodontal ligament space with an ill-defined lamina dura that blends with the abnormal bone pattern.

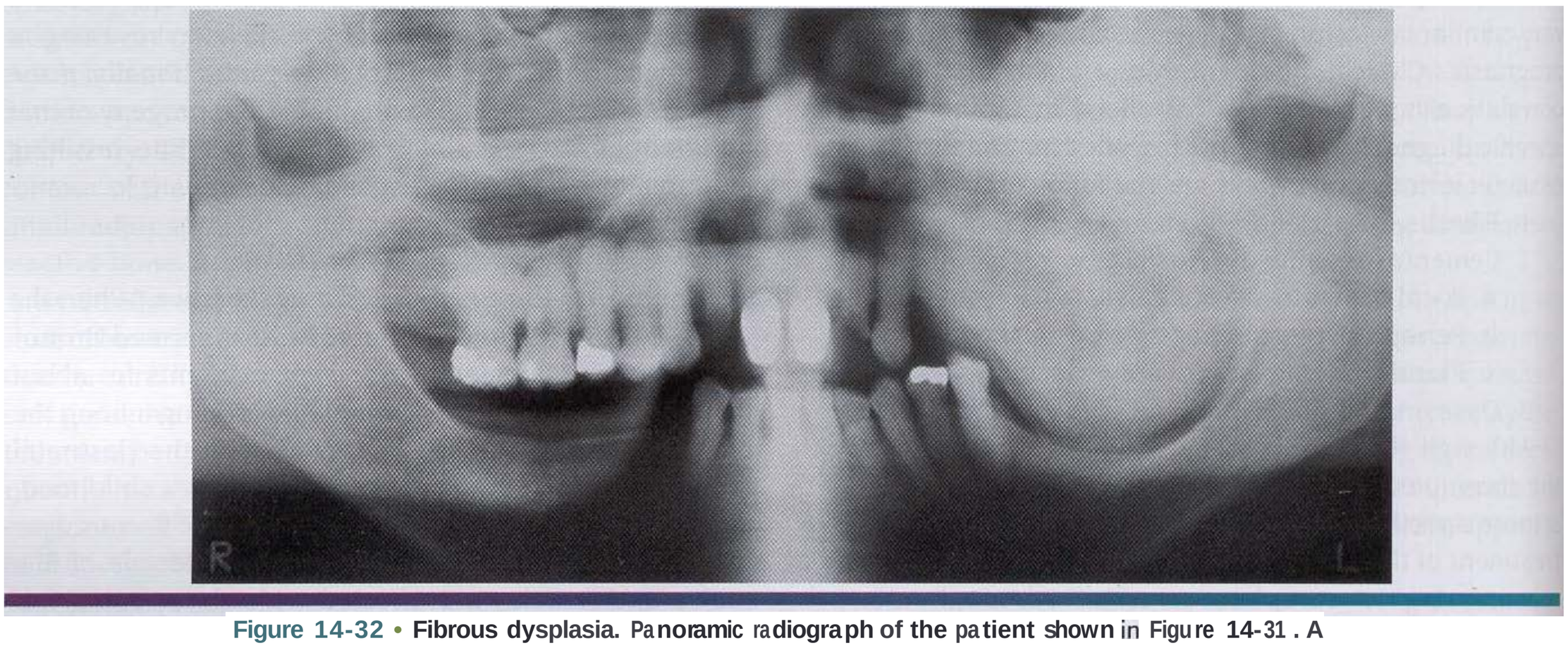

Figure 14-32 • Fibrous dysplasia. Panoramic radiograph of the patient shown in Figure 14-31. A diffuse "ground-glass" radiopacity is evident. (Courtesy of Dr. Richard Brock.)

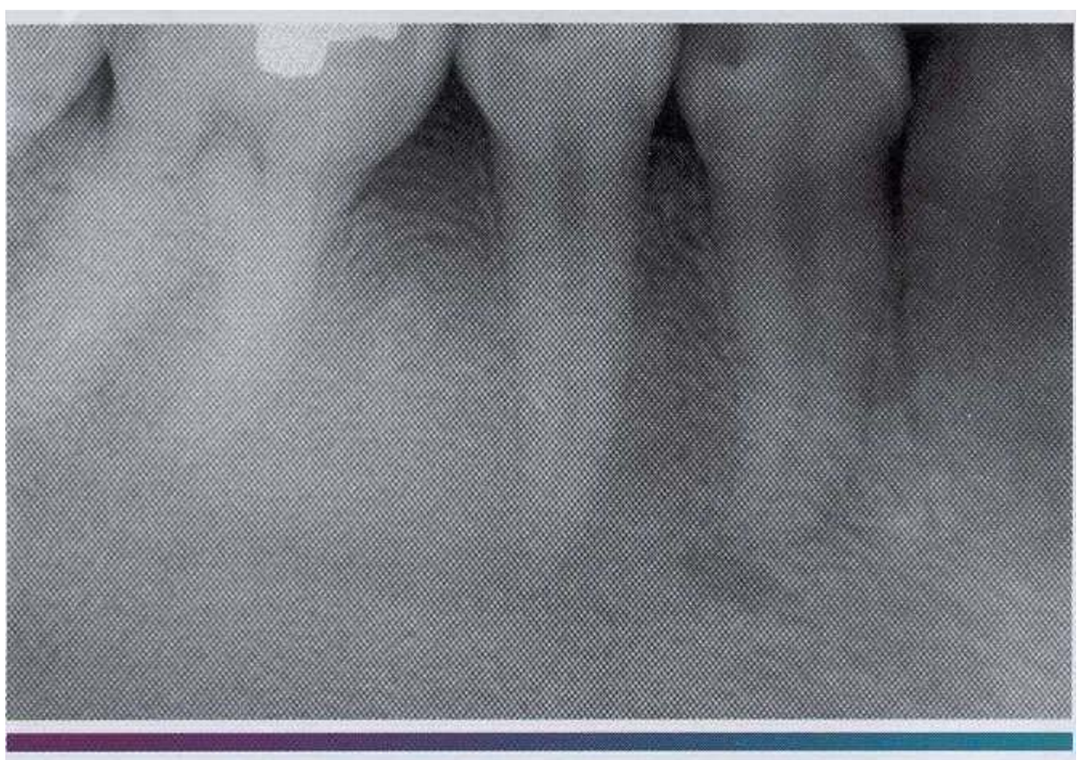

Figure 14-33 • Fibrous dysplasia. Periapical radiograph showing a diffuse "ground-glass" radiographic appearance.

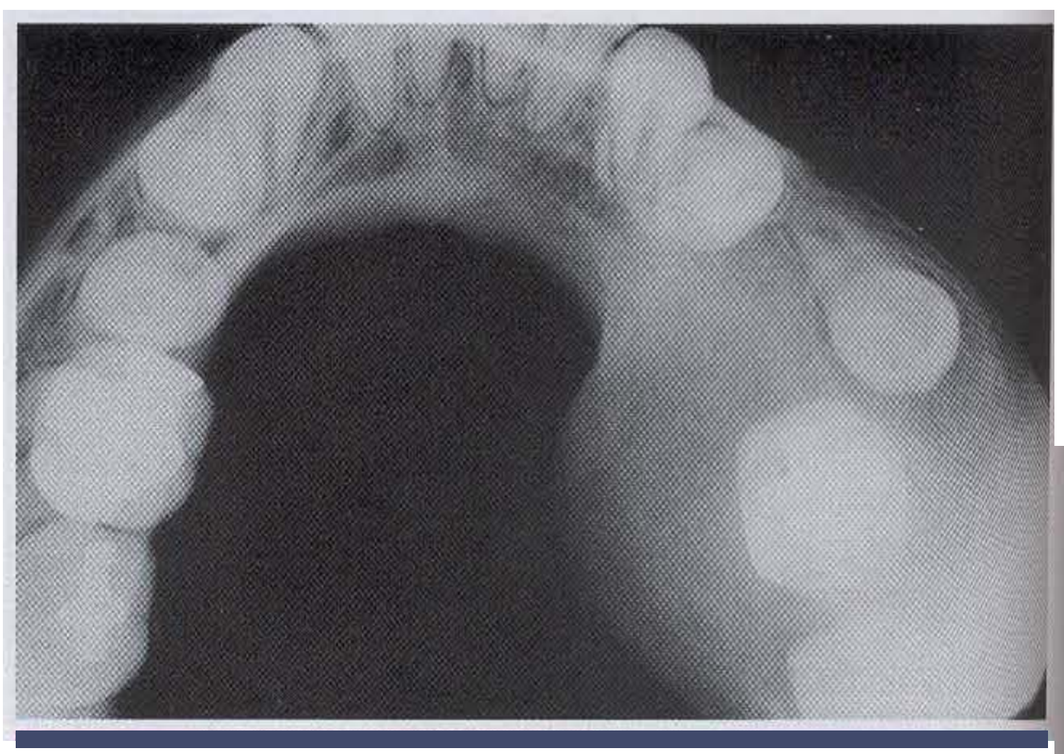

Figure 14-34 • Fibrous dysplasia. Occlusal radiograph showing localized expansion of the mandible and the "ground-glass" radiographic appearance. The margins of the lesion are not well defined and blend into the adjacent bone. (From Waldron CA, Giansanti JS: Benign fibre-osseous lesions of the jaws: a clinical-radiologic-histologic review of 65 cases. Part I. Fibrous dysplasia of the jaws, *Oral Surg Oral Med Oral Pathol* 35:190-201, 1973.)

When the maxilla is involved. the lesional tissue displaces the sinus floor superiorly and commonly obliterates the maxillary sinus. Imaging studies in cases with maxillary involvement may show increased density of the base of the skull involving the occiput. sphenoid. roof of the orbit, and frontal bones (Figure 14-35). This is said to be the most characteristic radiographic feature of fibrous dysplasia of the skull.

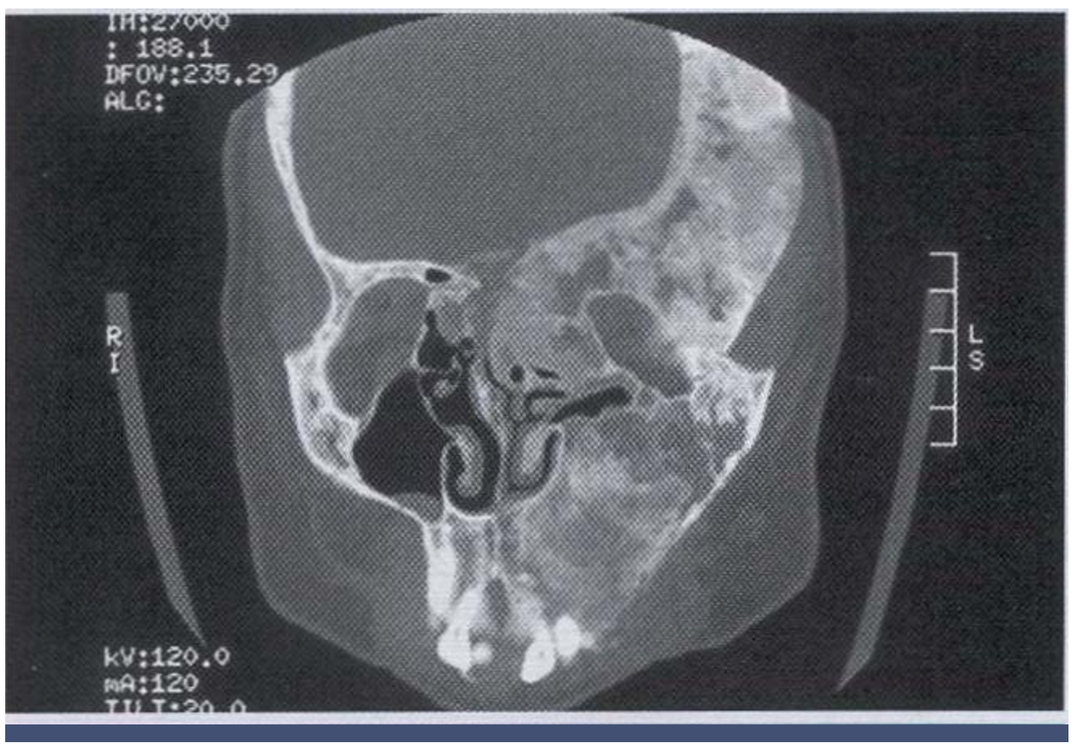

Figure 14-35 • Fibrous dysplasia. Computed tomography (CT) image showing extensive involvement of the maxilla and skull.

***Polyostotic** fibrous dysplasia; **Jaffe-Lichtenstein** syndrome; McCune-Albright syndrome.* Involvement of two or more bones is termed polyostotic fibrous dysplasia. a relatively uncommon condition. The number of *involved* bones *varies* from a few to 75% of the entire skeleton. When seen with *café au lait* (coffee with milk) pigmentation, the process is termed Iaffe-LIchtenstein syndrome. Polyostotic fibrous dysplasia also may be combined with *café au lait* pigmentation and multiple endocrinopathies, such as sexual precocity. pltultary adenoma. or hyperthyroidism. This pattern is known as the McCune-Albright syndrome.

Although the skull and jaws may be affected with resultant facial asymmetry, the clinical picture in patients with polyostotic fibrous dysplasia is usually dominated by symptoms related to the long bone lesions (Figure 14-36>' Pathologic fracture with resulting pain and deformity is frequently noted. Leg length discrepancy is *very* common as a result of involvement of the upper portion of the femur (hockey stick deformity).

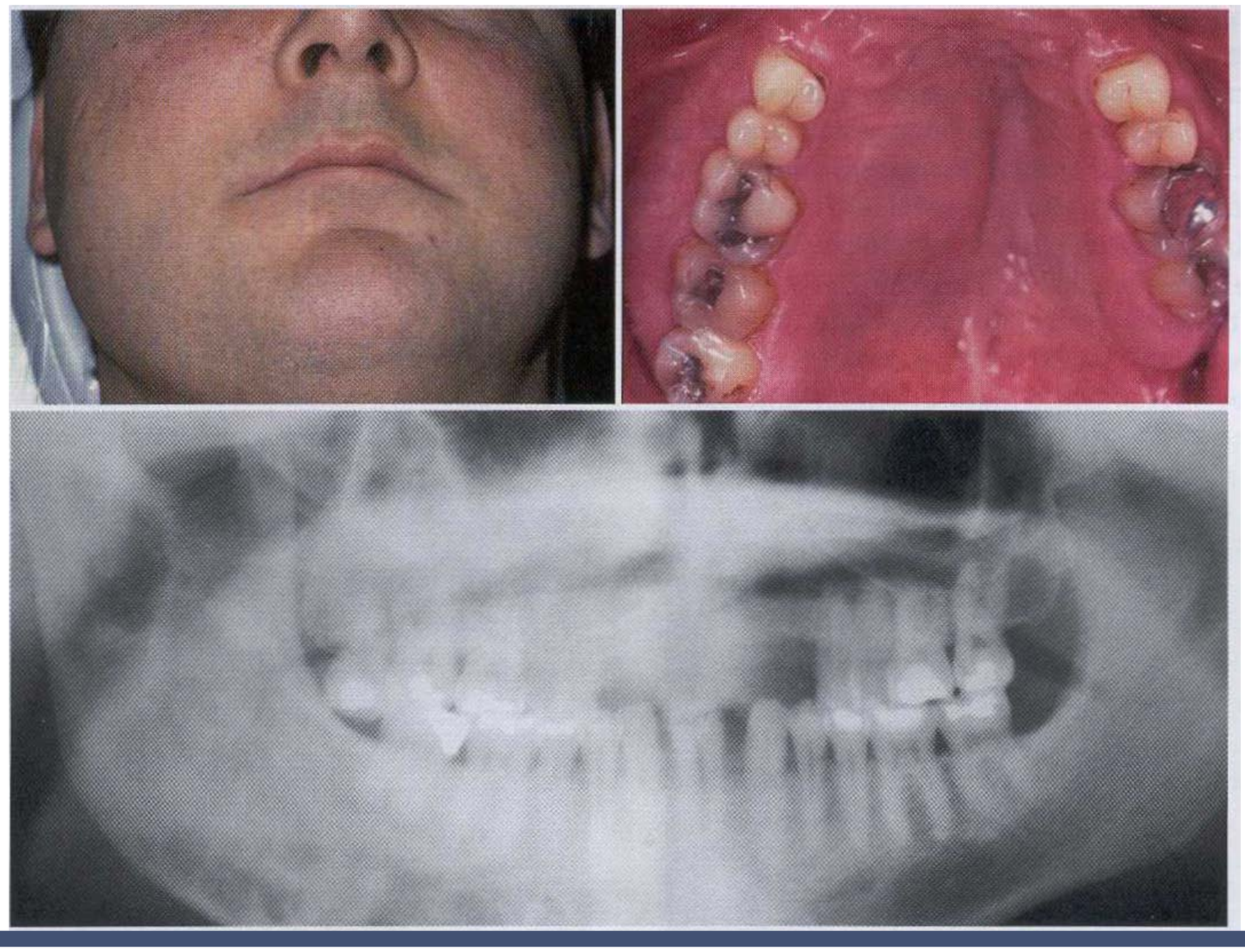

Figure 14-36 • Polyostotic fibrous dysplasia. jaffe-Lichtensteln syndrome: **A.** young man exhibiting enlargement of the right maxilla and mandible; **B.** intraoral photograph showing unilateral maxillary expansion; **C.** panoramic radiograph showing ill-defined lesions of the right side of both Jaws.

When present, the *café au lait* pigmentation consists of well-defined, generally unilateral tan macules on the trunk and thighs. These pigmented lesions may be congenital, and pigmented oral mucosal macules also may be present. The margins of the *café au lait* spots are typically very irregular, resembling a map of the coastline of Maine (Figure 14-37). This is in contrast to the *café au lait* spots of neurofibromatosis (see page 458), which have smooth borders (like the coast of California).

In McCune-Albright syndrome, sexual precocity is the **most common endocrine manifestation of the syndrome.** particularly in females. Menstrual bleeding may occur during the first few months of life. Breast development and pubic hair may be apparent within the first few years of life in affected girls.

Histopathologic Features

The typical microscopic findings of fibrous dysplasia show irregularly shaped trabeculae of immature (woven) bone in a cellular, loosely arranged fibrous stroma. The bone trabeculae are not connected to each other. They **often assume curvilinear shapes, which have been** likened to Chinese script writing. The bone trabeculae **are considered to arise by metaplasia and are not sur-** rounded by plump appositional osteoblasts (Figure 14-38). Tiny calcified spherules may be seen rarely but **are never numerous. In contrast to ossifying fibroma and** cementa-osseous dysplasia, fibrous dysplasia typically **demonstrates a rather monotonous pattern throughout** the lesion rather than being a haphazard mixture of woven bone, lamellar bone, and spheroid particles. The lesional bone fuses directly to normal bone at the periphery of the lesion, so that no capsule or line of demarcation is present. Although fibrous dysplasia of the long bones does not undergo maturation, jaw and skull lesions tend to be more ossified than their counterparts in the rest of the skeleton. This is particularly true in **specimens from older patients.**

Serial biopsy specimens in some cases have shown that histopathologically classic fibrous dysplasia of the **jaws undergoes progressive maturation to a lesion con-** sisting of lamellar bone in a moderately cellular connective tissue stroma (Figure 14-39). The bone trabeculae in **these mature lesions tend to run parallel to one another.**

Treatment and Prognosis

Clinical management of fibrous dysplasia of the jaws may present a major problem. Although smaller lesions, particularly in the mandible, may be surgically resected in their entirety without too much difficulty, the diffuse nature and large size of many lesions, particularly those **of the maxilla, preclude removal without extensive sur-** gery. In many cases, the disease tends to stabilize and

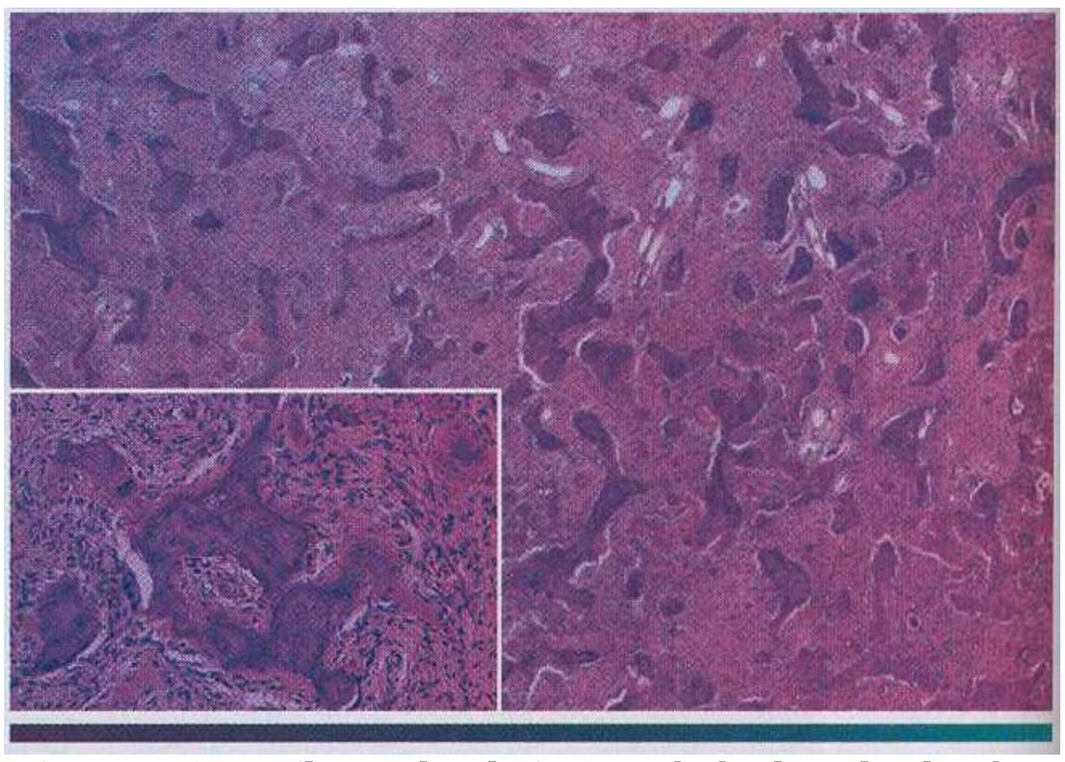

Figure 14-38 • Fibrous dysplasia. Irregularly shaped trabeculae of woven bone in a fibrous stroma.

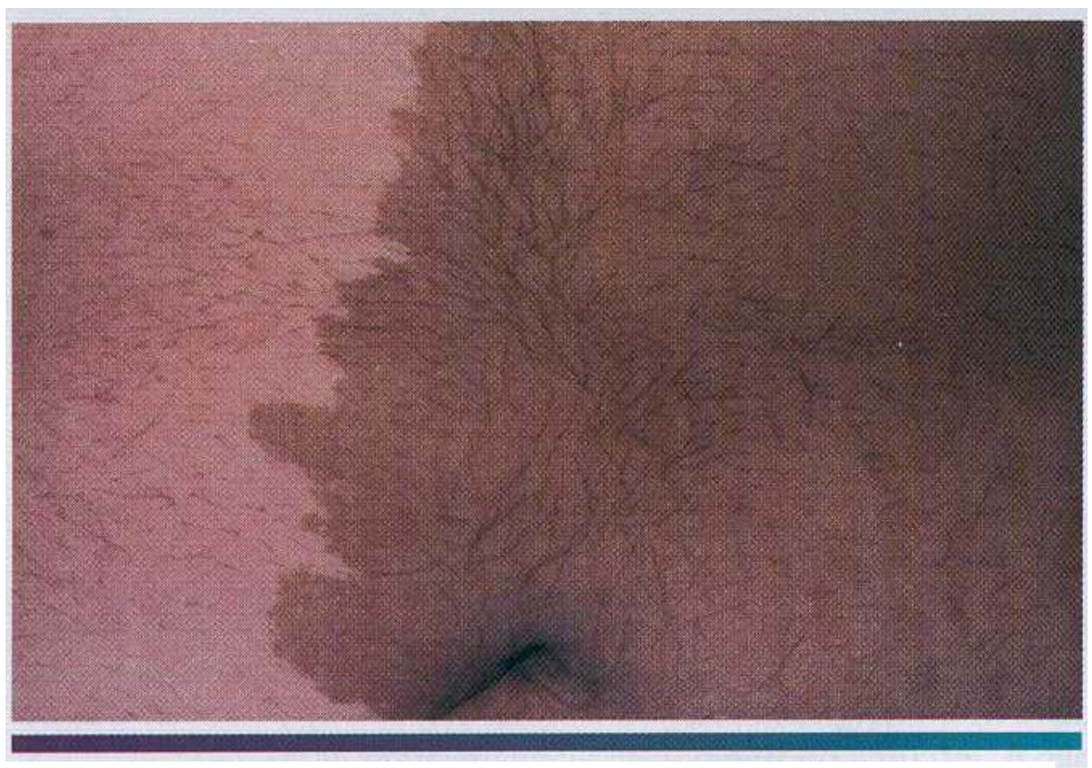

Figure 14-37 • Polyostotic fibrous dysplasia. [affe-Lichtenstein syndrome: *Café au Jait* pigmentation of the abdomen. This is the same patient as shown in Figure 14-36.

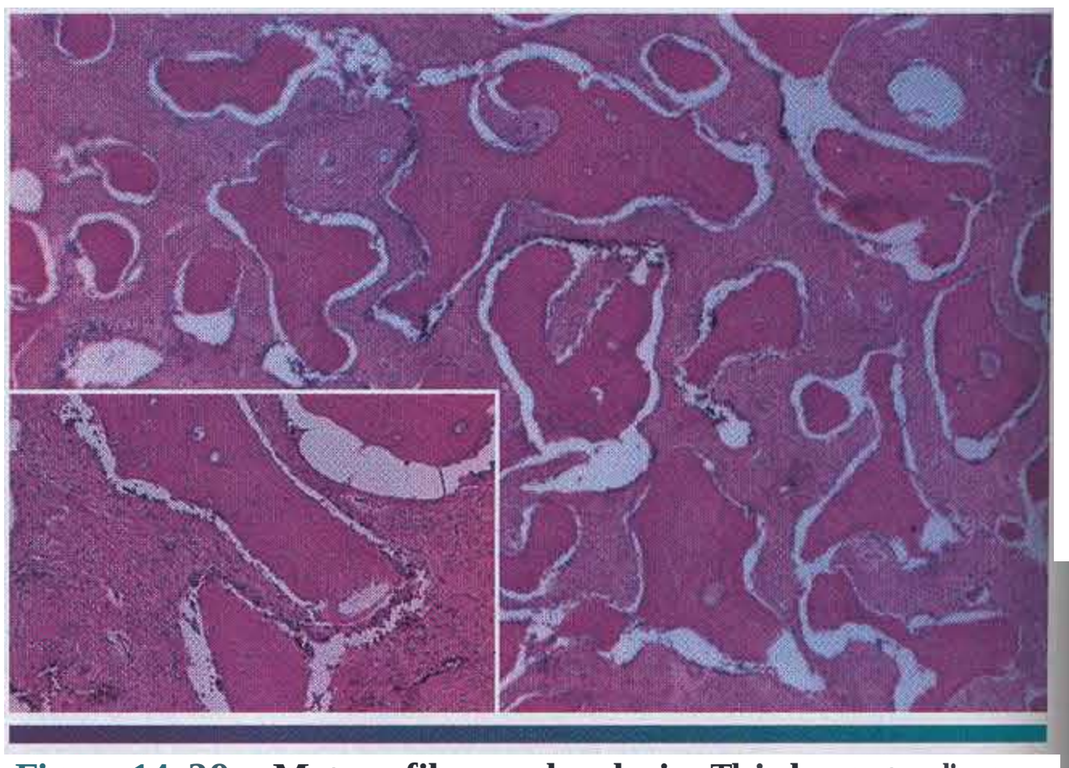

Figure 14-39 • Mature fibrous dysplasia. This long-standing lesion shows scattered trabeculae of bone within fibrous connective tissue. Note the lamellar maturation of the bone.

essentially stops enlarging when skeletal maturation is reached. Some lesions. however, continue to grow. although generally slowly. in adult patients.

Some patients with minimal cosmetic or functional deformity may not require or desire surgical treatment. Cosmetic deformity with associated psychologic problems or functional deformity may dictate surgical intervention in the younger patient. Such a procedure usually entails surgical reduction of the lesion to an acceptable contour without attempts to remove the entire lesion. The cosmetic result is usually good, but regrowth of the lesion occurs over time.

The prevalence of regrowth after surgical reduction is difficult to determine, but it has been estimated that between 25% and 50% of patients show some regrowth after surgical shave-down of the lesion. The regrowth is more common in younger patients, and many surgeons believe that surgical intervention should be delayed for as long as possible.

Malignant change. usually development of an osteosarcoma, has been rarely associated with fibrous dysplasia. Most examples have been found in patients who had received radiation therapy for fibrous dysplasia. but a few examples of spontaneous sarcomatous changes have been reported. Radiation therapy for fibrous dysplasia is contraindicated because it carries the risk for development of postirradiation bone sarcoma.

CEMENTO-OSSEOUS DYSPLASIAS (OSSEOUS DYSPLASIA)

Cementa-osseous dysplasia occurs in the tooth-bearing areas of the jaws and is probably the most common ffbro-osseous lesion encountered in clinical practice. In spite of its frequency, the associated nomenclature and diagnostic criteria remain an area of debate. Because the pathologic features share many similarities with fibrous dysplasia and ossifying fibroma. correct diagnosis can be problematic but is critical to appropriate management.

Because cementa-osseous dysplasia arises in close approximation to the periodontal ligament and exhibits histopathologic similarities with the structure, some investigators have suggested these lesions are of periodontal ligament origin. Others believe cementa-osseous dysplasia represents a defect in extraligamentary bone remodeling that may be triggered by local factors and possibly correlated to an underlying hormonal imbalance.

Based on the clinical and radiographic features. it is convenient to separate cementa-osseous dysplasias into three groups: (I) focal. (2) periapical. and (3) florid. Although the focal pattern is somewhat different from the other two forms. it is likely that these categories may represent variants of the same pathologic process.

Clinical and Radiographic Features

***Focal** cementa-osseous **dysplasia**.* Focal cemento-osseous dysplasia exhibits single site of involvement. The concept of focal osseous dysplasia was not clarified until the mid-I990s. Before that time, most cases were misdiagnosed as a variant of ossifying fibroma.

An examination of this pattern reveals slightly different epidemiology from the other two variants. About 90% of cases of focal cementa-osseous dysplasia occur in females. with an approximate mean age of 38 and a predilection for the third to sixth decades. In contrast to the periapical and florid variants. a higher percentage of cases have been diagnosed in whites.

Focal cementa-osseous dysplasia may occur in any area of the jaws, but the posterior mandible is the predominant site. The disease is typically asymptomatic and is detected only on a radiographic examination. Most lesions are smaller than 15 ern 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 (Figure 14-40). The lesion tends to be well defined, but the borders arc usually slightly irregular. Lesions occur in dentulous and edentulous areas, with many examples noted in extraction sites. Occasionally. an apparently focal lesion may represent an early stage in the transition to multifocal involvement and, as would be expected, this is seen most frequently in black females.

***Periapical** cementa-osseous **dysplasia (osseous dysplasia; cementa! dysplasia; cementomas)**.* Periapical cementa-osseous dysplasia predominantly involves the periapical region of the anterior mandible. Solitary lesions may occur. but multiple foci are present more frequently. There is a marked predilection for female patients (ranging from 10:I to 14:I) and approxtmarely 70% of cases affect blacks. Most patients are diagnosed initially between the ages of 30 and 50, with the diagnosis almost never made in individuals under the age of 20 years. Teeth associated with the lesions are almost invariably vital and seldom have restorations.

Periapical cementa-osseous dysplasia is an asymptomatic condition that is discovered when radiographs are taken for other purposes. Early lesions appear as circumscribed areas of radiolucency involving the apical area of a tooth. At this stage, the lesion cannot be differentiated radiographically from a periapical granuloma or periapical cyst (Figure 14-41). With time. adjacent lesions often fuse to form a linear pattern of radiolucency that envelopes the apices of several teeth (Figure 14-42).

Serial radiographic studies reveal that the lesions tend to "mature" over time to create a mixed radiolucent and radiopaque appearance (Figure 14-43). In the end stage.

the lesions show a circumscribed dense calcification surrounded by a narrow radiolucent rim. However. the periodontal ligament is intact, and fusion to the tooth is not seen. Individual lesions seldom exceed J.Ocm in diameter. Each lesion is self-limiting and does not typically expand the cortex. Progressive growth seldom. if ever. occurs.

Florid cementa-osseous dysplasia, Florid cemento-osseous dysplasia appears with multifocal involvement not limited to the anterior mandible. Although many cases demonstrate multifocal lesions only In the posterior portions of the jaws, many patl ents also reveal synchronous involvement of the anterior mandible (Figure 14-44). Like the periapical pattern. this form predominantly involves black women (in some series. more than 90% of patients) with a marked predilection for middle-aged to the elderly.

The lesions show a marked tendency for bilateral and often quite symmetric involvement. and it is not unusual to encounter extensive lesions in all four posterior quadrants. The disease may be completely asymptomatic and, in such cases. is discovered only when radiographs are taken for some other purpose. In other instances. the

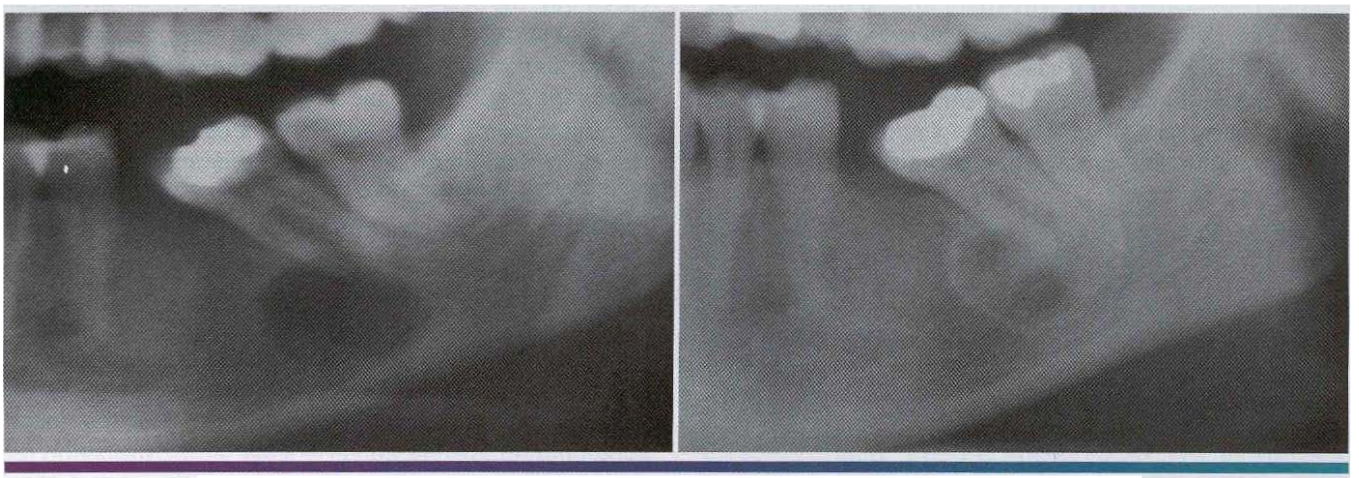

Figure 14-40 • Focal cementa-osseous dysplasia. A, A radiolucent area involves the edentulous first molar area and the apical area of the second molar. B, Radiograph of the same patient taken 9 years later showing a mixed radiolucent and radiopaque pattern.

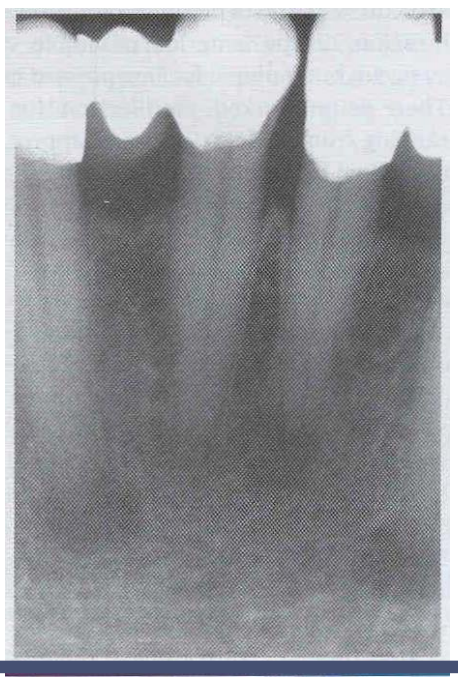

Figure 14-41 • Periapical cemento-osseous dysplasia. Periapical radiograph showing multiple radiolucent lesions at the apices of the anterior mandibular teeth. (Courtesy of Dr. Aaron Carner.)

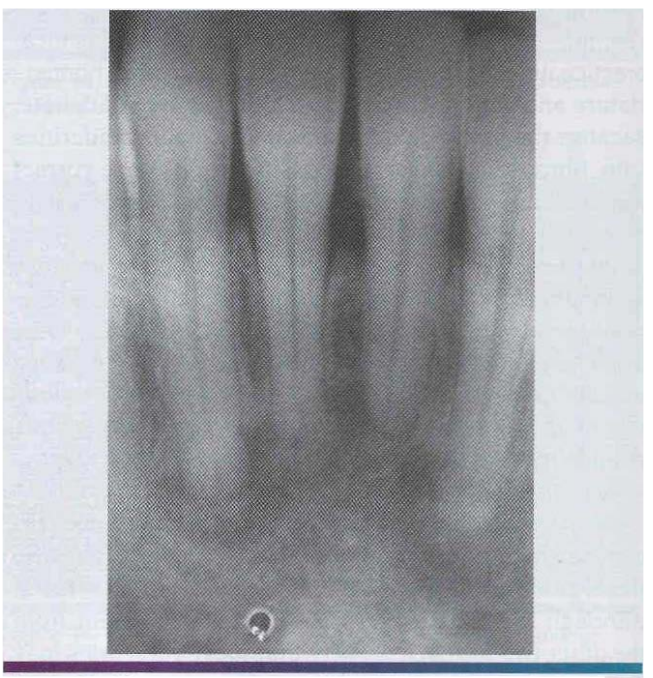

Figure 14-42 • Periapical cemento-osseous dysplasia. Later stage lesions exhibiting significant mineralization.

patient may complain of dull pain. and an alveolar sinus traer may be present, exposing yellowish. *avascular* bone to the oral cavity (Figure 14-45). Although rarely prominent, some degree of expansion may be noted in one or more of the involved areas,

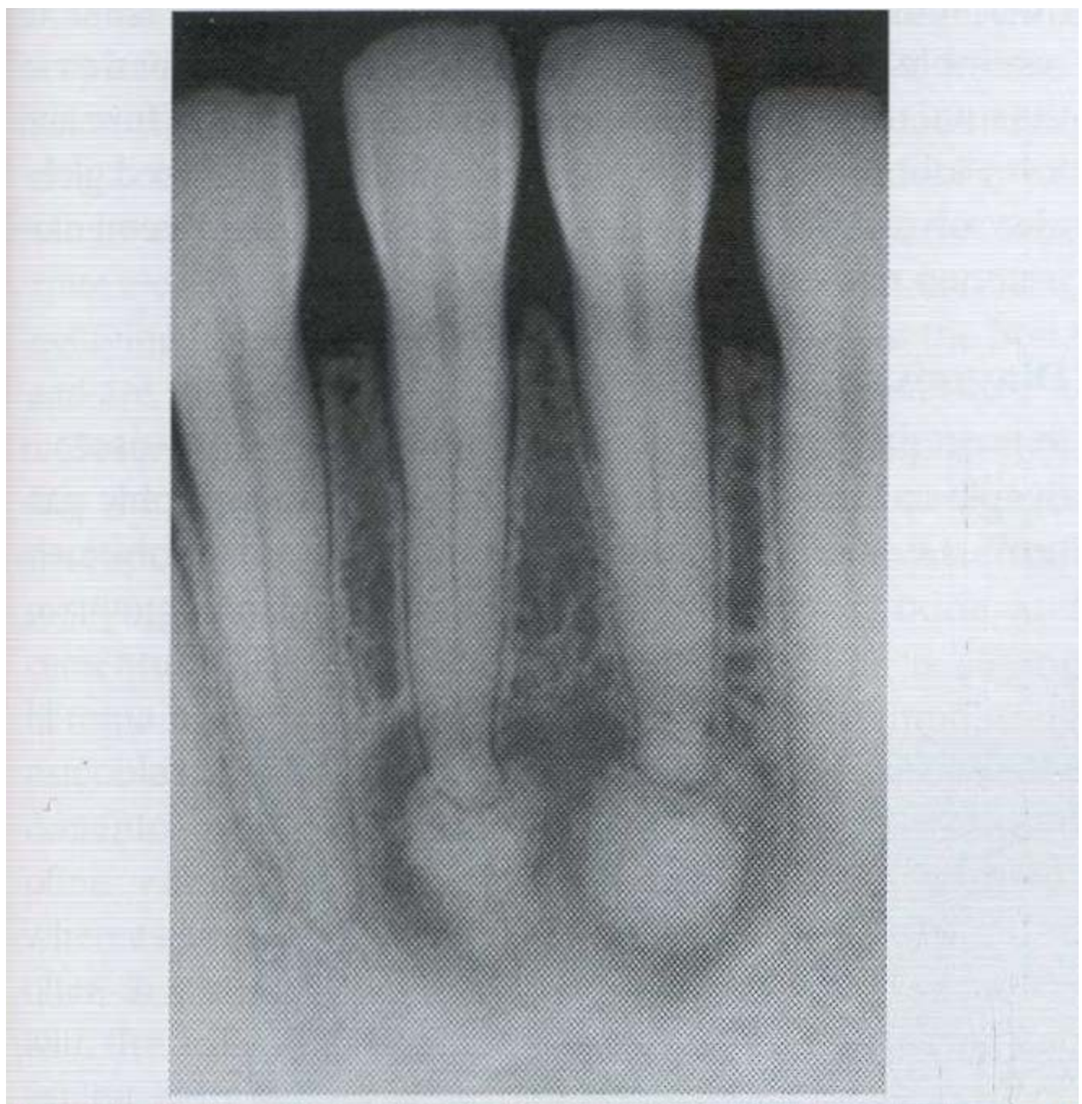

Figure 14-43 • Periapical cemento-osseous dysplasia. Later stage lesions exhibiting significant mineralization.

Radiographically. the lesions typically demonstrate an identical pattern of maturation noted in the other two forms. Initially, the lesions are predominantly radiolucent but with time become mixed. then predominantly radiopaque with only a thin peripheral radiolucent rim (Figure 14-46). On occasion, a lesion can become almost totally radiopaque and blend with the adjacent normal-appearing bone.

Both dentulous and edentulous areas may be affected, and involvement appears to be unrelated to the presence or absence of teeth. More sharply defined radiolucent areas. which on surgical exploration prove to be simple bone cysts (see page 549) may be intermixed with the other lesional elements. The cysts may be single or multiple and, in some cases, represent a sizable portion of the lesion. It has been suggested that these simple bone cysts arise from obstruction to drainage of the normal interstitial fluid by the ftbro-osscous proliferation.

Histopathologic Features

All three patterns of cemcnto-osseous dysplasia demonstrate similar histopathologic features. The tissue consists of fragments of cellular mesenchymal tissue composed of spindle-shaped fibroblasts and collagen fibers with numerous small blood *vessels* (Figure 14-47). Free hemorrhage is typically noted interspersed throughout the lesion.

Within this fibrous connective tissue background is a mixture of *woven* bone. lamellar bone, and cementum-

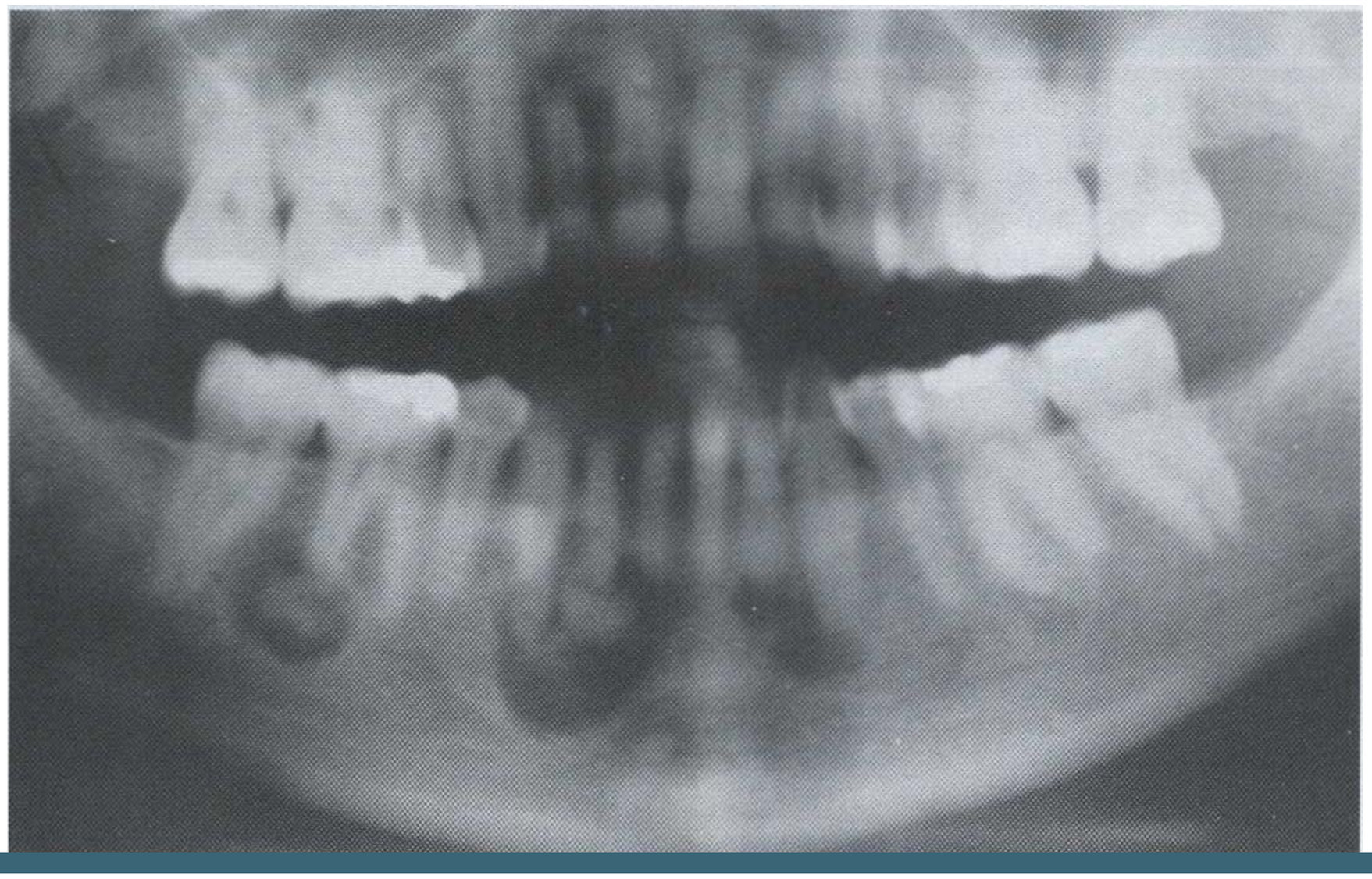

Figure 14-44 • Florid cemento-osseous dysplasia. Multiple mixed radiolucent and radiopaque lesions involving the anterior and posterior regions of the mandible.

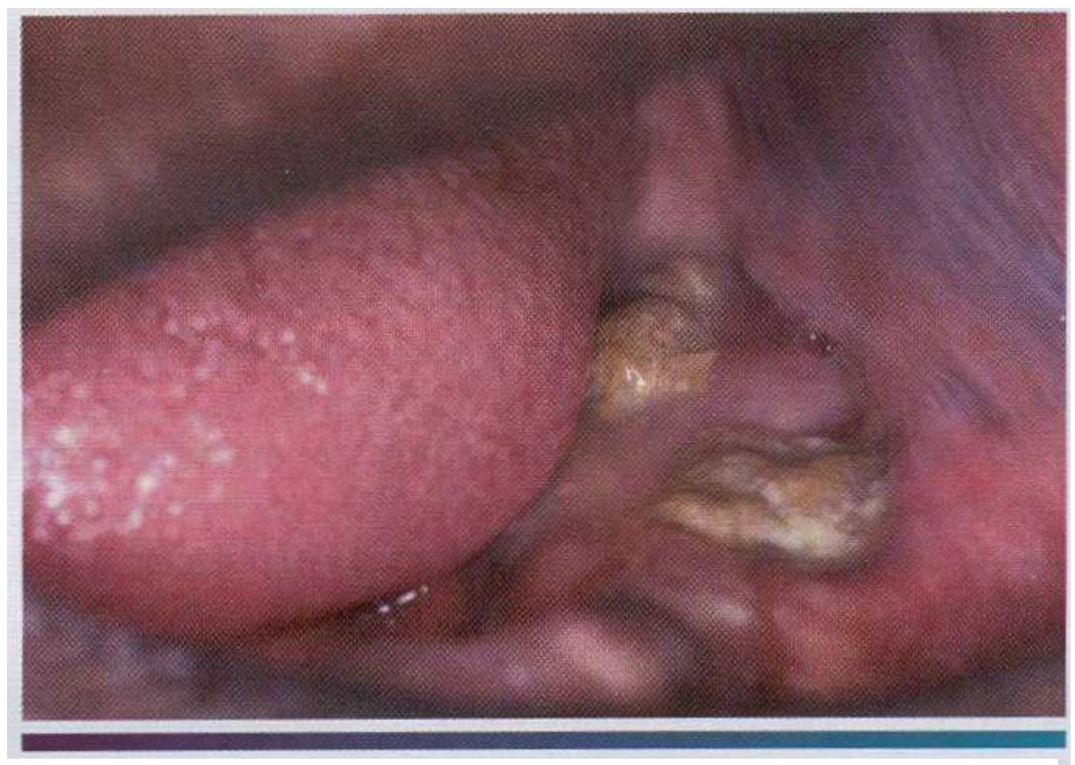

Figure 14·45 • Florid cementa-osseous dysplasia. Yellowish. avascular cementum-like material is beginning to exfoliate through the oral mucosa.

like particles (Figure 14-48). The proportion of each mineralized material varies from lesion to lesion and from area to area in individual sites of involvement. As the lesions mature and become more sclerotic. the ratio of fibrous connective tissue to mineralized material decreases. With maturation, the bone trabeculae become thick curvilinear structures that have been said to resemble the shape of ginger roots. With progression to the final radiopaque stage, individual trabeculae fuse and form lobular masses composed of sheets or fused globules of relatively acellular and disorganized cementoosseous material (Figure 14-49).

Diagnosis

In most instances of periapical or florid cementa-osseous dysplasia, the distinctive clinical and radiographic patterns (t.e.. a black female with multiquadrant involvement

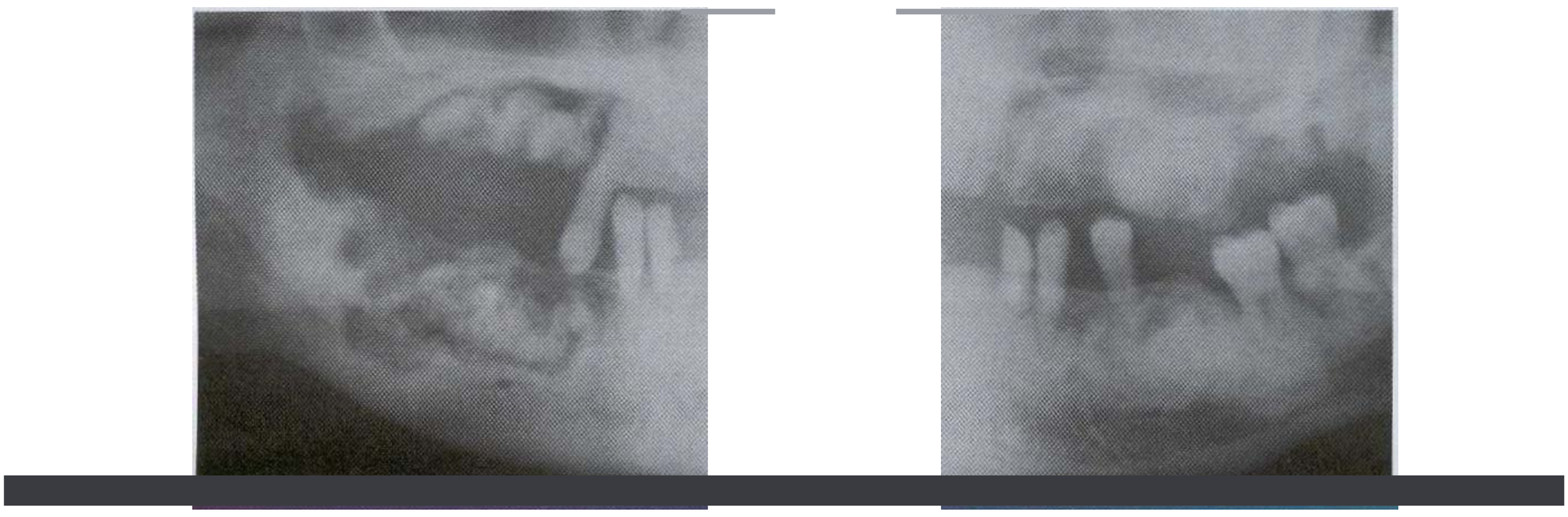

Figure 14-46 • Florid cementa-osseous dysplasia. Densely sclerotic lesions involve the four posterior quadrants. The mass in the upper right quadrant is exposed to the mouth and is sequestrating.

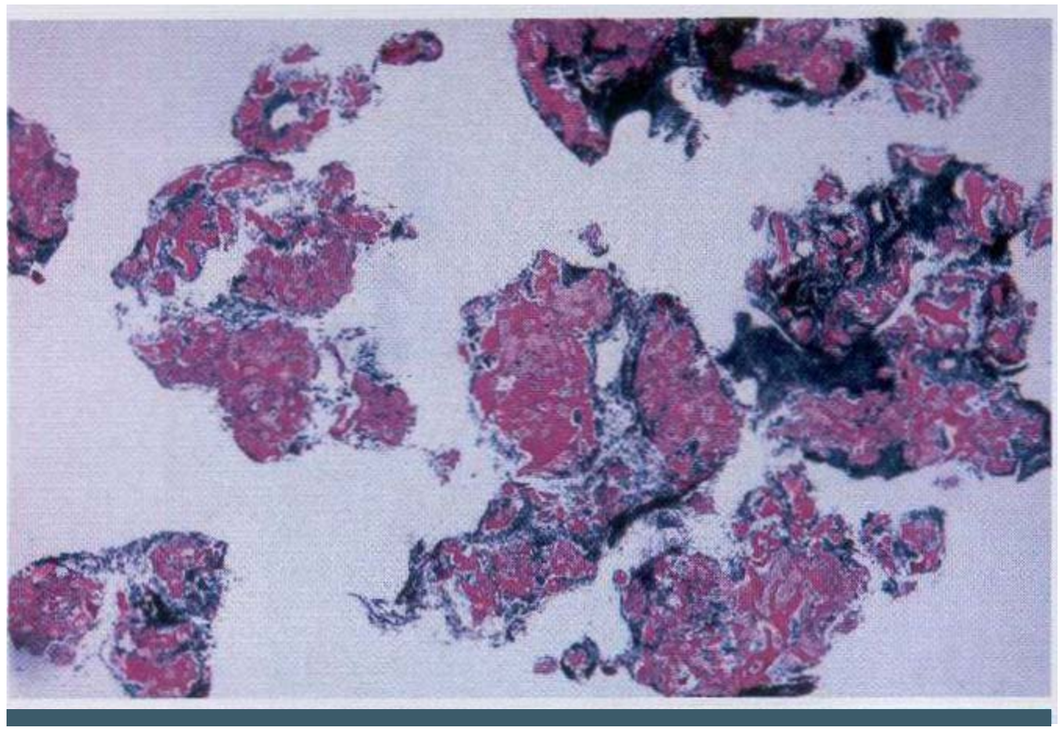

Figure 14-47 • Cementa-osseous dysplasia. low-power photomicrograph showing fragments of cellular fibrous connective tissue containing scattered trabeculae of bone.

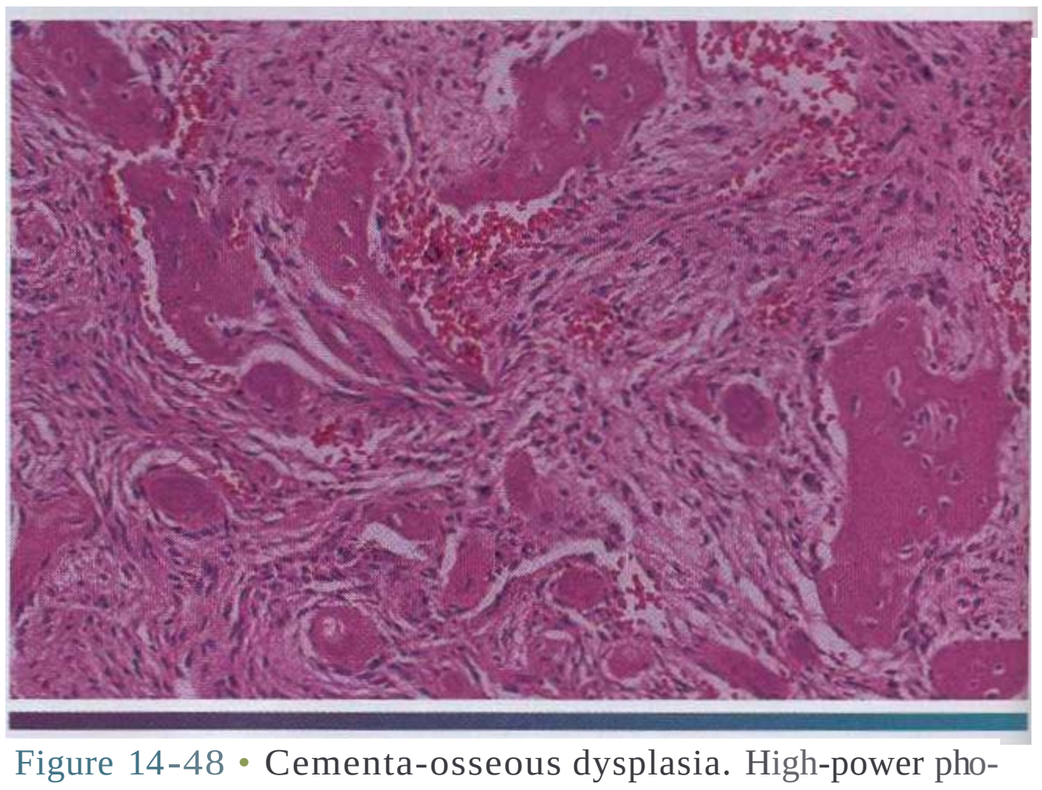

Figure 14-48 • Cementa-osseous dysplasia. High-power photomicrograph showing spicules of bone and cementum-like hard tissue within moderately cellular fibrous connective tissue, Note the hemorrhage around the bony trabeculae.

or multiple lesions involving vital lower incisor teeth), allow a strong presumptive diagnosis without the necessity of biopsy. The features of focal cementa-osseous dysplasia are less specific and often mandate surgical investigation. Even upon histopathologic review, distlnguishlng focal cementa-osseous dysplasia from ossifying fibroma often can be difficult. The findings at surgery are very helpful in discriminating between these two lesions. Before the final sclerotic stage, cementa-osseous dysplasia consists of easily fragmented and gritty tissue that can be curetted easily from the defect but does not separate cleanly from the adjacent normal bone. In contrast, ossifying fibromas tend to separate cleanly from the bone and are removed in one or several large masses.

Several histopathologic features also can help to confirm the impression obtained from the surgical and gross descriptions. Although cementa-osseous dysplasia and ossifying fibroma demonstrate a mixture of bone and cementum-like particles, the trabeculae in ossifying fibroma tend to be more delicate and often demonstrate osteoblastic rimming. The cementum-like particles in cementa-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 hemorrhage along the margins of the specimen, cementa-osseous dysplasia typically reveals free hemorrhage throughout the lesion and a sinusoidal vascularity in close association with the bony trabeculae.

Treatment and Prognosis

The various forms of cernento-osseous dysplasia do not appear neoplastic; therefore, they generally do not require removal. However, these lesions can cause significant clinical problems for some patients. During the predominantly radiolucent phase, the lesions cause few problems. Once significant sclerosis is present, the lesions of cementa-osseous dysplasia tend to be hypovascular and prone to necrosis with minimal provocation. For the asymptomatic patient, the best management consists of regular recall examinations with prophylaxis and reinforcement of good home hygiene care to control periodontal disease and prevent tooth loss.

Because the onset of symptoms is usually associated with exposure of the sclerotic masses to the oral cavity. biopsy or elective extraction of teeth should be avoided. In other instances, symptoms begin after exposure of the sclerotic masses to the oral cavity as a result of progressive alveolar atrophy under a denture. Affected patients should be encouraged to retain their teeth to prevent development of symptoms later.

Management of the symptomatic patient is more difficult. At this stage, there is an inflammatory component to the disease and the process is basically a chronic osteomyelitis involving dysplastic bone and cementum. 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. Although a single case of a malignant fibrous histiocytoma arising within a focus of florid cementa-osseous dysplasia has been reported, such neoplastic transformation appears unique, and the prognosis for patients with cementa-osseous dysplasia is good. When simple bone cysts arise within foci of cernento-osseous dysplasia, surgical exploration is necessary to establish the diagnosis.

These simple bone cysts often do not heal as rapidly as those noted in a younger patient who does not have cementa-osseous dysplasia. In some cases, the cysts persist or enlarge after surgical intervention; when they fill in, the bone retains an abnormal radiographic appearance. To assist healing, the cyst and the surrounding fibreosseous proliferation are usually curetted thoroughly.

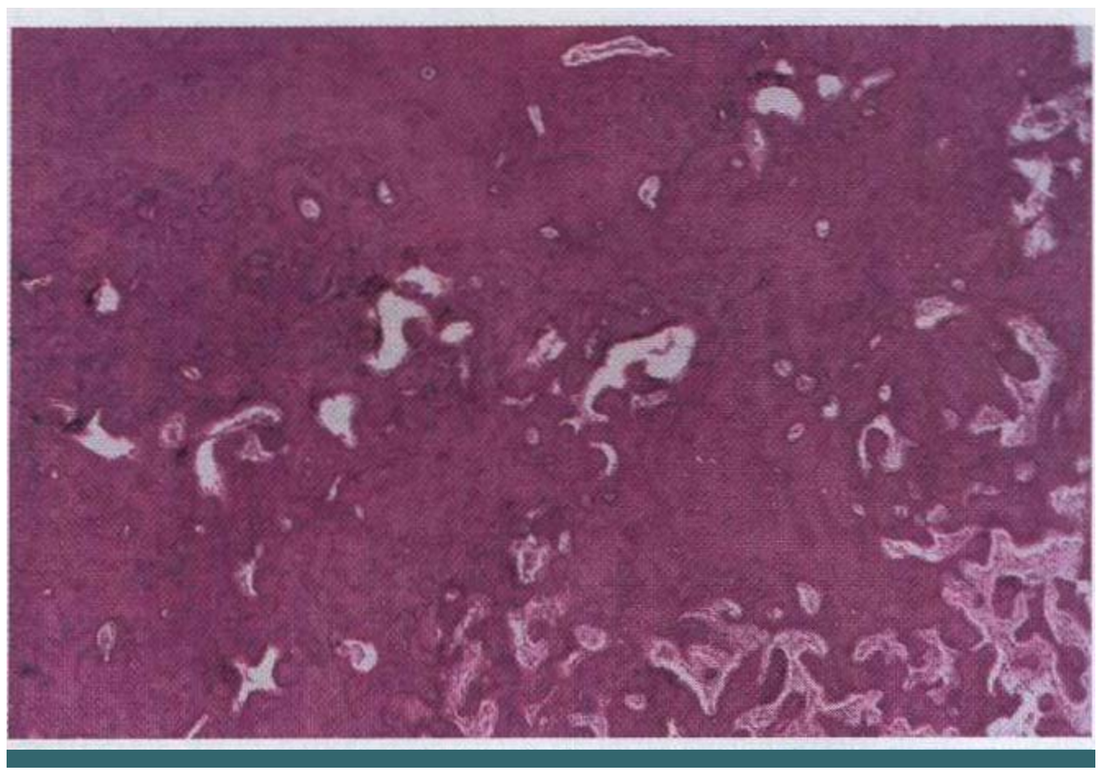

Figure 14-49 • Cemento-osseous dysplasia. Late-stage lesion showing a sclerotic mass of cemento-osseous material.

FAMILIAL GIGANTIFORM CEMENTOMA

Although the term gigantiform cementoma has been used in the past as a synonym for florid cementa-osseous dysplasia, most authorities now restrict use of this term to an uncommon hereditary disorder that is significantly different than conventional cementa-osseous dysplasia. Familial gigantiform cementoma is a disorder of gnathic bone that ultimately leads to the formation of massive sclerotic masses of disorganized mineralized material.

Clinical and Radiographic Findings

Familial gigantiform cementoma is an autosomal dominant disorder that demonstrates high penetrance and variable expressivity. Although the majority of reported cases have occurred in Caucasians, well-documented

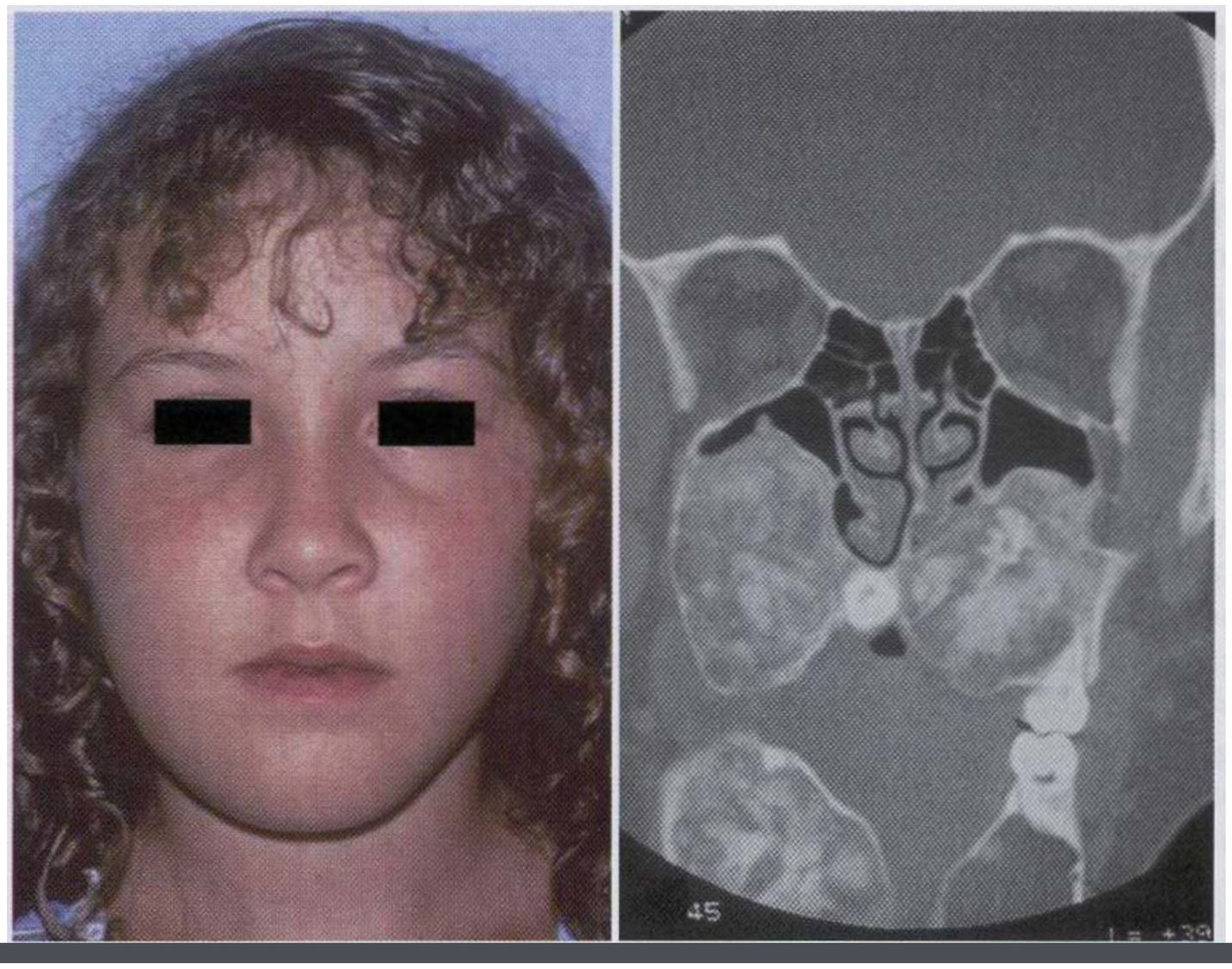

Figure 14-50 • Familial gigantiform cementoma. Young woman with massive lesions involving all four quadrants of the jaws. (Part A from Abdelsayed RA, Eversole LR, Singh BS, et al: Gigantiform cementoma: clinicopathologic presentation of 3 cases, *Oral Surg Oral Med Oral Pathof Oral Radiol Endod* 91:438-444, 2001. Part B courtesy of Dr. Rafik Abdelsayed.)

examples have been seen in African blacks. No sexual predilection has been observed.

Most affected patients begin to develop radiographic alterations during the first decade of life. By adolescence, clinically obvious alterations are typically noted and are followed by a rapid and expansive growth pattern (Figure 14-50). The osseous pathosis appears limited to the jaws and typically demonstrates multifocal involvement of both the maxilla and mandible. Although the course is variable, the gnathic enlargement in most patients results in significant facial deformity, as well as impaction, malposition, and malocclusion of the involved dentition. If not treated, the osseous enlargement eventually ceases during the fifth decade.

Radiographically, the initial features resemble those seen in cementa-osseous dysplasia, appearing as multiple radiolucencies in the periapical regions. 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 cernento-osseous dysplasia, the affected bone during the final radiopaque stage is very sensitive to inflammatory stimuli and becomes necrotic with minimal provocation. Before therapy, 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, all affected females demonstrated multifocal polypoid adenomas of the uterus that were associated with chronic hemorrhage and thought responsible for the anemia. A gynecologic examination appears prudent in all affected females, especially those with anemia.

Histopathologic Features

Histopathologically, familial gigantiform cementoma shows the same spectrum of changes seen in florid cernento-osseous dysplasia, and the two cannot be distinguished microscopically.

Treatment and Prognosis

Before the final sclerotic stage, attempts to improve aesthetics by shave-down surgical procedures have not been successful because the dysplastic tissue rapidly regrows. Once the lesions are predominantly radiopaque, partial removal may lead to sequestration of the remaining affected bone. Therefore, extensive resection of the altered bone and reconstruction of the facial skeleton and associated soft tissues have been recommended and can produce acceptable functional and aesthetic results. The extent of the required surgical procedures often is greater for patients who are treated during the later stages of the disease.

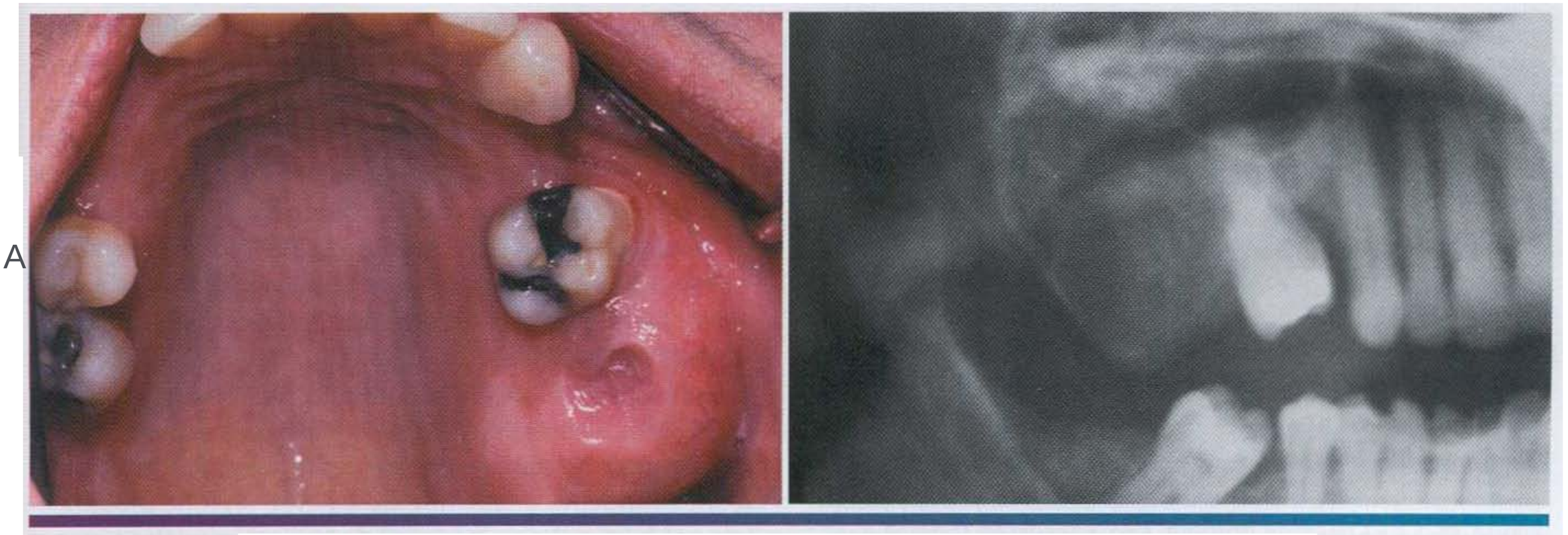

Figure 14-51 • **Ossifying fibroma. A,** Enlargement of the posterior maxilla caused by a large ossifying fibroma. **B,** Note the mixed radiolucent and radiopaque lesion expanding the posterior maxilla.

OSSIFYING FIBROMA (CEMENTIFYING FIBROMA; CEMENTO-OSSIFYING FIBROMA)

Although it can resemble focal cementa-osseous dysplasia radiographically and, to a lesser extent, histopathologically, ossifying fibroma is a true neoplasm with a significant growth potential. Before the refining of the concept of focal cementa-osseous dysplasia in the mid-1990s, ossifying fibroma was thought to be a common neoplasm. **In reality, true ossifying fibromas are relatively rare,** with many previously reported examples actually being focal cementa-osseous dysplasia.

The neoplasm is composed of fibrous tissue that contains **a variable mixture of bony trabeculae, cementum-**like spherules, or both. Although the lesions do contain **a variety of mineralized structures. most authorities** agree the same progenitor cell produces the different materials. It has been suggested that the origin of these **tumors is odontogenic or from** periodontal ligament. **but** microscopically identical neoplasms with cementum-like differentiation also have been reported in the orbital. frontal. ethmoid, sphenoid, and temporal bones, leaving these prior theories of origin open to question. Today, many authorities prefer to designate the cementum-like **material present in ossifying fibromas as a variation of** bone. The designations ossifying fibroma, cemento-ossifying fibroma, and cementifying fibroma are all appropriate for this tumor and continue to be used by many. In spite of this, however, it is agreed that these are the **same lesion and are classified best as osteogenic neo-**plasms. In this section, all of these variations will be combined under the term, ossifying fibroma.

Clinical and Radiographic Features

The epidemiology of ossifying fibroma is unclear because **many previous reports confused focal cementa-osseous** dysplasia with true ossifying fibromas. It appears ossifying fibromas occur over a wide age range with the **greatest number of cases encountered during the third** and fourth decades of life. There is a definite female predilection, with the mandible involved far more often than the maxilla. The mandibular premolar and molar **area is the most common site.**

Small lesions seldom cause any symptoms and are **detected only on radiographic examination. Larger tumors** result in a painless swelling of the involved bone (Figure 14-51); they may cause obvious facial asymmetry, which **on occasion reaches grotesque size. Pain and paresthesia** are rarely associated with an ossifying fibroma.

Radiographically, the lesion most often is well defined and unilocular. Some examples show a sclerotic border. Depending on the amount of calcified material produced in the tumor, it may appear completely radiolucent, or more often varying degrees of radiopacity. True ossifying fibromas that become largely radiopaque with only a thin **radiolucent periphery are uncommon; many reported** examples with this radiographic pattern likely represent end-stage focal cementa-osseous dysplasia. Root divergence or resorption of roots of teeth associated with the tumor may be noted. Large ossifying fibromas of the **mandible often demonstrate a characteristic downward** bowing of the inferior cortex of the mandible.

Histopathologic Features

At surgical exploration, the lesion is well demarcated from the surrounding bone, thus permitting relatively easy separation of the tumor from its bony bed. A few ossifying fibromas will show grossly and microscopically a fibrous capsule surrounding the tumor. Most are not encapsulated but are well demarcated grossly and microscopically from the surrounding bone.

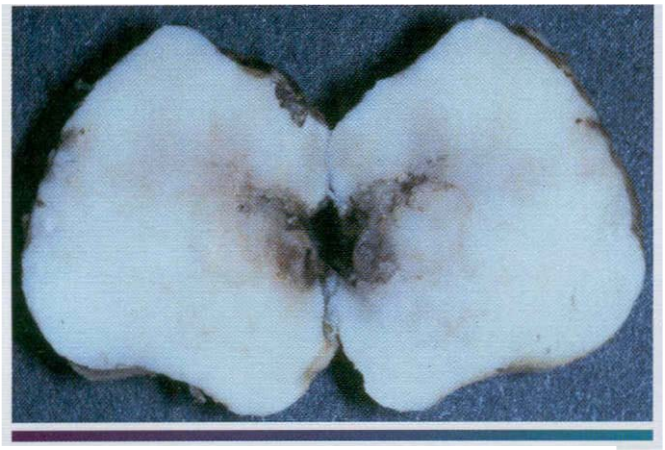

figure 14-52 • Ossifying fibroma. Gross specimen showing a well-circumscribed tumor that shelled out in one piece.

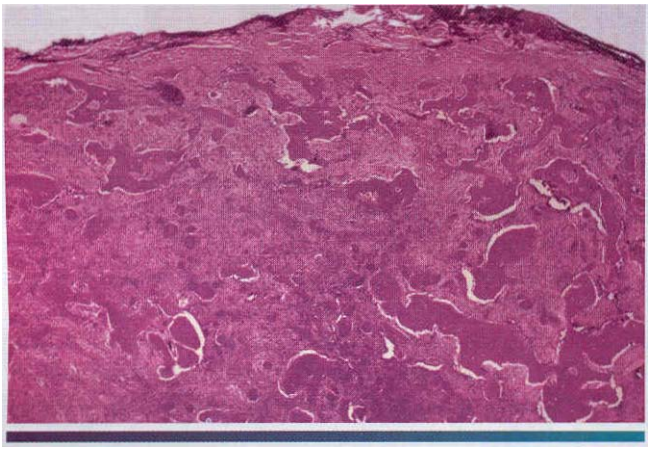

Figure 14-53 • Ossifying fibroma. This low-magnification photomicrograph shows a well-circumscribed solid tumor mass. Trabeculae of bone and droplets of cementum-like material can be seen forming within a background of cellular fibrous connective tissue.

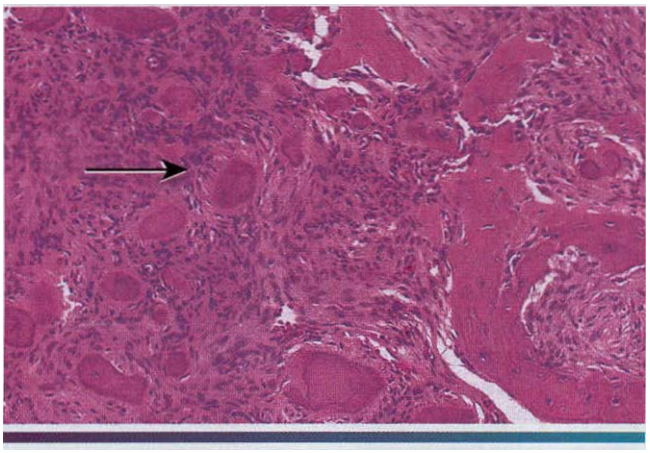

Figure 14-54 • Ossifying fibroma. High-power photomicrograph showing a mixture of woven bone and cementum-like material. Note the spherules demonstrating peripheral brush borders *(arrow)*.

On gross examination, the tumor is usually submitted in one mass or as a few large pieces (Figure 14-52). Ossifying fibromas consist of fibrous tissue that exhibits varying degrees of cellularity and contains mineralized material (Figure 14-53). The hard tissue portion may be in the form of trabeculae of osteoid and bone or basophilic and poorly cellular spherules that resemble cementum. Admixtures of the two types are typical. The bony trabeculae vary in size and frequently demonstrate a mixture of woven and lamellar patterns. Peripheral osteoid and osteoblastic rimming are usually present. The spherules of cementum-like material often demonstrate peripheral brush borders that blend into the adjacent connective tissue (Figure 14-54). Significant intralesional hemorrhage is unusual. Variation in the types of mineralized material produced may be helpful in distinguishing OSSifying fibroma from fibrous dysplasia, which has a more uniform pattern of osseous differentiation.

Treatment and Prognosis

The circumscribed nature of the OSSifying fibroma generally permits enucleation of the tumor with relative ease. Some examples, however, which have grown large and destroyed considerable bone, may necessitate surgical resection and bone grafting. The prognosis, however, is very good, and recurrence after removal of the tumor is rarely encountered. There is no evidence that ossifying fibromas ever undergo malignant change.

JUVENILE OSSIFYING FIBROMA (JUVENILE ACTIVE OSSIFYING FIBROMA; JUVENILE AGGRESSIVE OSSIFYING FIBROMA)

The juvenile ossifying fibroma is a controversial lesion that has been distinguished from the larger group of ossifying fibromas on the basis of the age of the patients, most common sites of involvement, and clinical behavior. Two different neoplasms have been reported under the term, and disagreement exists over the spectrum of what should be accepted as juvenile OSSifying fibromas. Although the two forms demonstrate different histopathologic and clinical features, several investigators have chosen to compromise and accept two patterns of juvenile OSSifying fibroma: (1) trabecular and (2) psammomatoid.

Clinical and Radiographic Features

No significant sexual predilection is noted in either form. In most instances, the neoplasms grow slowly, are well-circumscribed, and lack continuity with the adjacent normal bone. The lesions are circumscribed radiolucencies that in some cases contain central radiopacities (Figure 14-55). Those present within a sinus may appear radiodense and often create a clouding that may be confused with sinusitis.

The age at diagnosis varies. with reported cases occurring in patients from less than 6 months to *over 70* years of age. Although both patterns *reveal* similar radiographic features and growth patterns. the trabecular form is diagnosed initially in younger patients. The mean age of trabecular juvenile ossifying fibromas is approximately II years. whereas the age of patients diagnosed with the psammomatoid variant approaches 22 years. Both patterns occur in either jaw but *reveal* a maxillary predominance. Although many of these tumors are initially discovered upon routine radiographic examination. cortical expansion may result in clinically detectable facial enlargement. The psammomatoid variant frequently appears outside of the jaws. with *over 70%* arising in the orbital and frontal bones and paranasal sinuses.

Complications secondary to the neoplasm are typically due to impingement on neighboring structures. With persistent growth. lesions arising in the paranasal sinuses penetrate the orbital. nasal. and cranial cavities. Nasal obstruction. exophthalmos. or proptosis may be seen. Rarely. temporary or permanent blindness occurs.

Intracranial extension has been discovered in neoplasms arising adjacent to the cribriform plates. Because of the circumscribed growth pattern of the tumor. the frontal lobe is typically elevated without any associated neurologic signs. Rarely. intracranial extension has resulted in meningitis. with one report of a maxillary tumor leading to convulsions and death from pneumococcal meningitis.

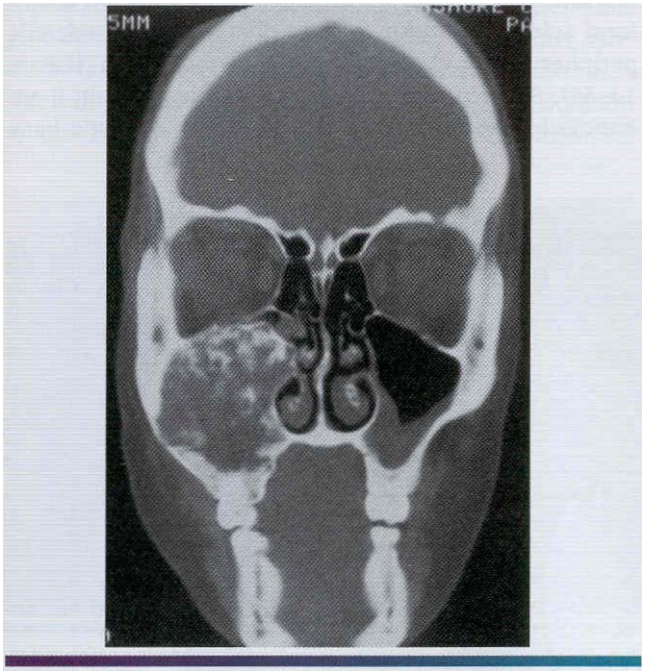

Figure 14-55 • Juvenile ossifying fibroma. Computed tomography (CT) scan showing a large tumor involving the left maxilla and maxillary sinus of a 12-year-old girl. Clinically, the tumor was growing rapidly.

Histopathologic Features

Both patterns are typically nonencapsulated but well demarcated from the surrounding bone. The tumor consists of cellular fibrous *connective* tissue that exhibits areas that are loose and other zones that are so cellular that the cytoplasm of individual cells is hard to discern because of nuclear crowding. Myxomatous foci are not rare and often are associated with pseudocystic degeneration. Mitotic figures can be found but are not numerous. Areas of hemorrhage and small clusters of multinucleated giant cells are usually seen.

The mineralized component in the two patterns is *very* different. The trabecular variant shows irregular strands of highly cellular osteoid encasing plump and irregular osteocytes (Figure 14-56). These strands often are lined by plump osteoblasts and in other areas by multinucleated osteoclasts. In contrast. the psammomatoid pattern forms concentric lamellated and spherical ossicles that *vary* in shape and typically *have* basophilic centers with peripheral eosinophilic osteoid rims (Figure 14-57). A peripheral

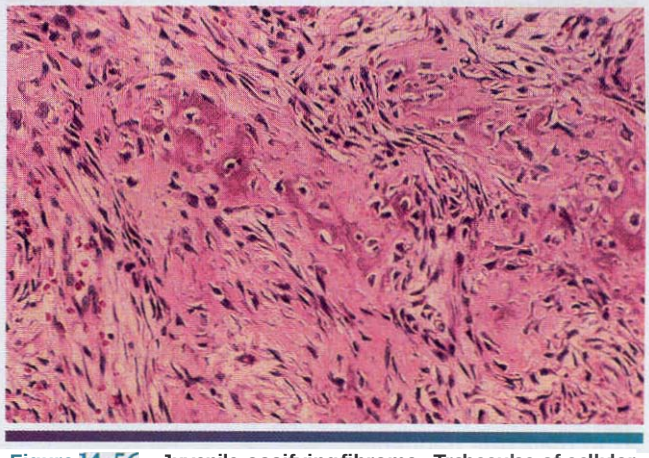

Figure 14-56 • Juvenile ossifying fibroma. Trabeculae of cellular woven bone are present in a cellular fibrous stroma.

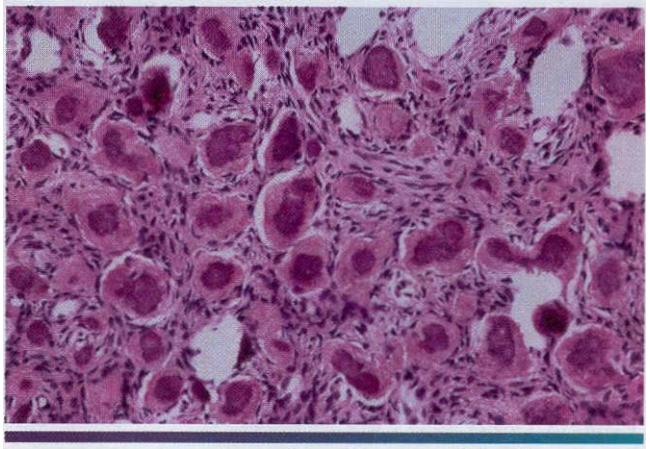

Figure 14-57 • Juvenile ossifying fibroma. Cellular fibrous connective tissue containing spherical ossicles with basophilic centers and peripheral eosinophilic rims.

brush border blending into the surrounding stroma is noted in many of the osslclcs. Occasionally. individual ossicles undergo remodeling and form crescentic shapes.

Treatment and Prognosis

The clinical management and prognosis of the juvenile ossifying fibroma are uncertain. Although many tumors **demonstrate slow but progressive growth, some juvenile** ossifying fibromas demonstrate rapid enlargement. The **more aggressive neoplasms tend to arise in infants and** young children.

For smaller lesions, complete local excision or thorough curettage appears adequate. For some rapidly growing **lesions. wider resection may be required.**

In contrast to the negligible recurrence rate seen in the common types of ossifying fibromas. recurrence rates of 30% to S8% have been reported for juvenile ossifying fibromas. Malignant transformation has not been documented.

OSTEOMA

Osteomas are benign tumors composed of mature com-pact or cancellous bone. Osteomas are essentially restricted to the craniofacial skeleton and rarely. if ever. are diagnosed in other bones. There Is some question as **to whether osteomas represent true neoplasms. and not** all lesions designated as an "osteoma" may represent a single entity. Some likely represent the end stage of an injury or inflammatory process or the end stage of a hamartomatous process, such as fibrous dysplasia. The common palatal and mandibular tori and buccal exostoses (see page t8) are not considered to represent osteomas. although they are histopathologically identical **to osteomas. Because many osteomas are small.** asymptomatic lesions. there is little reliable information as to their true frequency.

Clinical and Radiographic Features

Osteomas of the jaws may arise on the surface of the bone, as a polypoid or sessile mass (periosteal osteoma). or they may be located in the medullary bone (endosteal **osteoma). Most jaw osteomas are detected in young** adults and are generally asymptomatic, solitary lesions. There is little valid information as to whether there is any gender predilection. The most common gnathic locations are the body of the mandible or the condyle. When located **in the body, most** osteomas **occur posterior to the pre-molars on the lingual surface.**

Periosteal osteomas appear as slowly growing masses on the surface of the mandible or maxilia. Some types may reach a large size, resulting in facial deformity. Small **endosteal osteomas are asymptomatic. but large lesions** cause a slowly progressive enlargement of the affected **area.**

An osteoma involving the mandibular condyle may cause a slowly progressing shift in the patient's occlusion, with deviation of the midline of the chin toward the unaffected side. Other reported signs and symptoms include facial swelling. pain, and limited mouth opening.

Condylar osteomas are considered by some to be a true neoplasm, whereas others designate them as hyperostoses. Distinguishing this process from condylar hyperplasia can be difficult; however, condylar osteomas are typically lobulated. whereas the condyle retains its original shape when hyperplastic. Osteomas arising in **the** paranasal **sinuses may cause such symptoms as** sinusitis, headache. or ophthalmologic manifestations.

Radiographicaliy. osteomas appear as circumscribed **sclerotic masses. Periosteal osteomas may show a uni-form sclerotic pattern or may demonstrate a sclerotic** periphery with a central trabecular pattern (Figure 14-S8). Smaller endosteal osteomas are difficult. if not impossible. to differentiate from foci of sclerotic bone

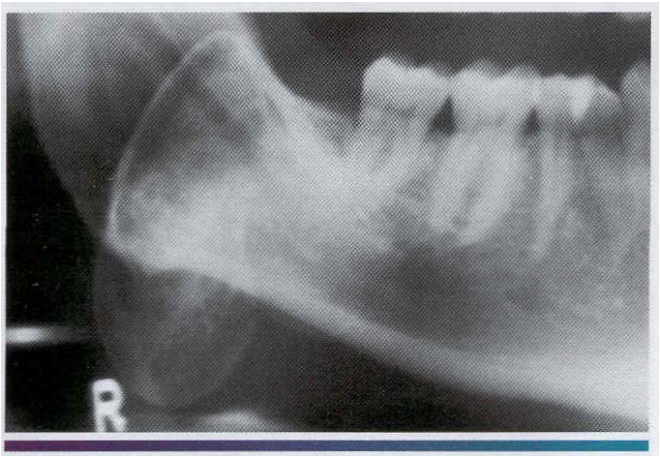

Figure 14-58 • **Osteoma. The radiograph shows a pedunculated cancellous osteoma arising from the lingual surface of the mandible near the crest of the alveolar ridge.**

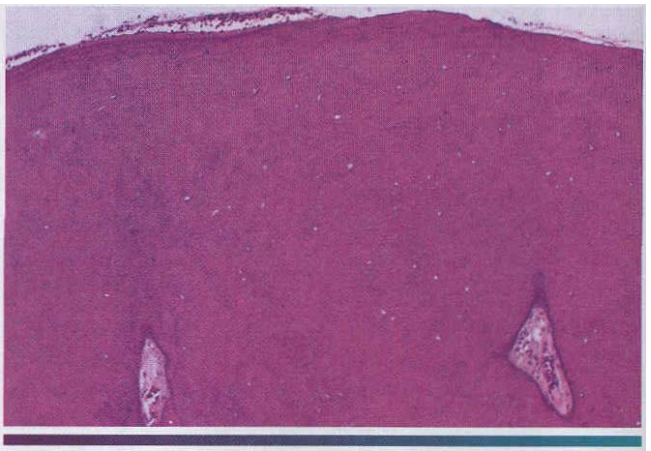

figure 14-59 . **Osteoma. This compact osteoma is composed of dense bone. with only minimal marrow elements.**

representing the end stage of an inflammatory process (condensing osteitis. focal chronic sclerosing osteomyelitis) or from noninflammatory foci of sclerotic bone (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 showing minimal marrow tissue (Figure 14-59). Cancellous osteomas are composed of trabeculae of bone and fibrofatty marrow. Osteoblastic activity may be fairly prominent.

Treatment and Prognosis

larger osteomas of the mandibular body causing symptoms or cosmetic deformity are treated by conservative surgical excision. Small. asymptomatic osteomas. particularly those located endosteally. probably do not need to be treated but should be observed periodically. Because of the frequency of associated symptoms. osteomas arising in the condyle are usually removed surgically. Large lesions mandate condylectomy. whereas peripheral osteomas are treated by local resection. Osteomas are completely benign. and patients do not experience malignant change or recurrences after excision.

GARDNER SYNDROME

Gardner syndrome is a rare disorder that is inherited as an autosomal dominant trait with near 100% penetrance; approximately one third of cases occur spontaneously and appear to represent new gene mutations. The responsible gene has been mapped to chromosome 5. Gardner syndrome is considered to be part of a spectrum of diseases characterized by familial colorcctal polyposis. In addition to the colonic manifestations, other gastrointestinal abnormalities are seen along with a variety of findings that may involve the skin. soft tissues. retina. skeletal system. and teeth. Several of the extracolonic manifestations are distinctive and have led to the discovery of the syndrome.

Clinical and Radiographic Features

The reported prevalence of Gardner syndrome varies from 1:8.300 to 1: 16.000 live births. The associated colonic polyps typically develop during the second decade; and because these are adenomatous, they ultimately transform into adenocarcinoma. In addition. detection of extracolonic polyps is not rare in the small intestine or stomach. with a small percentage exhibiting carcinomatous transformation.

Up to 90% of patients with Gardner syndrome demonstrate skeletal abnormalities. the most common of which are osteomas. Although the osteomas may affect any part of the skeleton. the most commonly involved areas are the skull. paranasal sinuses. and the mandible. When gnathic lesions are seen. they often occur in the region of the mandibular angles and are frequently associated with prominent facial deformity (Figure 14-60). The osteomas are usually noted during puberty and precede the development of, or any symptoms from. the bowel polyps (Figure 14-61). Most patients demonstrate between three and six osseous lesions. The osteomas appear as areas of increased radiodensity that vary from slight thickenings to large masses. On occasion, large osteomas of the mandible or condyle will limil the mandibular opening. Dental abnormalities include an increased prevalence of odontomas. supernumerary teeth. and impacted teeth. Although up to 20% of affected patients demonstrate supernumerary teeth. the frequency of extra teeth is not nearly as high as that noted in cleidocranial dysplasia.

Most patients show one or several epidermoid cysts of the skin (Figure 14-62). Desmoid tumors (locally

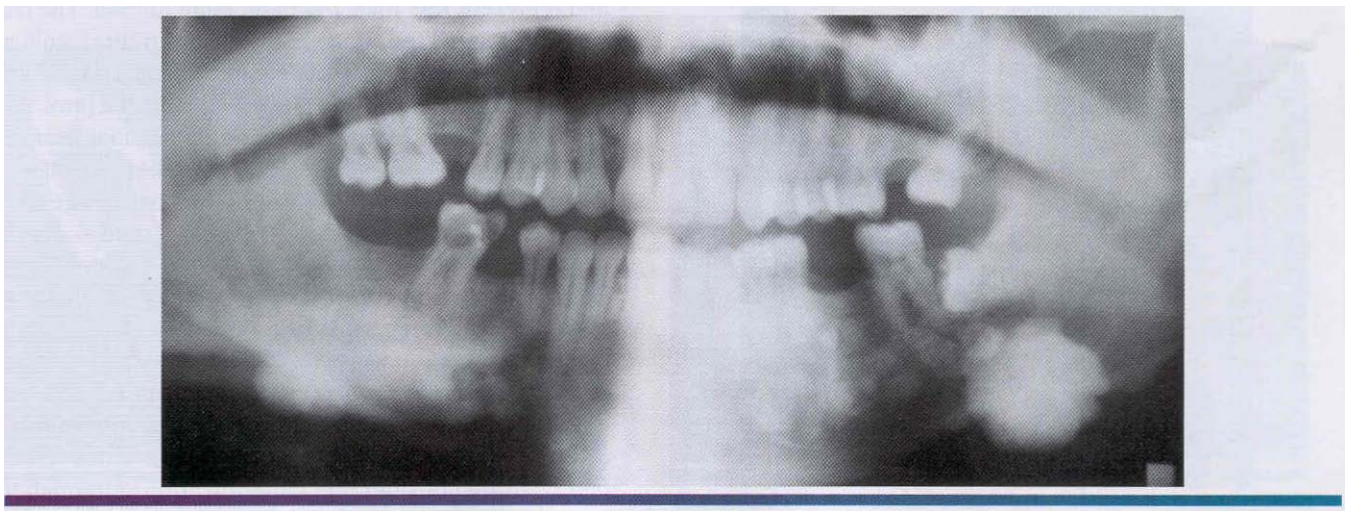

Figure 14-60 • Gardner syndrome. Panoramic radiograph showing multiple osteomas of the mandible.

aggressive fibrous neoplasms) of the soft tissue arise in approximately 10% of affected patients. These lesions are three times more frequent in females and often develop in the abdominal scar that forms after colectomy.

Although lesser known, an increased prevalence of thyroid carcinoma also is noted, with females demonstrating a 100-fold increase. In addition, pigmented lesions of the ocular fundus are evident in nearly 90% of affected patients. Identification of this ocular abnormality is useful when evaluating patients for the syndrome.

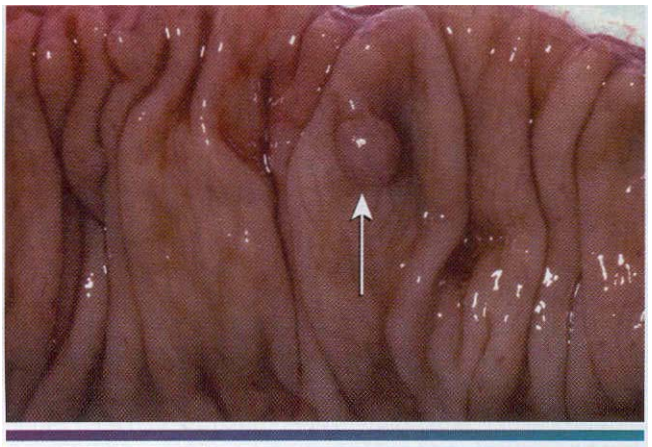

Figure 14-61 • Gardner syndrome. A segment of resected large bowel showing polyp formation *(arrow)*.

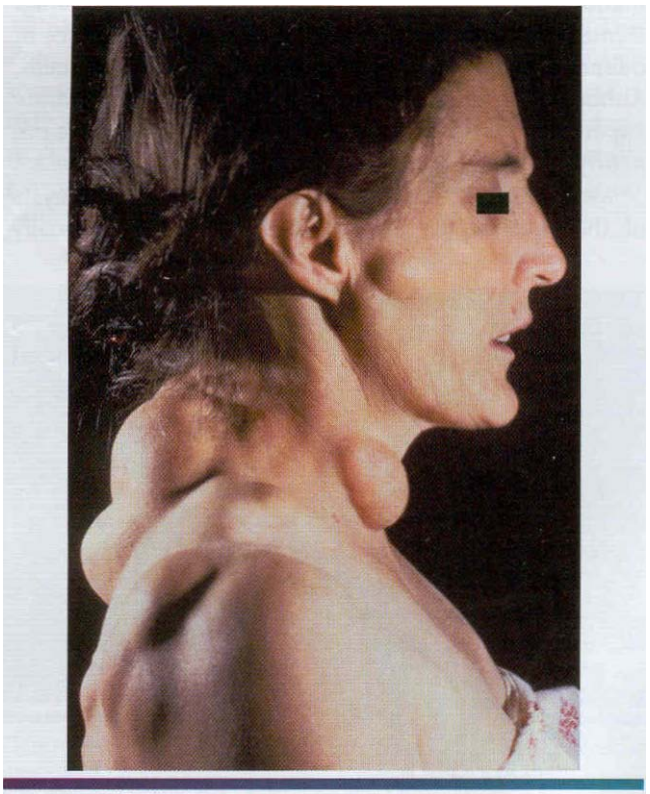

Figure 14-62 • Gardner syndrome. This patient has multiple, large epidermoid cysts. (Courtesy of Dr. William Welton.)

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 rate of malignant transformation of bowel polyps into invasive adenocarcinoma. By age 30, about 50% of patients with Gardner syndrome will develop colorectal carcinoma. The frequency of malignant change approaches 100% in older patients.

Prophylactic colectomy is usually recommended. Removal of jaw osteomas and epidermoid cysts for cosmetic reasons sometimes may be indicated, but the long-term prognosis depends on the behavior of the bowel **adenocarcinomas.**

OSTEOBLASTOMA AND OSTEOID OSTEOMA

Osteoblastoma is a benign neoplasm of bone that arises from osteoblasts. The features of this tumor closely resemble those present in the cementoblastoma. A number of noted authorities in orthopedic pathology consider cementoblastoma and osteoblastoma to be identical lesions and prefer to designate both as osteoblastomas. Because of significant radiographic and histopathologic similarities, the primary difference between an osteoblastoma and a cernentoblastorna indeed depends on whether the lesion is fused to a tooth or not, and this ability is most likely due to the final histogenesis of the tumor cell responsible. Because of these similarities, cernentoblastorna is presented in the next section of this chapter rather than in Chapter 15.

Clinical and Radiographic Features

Osteoblastoma. Ostcoblastornas **are rarely** encountered and represent less than I% of all bone tumors. The most frequently affected bones are the vertebral column, sacrum, calvarium, long bones, and the small bones of the hands and feet. For those developing within the jaws, there is a slight mandibular predilection, with most examples arising in the posterior regions. A slight male predominance is noted, and approxlmately 85% occur before age 30.

Most osteoblastomas are between 2 and 4 ern, but they may be as large as 10 cm. Pain is a common presenting feature. In contrast to the osteoid osteoma (see the following paragraph), the pain associated with an osteoblastoma is not as well relieved by aspirin. Radiographically, the osteoblastorna may appear as a well-defined or ill-defined radiolucent lesion often with patchy areas of mineralization (Figure 14-63). Other lesions demonstrate considerable mineralization. Although **frequently noted in osteoid osteomas, reactive sclerosis surrounding the lesion is not a constant feature.**

Osteoid osteoma and osteoblastorna are closely related benign bone tumors. There is general agreement that the histopathologic features of these two lesions are identical, but it has been shown that the tumor nidus in **osteoid osteomas contains a concentration of peripheral nerves not seen in other fibro-osseous neoplasms. In** addition, the tumor produces prostaglandins that result in significant pain that is relieved by prostaglandin inhibitors such as aspirin. Classically, the distinction depends on the size of the lesion, with osteoid osteoma being under 2 cm and osteoblastoma being larger than 2 cm. Some authors prefer to classify both of these lesions as osteoblastomas.

Osteoid osteomas occur most often in the femur. tibia. and phalanges. They are very rare in the jaws. Pain is the most common presenting symptom. It is usually nocturnal in nature and alleviated by salicylates. Radiographically, the osteoid osteoma appears as a well-circumscribed radiolucent defect, usually less than I cm **in diameter. with a surrounding zone of reactive sclerosis** of varying thickness. A small radiopaque nidus may be present, resulting in a target like appearance radiographically (Figure 14-64).

A small group of osteoblastomas (aggressive osteoblastomas) is characterized by more atypical hlstopathologic features and locally aggressive behavior. These tumors usually occur in older patients, with most being over 30 years of age. A variety of bones, including the mandible, may be involved. Pain is a common symptom and may be severe. Radiographically, these lesions show the features of conventional osteoblastomas but tend to be larger.

Histopathologic Features

The lesions reveal mineralized material that demon-strates prominent reversal lines. The material may be present in large sheets or irregular trabeculae. At the periphery of the large masses and surrounding the trabeculae are scattered multinucleated osteoclast-like cells and numerous osteoblasts that have ample cytoplasm and hyperchromatic nuclei (Figure 14-65). The **supporting stroma consists of loose fibrous connective** tissue that contains scattered dilated vascular channels. Focal areas of hemorrhage are not rare, and osteoblas-**tomas occasionally exhibit a central zone of increased** vascularity.

Microscopically. aggressive osteoblastomas are char-acterized by the presence of large (epithelioid) osteoblasts with increased mitotic activity and nontrabecular sheets or lacelike areas of osteoid production. On occasion, osteoblastornas may demonstrate a rich cellularity **that has led to erroneous diagnoses of osteosarcoma. Differentiation between some osteoblastomas and low-**grade osteosarcomas may be very difficult. Some low-grade osteosarcomas may closely resemble the micro-

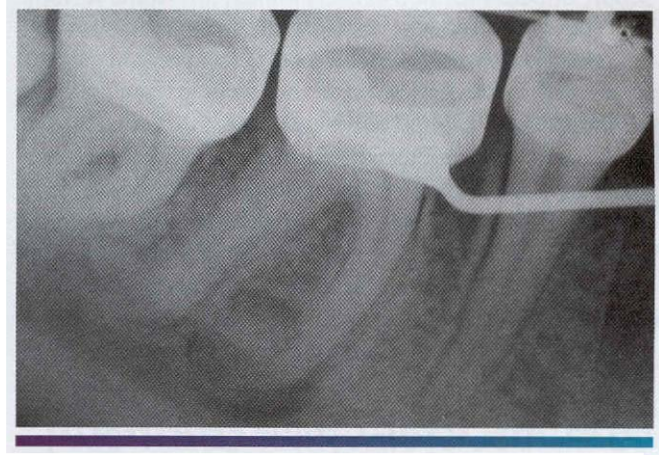

Figure 14-64 • Osteoid osteoma. A circumscribed. mixed radiolucent and radiopaque lesion near the apex of mesial root of mandibular first molar. The patient had dull. nocturnal pain that was relieved by aspirin. (Courtesy of Dr. Ellen Eisenberg.)

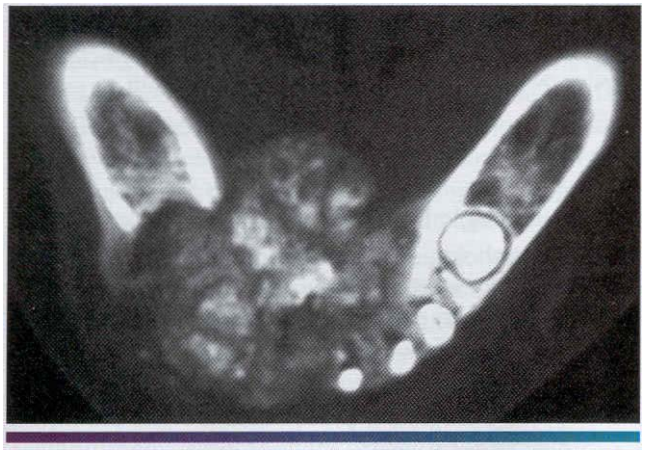

Figure 14-63 • Osteoblastoma. Computed tomography (CT) image showing a large. destructive radiolucent and radiopaque lesion of the mandible. (Courtesy of Dr. Ed Marshall.)

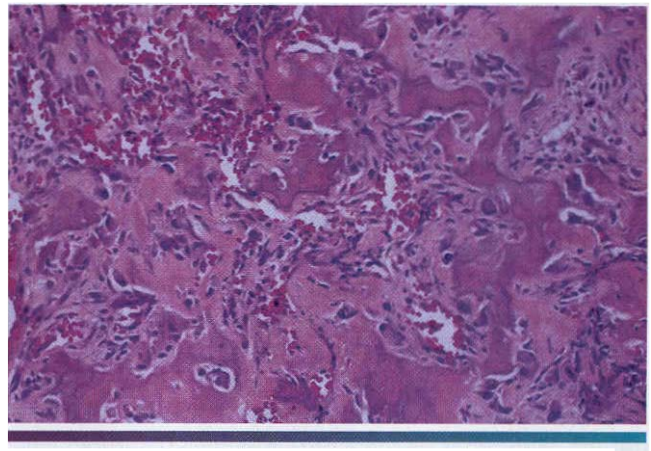

Figure 14-65 • Osteoblastoma. High-power photomicrograph showing irregular bony trabeculae with prominent osteoblastic rimming and osteoclasts.

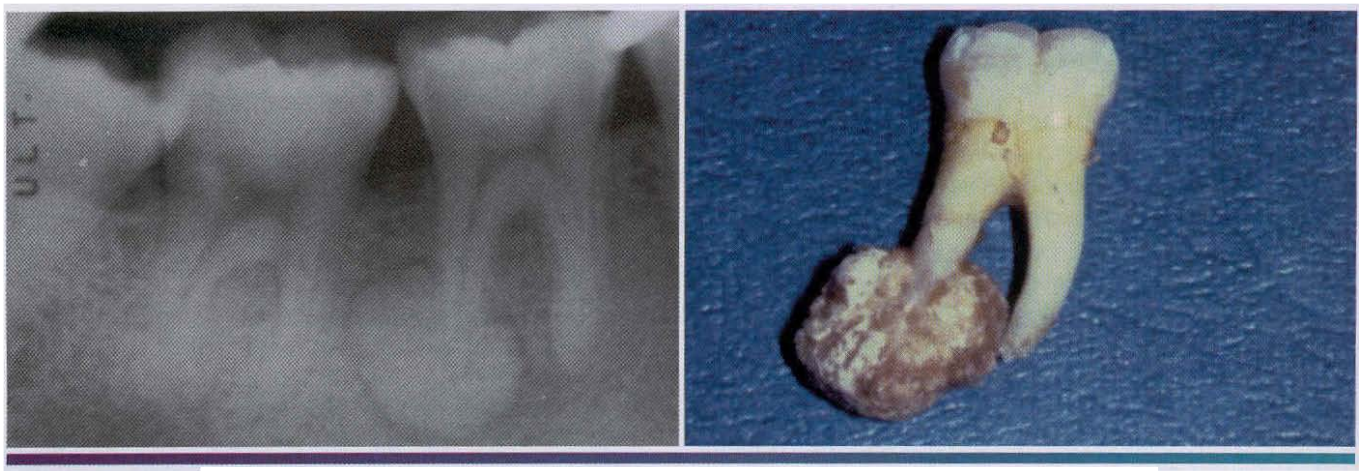

Figure 14-66 • **Cementoblastoma. A.** A densely mineralized mass is seen at the apex of the distal root of the first molar. The root is partially resorbed. **B,** The surgical specimen shows that the mass is attached to the root. (Courtesy of Dr. John Wright.)

scopic appearance of osteoblastornas, and some lesions **may have microscopic features intermediate between asteoblastoma and osteosarcoma.**

Treatment and Prognosis

Most cases of osteoid osteoma and osteoblastoma are treated by local excision or curettage. The prognosis is good, and some lesions will regress even after incomplete excision. **A small number of lesions will recur; in rare instances. an astcoblastoma may undergo transformation** into an osteosarcoma. Although about 50% of aggressive osteoblastornas **will recur, metastasis or** death from the tumor has not been reported.

CEMENTOBLASTOMA (TRUE CEMENTOMA)

Cementoblastoma is an odontogenic neoplasm of cernentoblasts, and many authorities believe this neopiasm represents the only true neoplasm of cementum.

Clinical and Radiographic Features

Cementoblastomas are rare neoplasms, representing less than 1% of all odontogenic tumors. Greater than 75% arise in the mandible. with 90% arising in the moiar and premolar region. Almost 50% involve the first permanent molar. Cementoblastomas rarely affect deciduous teeth. There is no significant sex predilection. The neoplasm occurs predominantly in children and young adults, with about 50% arising under the age of 20 and 75% occurring before 30 years of age. Pain and swelling are present in approximately two thirds of reported patients.

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 (Figure t4-66). The outline of the root or roots of the involved tooth is usually obscured as a result of root resorption and fusion of the tumor with the tooth.

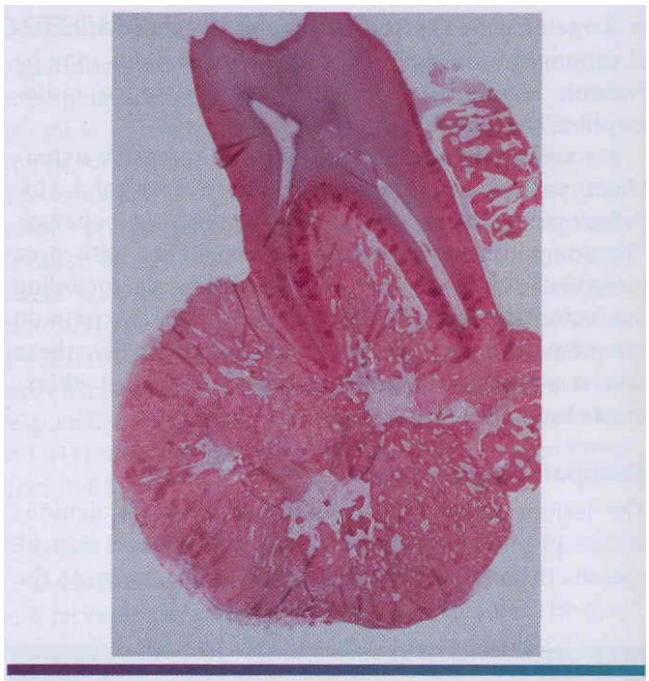

Figure 14-67 • **Cementoblastoma.** low-power photomicrograph showing the tumor attached to the roots of the tooth.

Histopathologic Features

The histopathologic presentation of cementoblastoma closely resembles that of osteoblastorna, with the primary distingu ishing feature being tumor fusion with the involved tooth (Figure 14-67). The majority of the tumor consists of sheets and thick trabeculae of mineralized material with irregulariy placed lacunae and prominent basophilic reversal lines. Cellular fibrovascuiar tissue is present between the mineralized trabeculae. Multinucleated giant cells often are present. and the mineralized

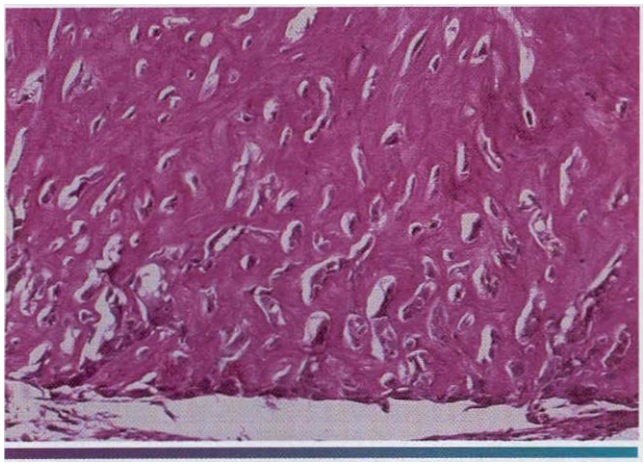

Figure 14-68 • Cementoblastoma. Mineralized tissue containing numerous plump cementoblasts.

trabeculae are frequently lined by prominent blastlike cells (Figure 14-68). The periphery of the lesion, corresponding to the radiolucent zone seen on the radiograph, is composed of uncalctfted matrix. which often is arranged in radiating columns.

Treatment and Prognosis

Treatment of a cernentoblastoma usually consists of surgicai extraction of the tooth together with the attached calcified mass. Surgical excision of the mass with root amputation and endodontic treatment of the involved tooth may be considered. The prognosis is excellent. and the tumor does not recur after total removal. Progressive growth of the tumor after extraction of the involved tooth and incomplete removal of the mass has been documented.

CHONDROMA

Chondromas are benign tumors composed of mature hyaline cartilage. Chondromas are one of the more common bone tumors and are located most often in the short tubular bones of the hands and feet. A diagnosis of chondroma in the jaws, facial bones. and base of the skull should be viewed with great skepticism because many so-called benign chondromas of the craniofacial complex have recurred and acted in a malignant manner. No major series has reported enchondromas arising in the craniofacial bones. In spite of this. individual reports and small series of gnathic chondromas can be found. with most examples thought to arise from vestigial cartilaginous rests. Such rests are located in *the* anterior maxilla, symphysis, coronoid process, and condyle.

Clinical and Radiographic Features

Chondromas usually arise in the third and fourth decades without a significant sex predilection. Most gnathic examples have been found in the condyle or anterior maxilla of adult patients. When arising in the jaw. most chondromas are painless and slowly growing tumors. Tooth mobility and root resorption are noted occasionally. Radiographically, chondromas typically appear as radiolucencies with central areas of radiopacity.

In most cases, chondromas arise in a single site. Multiple and widespread involvement with a tendency to be unilateral is termed Oilier disease. In another presentation termed Maffucci syndrome. skeletal chondrornatosls is seen in association with soft tissue angiomas.

Histopathologic Features

Histopathologically. a chondroma appears as a circumscribed mass of mature hyaline cartilage that typically demonstrates well-formed lacunae containing small chondrocytes with pale cytoplasm and small. round nuclei. On occasion. the microscopic distinction between a benign chondroma and a low-grade chondrosarcoma of the jaws is difficult (see page 579).

Treatment and Prognosis

It is wise to consider any lesion diagnosed as chondroma of the jaws to represent a potential chondrosarcoma. Treatment is directed toward total surgical removal of the tumor. Condylar examples are usually treated by condylectomy.

CHONDROMYXOID FIBROMA

The chondromyxold fibroma is an uncommon benign neoplasm accounting for less than I% of all primary bone tumors. It Is located most commonly in the metaphyseal region of the long bones. Chondromyxoid fibromas rarely involve the jaws.

Clinical and Radiographic Features

Chondromyxoid fibromas of the jaws have been encountered in patients ranging in age from 10 to 67 years. The mean age of occurrence is approxtrnately 30 years. with the majority discovered in the second and third decades. There Is no gender predilection. Of the reported cases in the jaws. about three quarters occurred In the mandible. In about one fourth. pain was an initial symptom. and swelling was noted in approximately three fourths. Some cases have been asymptomatic, being detected only on a radiographic examination.

Radiographically. the lesion is a circumscribed radiolucent defect with sclerotic or scalloped margins. Central radiopacities sometimes are present within the lesion. On initial presentation, the size of reported chondromyxoid fibromas varied from I to 6.5 em.

Histopathologic Features

The tumor consists of lobulated areas of spindle-shaped or stellate cells with abundant myxoid or chondroid intercellular substance. The lobules characteristically

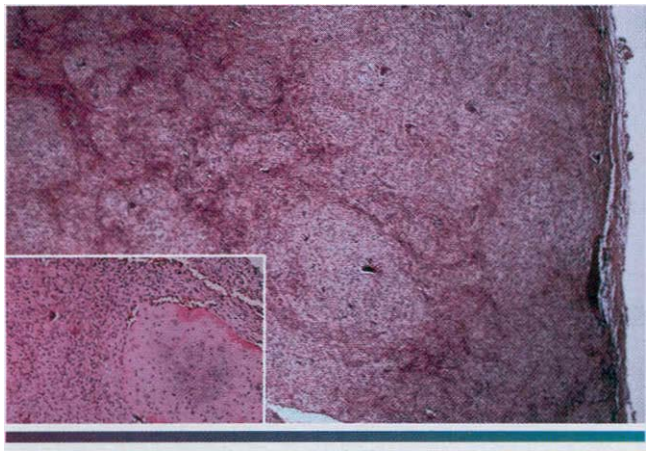

Figure 14-69 • Chondromyxoid fibroma. Well-circumscribed tumor consisting of nodular myxoid tissue with scattered giant cells. The inset demonstrates a focus of cartilaginous differentiation.

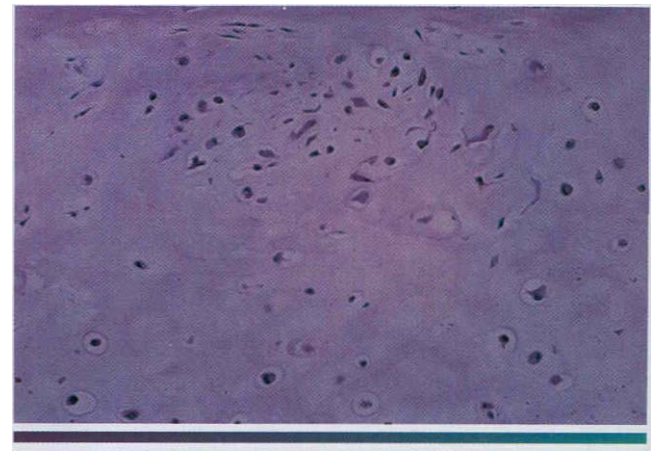

Figure 14-70 . Synovial chondromatosis. Photomicrograph from one of many nodules removed at the time of synovectomy. The cartilage shows some degree of atypia. and in a different clinical setting this histopathology could be interpreted to represent a low-grade chondrosarcoma.

are separated by zones of a more cellular tissue composed of spindle-shaped or round cells with varying numbers of multinucleated giant cells (Figure 14-69).

Large pleomorphic cells that may cause confusion with chondrosarcoma may be seen. Focal areas of calcification and spicules of residual bone also may be present within the tumor.

Treatment and Prognosis

Although the chondromyxoid fibroma is a benign tumor, approximately 25% of cases in the long bones recur after curettage. Some orthopedic surgeons recommend block excision as the initial treatment. Generally, chondromyxoid fibromas of the jaws have been small and treated by curettage; recurrence is uncommon. Because of the lobular growth and associated scalloped margins, larger gnathic lesions appear to justify resection in an attempt to prevent recurrence.

Differential diagnosis between a chondromyxoid fibroma and myxoid chondrosarcoma may be difficult. Examples of both underdiagnosis and overdiagnosis, with resultant improper treatment, have been described.

SYNOVIAL CHONDROMATOSIS (CHONDROMETAPLASIA)

Synovial chondromatosis is a rare, benign, nonneoplastic arthropathy characterized by the metaplastic development of cartilaginous nodules within the synovial membrane. The cause is unknown.

The process typically proceeds through three stages. In the first stage, foci of metaplastic cartilage arise in the synovial lining. With time, these foci increase in size and begin to detach, with cartilaginous material present in both the synovial membrane and the joint. In the final stage, metaplastic cartilage is found only in the joint.

Clinical and Radiographic Features

The disease most commonly affects large joints, such as the knee, elbow, hip, and shoulder. The number of reported cases involving the temporomandibular joint (TMJ) is less than 100. The disease is usually limited to one joint.

Synovial chondromatosis of the TMJ occurs *over* a wide age range, but most affected patients are middle-aged. In contrast to the findings in other joints, there is a predilection for females. Periarticular swelling, pain, crepitus, and limitation of joint motion are usually present. These features are common to a number of pathoses involving the TMJ and are not diagnostic for synovial chondromatosis. In rare instances, the disease may produce no symptoms.

Radiographically, the most common feature is the presence of loose bodies in the joint. These consist of rounded, irregularly shaped, and variably sized radiopaque structures in the region of the joint. Other features include irregularity of the joint space, widened joint space, and irregularity of the condylar head.

These findings, however, are not diagnostic of synovial chondromatosis and may be seen in other degenerative joint diseases. The absence of loose bodies does not preclude a diagnosis of synovial chondromatosis. Computed tomography (CT) scans and magnetic resonance imaging (MRI) have been advocated as more specific diagnostic imaging procedures.

Histopathologic Features

Nodules of cartilage are present within the *synovium* and lie loose in the joint space. As many as 100 nodules may be present. These cartilaginous nodules often become calcified and may ossify. The cartilage may appear atypical with hyperchromatic and binucleated chondroeytes (Figure 14-70). In another clinical situation, these fea-

tures would suggest a diagnosis of chondrosarcoma. but these changes are not considered significant in *synovial* chondromatosis.

Treatment and Prognosis

For patients with synovial chondromatosis, the involved synovium and all loose bodies are *removed* surgically. Some surgeons advocate total synovectomy to prevent recurrence. Meniscectomy may be necessary if the disc cannot be repaired. A few cases of erosion of the glenoid fossa and cranial extension of the process *have* been reported.

The prognosis is good. with a low frequency of recurrence after surgical excision. Malignant transformation of synovial chondromatosis of the TMJ has not been noted. Most patients experience improved joint function and pain relief after surgery.

DESMOPLASTIC FIBROMA

The desmoplastic fibroma of bone is an uncommon tumor of fibroblastic origin. It is thought to be the osseous counterpart of the soft tissue fibromatosis (desmold tumor) (see page 444).

Clinical and Radiographic Features

Most examples of desmoplastic fibroma of bone are discovered in patients younger than 30 years of age. The age range of reported gnathic examples is from 12 months to 46 years, with a mean of approximately 14 years. There is no sex predilection. Although the metaphyseal regions of the humerus and tibia are the sites of slightly more than 50% of all cases, the mandible is the fourth most frequently affected bone. Of the reported cases involving the jaws. 90% *have* occurred in the mandible, most often in the molar-angle-ascending ramus area.

Although some tumors are associated with limited opening, a painless swelling of the affected area is the most common initial complaint. Radiographically, the lesion appears as a unilocular or occasionally multilocular radiolucent area. The margins may be well-defined or ill-defined (Figure t4-7t). The bone is expanded, and the cortex is thinned; *however*, cortical reaction is not present. If the lesion erodes through the cortex. an accompanying soft tissue mass will be present. When this occurs, 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 secondary extension into bone. The roots of teeth *involved* in the lesion often show resorption.

Histopathologic Findings

The tumor is composed of small elongated fibroblasts and abundant collagen fibers (Figure t4-72). The degree of cellularity may *vary* from area to area in a *given* lesion, and the cellular areas may show plumper fibroblasts and less collagen. The fibroblasts are not atypical. *however*, and mitoses are essentially absent. Bone spicules may be present at the interface between the tumor and adjacent bone but are *never* an integral part of the lesion.

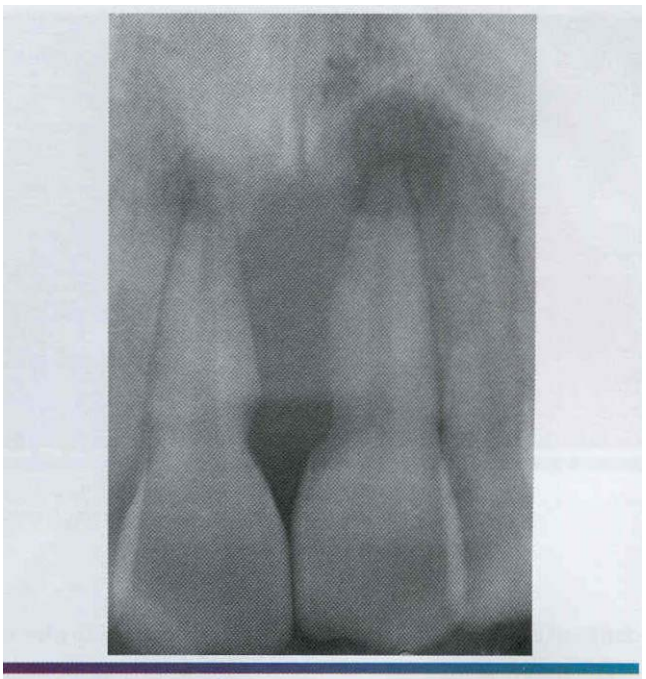

Figure 14-71 • Desmoplastic fibroma. Ill-defined, destructive radiolucency of the anterior maxilla. (Courtesy of Dr. H.T. Daniel.)

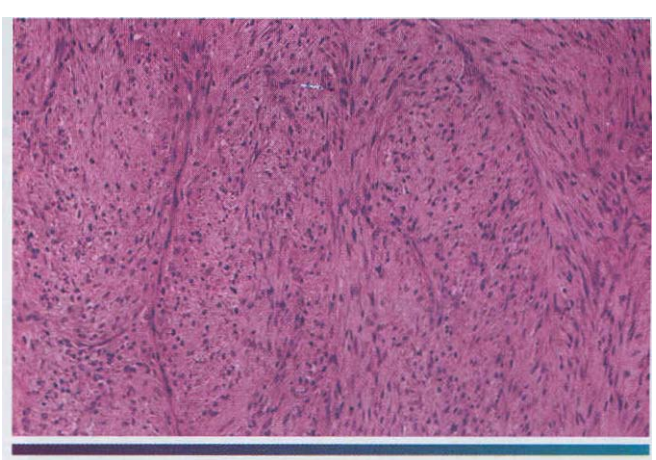

Figure 14-72 • Desmoplastic fibroma. The tumor consists of a cellular proliferation of fibroblasts arranged in interlacing fascicles.

Treatment and Prognosis

Although the desmoplastic fibroma is considered to be a benign tumor, it often behaves in a locally aggressive fashion. with extensive bone destruction and soft tissue extension, so that radical surgery may be required to control the disease. The treatment of choice is best determined by the apparent degree of clinical aggressiveness of each individual lesion. Localized lesions without evr-

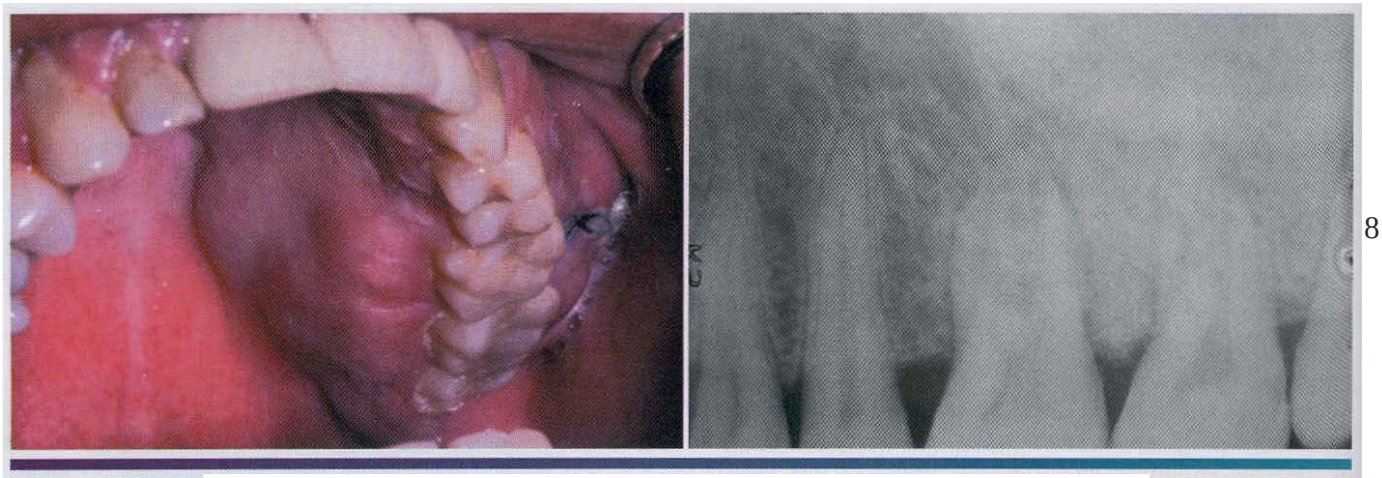

Figure 14-73 • Osteosarcoma. A, This patient shows a firm, painful swelling of the left maxilla of recent onset. B, The periapical radiograph shows a dense sclerotic change in the bone pattern. (Courtesy of Dr. len Morrow.)

dence of cortical perforation or soft tissue extension often are managed adequately by thorough curettage. Lesions exhibiting rapid growth. an ill-defined radiographic **appearance, cortical perforation. or soft tissue extension** often require segmental resection. Although metastases do not occur and the long-term prognosis is good, the lesion may be associated with considerable morbidity.

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 type of malignancy to originate within bone. **The majority of osteosarcomas demonstrate** intramedullary origin, but a small number may be juxtacortical (discussed in the following section) or rarely extraskeletal.

Clinical and Radiographic Features

Extragnathic osteosarcoma demonstrates a bimodal age distribution. Most arise in patients between the ages of 10 and 20 years, with a lesser number diagnosed in adults over the age of 50. 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. the axial skeleton and flat bones are involved most frequently: **Paget's disease and previous irradiation are associated** with an increased prevalence.

Osteosarcomas of the jaws are uncommon and represent 6% to 8% of all osteosarcomas. These gnathic tumors have been diagnosed in patients ranging from young children to the elderly, but they occur most often in the third and fourth decades of life. The mean age for patients with osteosarcoma of the jaw is about 33 years. which is 10 to 15 years older than the mean age for osteosarcomas of the long bones. As is seen in extragnathic locations. a slight male predominance is noted.

The maxilla and mandible are involved with about equal frequency. Mandibular tumors arise more frequently in the posterior body and horizontal ramus rather than the **ascending ramus. Maxillary lesions are discovered more** commonly in the inferior portion (alveolar ridge, sinus floor, palate) than the superior aspects (zygoma, orbital rim).

Swelling and pain are the most common symptoms (Figure 14-73). Loosening of teeth, 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 indicates that some osteosarcomas of the jaws grow rather slowly (Figure 14-74).

The radiographic findings vary from dense sclerosis **to a mixed sclerotic and radiolucent lesion to an entirely** radiolucent process. The peripheral border of the lesion Is usually ill-defined and indistinct, making it difficult to determine the extent of the tumor radiographically. In **some cases, an extensive osteosarcoma may show only** minimal and subtle radiographic change with only slight variation in the trabecular pattern. Occasionally, there is resorption of the roots of teeth Involved by the tumor. This feature is often described as "spiking" resorption as a result of the tapered narrowing of the root. The "classic" sunburst or sun ray appearance caused by osteophytic bone production on the surface of the lesion is noted in about 25% of jaw osteosarcomas. Often. this is appreciated best on an occlusal projection (Figure 14-75).

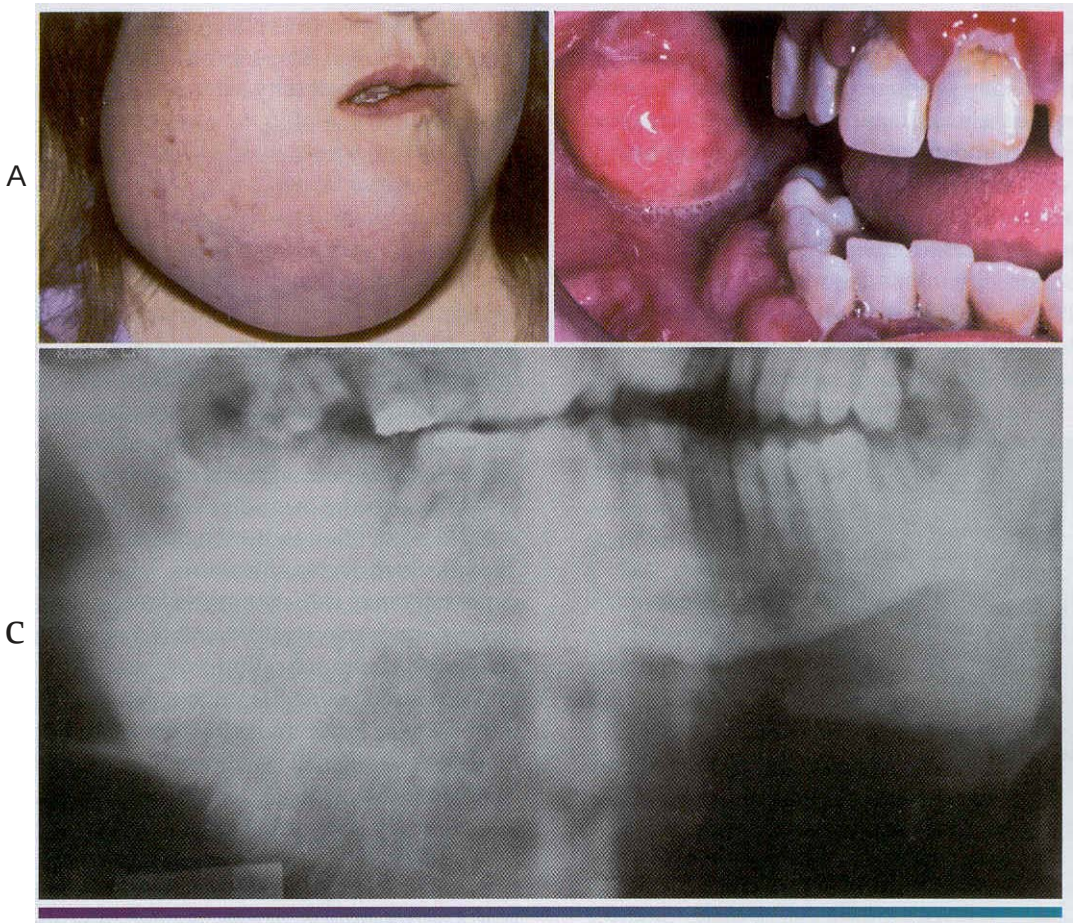

Figure 14-74 . Osteosarcoma. A, This massive tumor had been present for many months before the patient sought treatment. S, Intraoral photograph ofthe tumor mass. C. The panoramic radiograph shows a "sunburst" pattern of trabeculation within the tumor.

An important early radiographic change in patients **with osteosarcoma consists of a symmetric widening of** the periodontal ligament space around a tooth or several teeth. This is the result of tumor Infiltration aiong the periodonlal ligament space (Figure i4-76). Widening of the periodontal ligament space is not specific for **osteosarcoma and may be seen associated with other** maiignancies. This radiographic finding. when accompanied by pain or discomfort and other minimai radiographic changes. may be of great importance in the early **diagnosis of jaw osteosarcomas.**

Although periapical, occlusal. and panoramic radiographs often iead to the initial diagnosis. CT scans are excellent for demonstrating the degree of intramedullary **extension, tumor calcification, cortical involvement. and soft tissue involvement. These scans prove invaluable for** determining the extent of surgery.

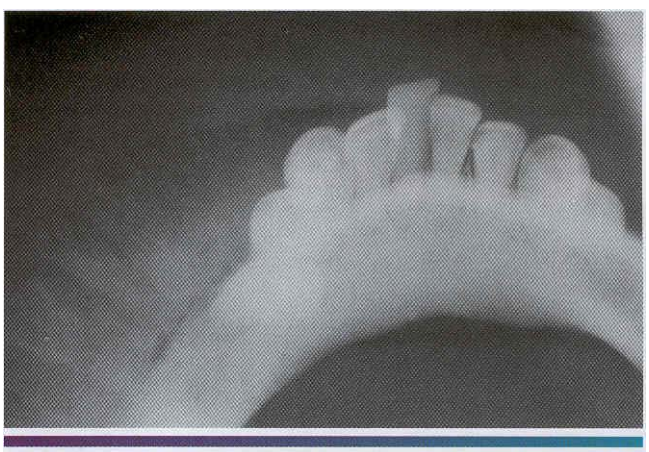

Figure 14-75 • Osteosarcoma. Occlusal radiograph demonstrating prominent exophytic tumor bone production on the buccal surface of the mandible. resulting in the "sunburst" pattern. (Courtesy of Dr. lewis Gilbert.)

Histopathologic Features

Osteosarcomas of the jaws display considerable histopathologic variability. The essential microscopic crite-

rion is the direct production of osteoid by malignant mesenchymal cells (Figure 14-77). In addition to osteoid, the cells of the tumor may produce chondroid material and fibrous connective tissue. The tumor cells may vary from relatively uniform round or spindle-shaped cells to highly pleomorphic cells with bizarre nuclear and cytoplasmic shapes. The amount of matrix material produced in the tumor may vary considerably. In some instances, osteoid production may be very minimal and difficult to demonstrate. Most osteosarcomas of the jaws tend to be better differentiated than osteosarcomas of the extragnathic skeleton.

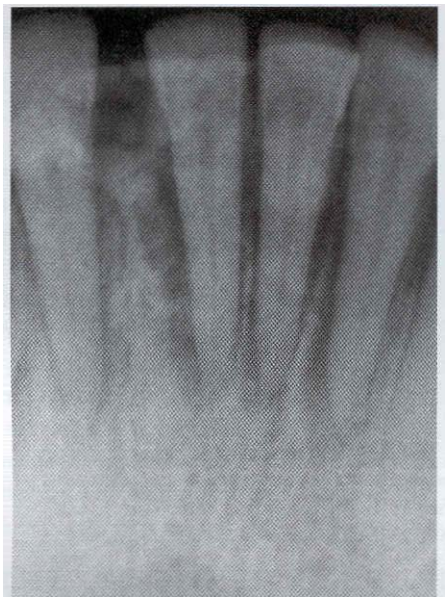

Figure 14-76. Osteosarcoma. This 26-year-old female presented with a 6-cm painful tumor of the anterior mandible. The periapical radiograph shows widening of the periodontal ligament spaces and a mottled radiopacity superimposed on the teeth. (Courtesy of Dr. Charles Ferguson.)

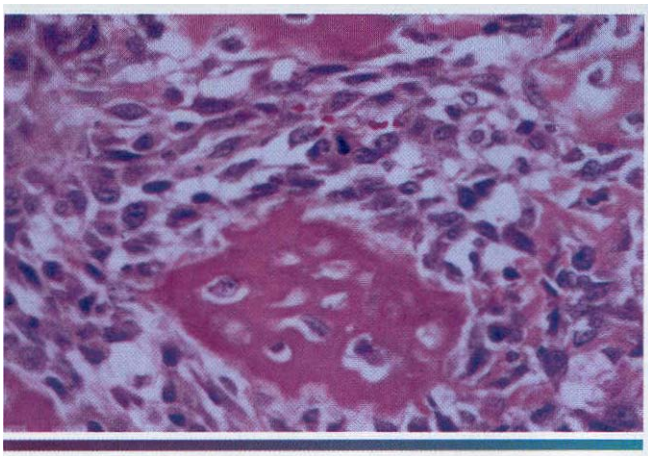

Figure 14-77 • Osteosarcoma. Anaplastic tumor cells forming cellular disorganized bone.

Depending on the relative amounts of osteoid, cartilage, or collagen fibers produced by the tumor, many pathologists subclassify osteosarcomas into the following types:

- Osteoblastic
- Chondroblastic
- Fibroblastic

These histopathologic subtypes, however, do not have any great bearing on the prognosis. Other less commonly encountered histopathologic variations include malignant fibrous histiocytoma-like, small cell, epithelioid, telangiectatic, and giant cell rich.

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 being identified (Figure 14-78). Such lesions, however, should be classified as osteosarcomas rather than chondrosarcomas.

Low-grade, well-differentiated osteosarcomas may show only minimal cellular atypia of the lesional cells 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.

Treatment and Prognosis

Many past and present investigators believe osteosarcoma of the jaws is less aggressive than those occurring in the long bones. Most gnathic osteosarcomas are low-grade, and metastases are seen less frequently. Despite these findings, many current clinicopathologic studies fail to support this contention and believe osteosarcomas of the jaws are aggressive neoplasms. The most important prognostic indicator is the ability to achieve initial complete surgical removal, a feat that is much more difficult to achieve in the jaws than the long bones. The aggressiveness of gnathic osteosarcoma remains an area

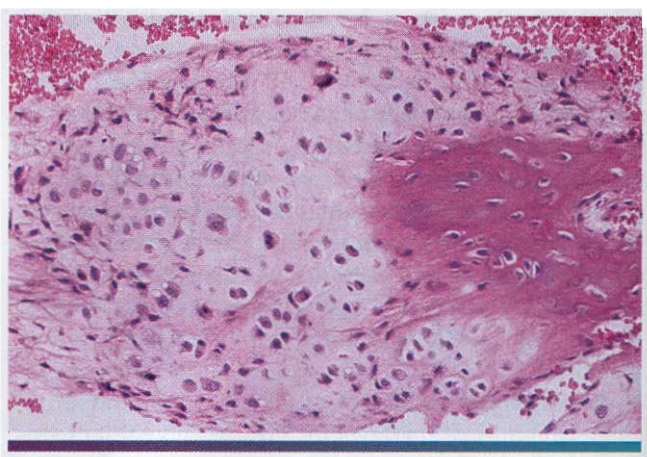

Figure 14-78. Osteosarcoma. This tumor produced a combination of malignant cartilage and bone.

of controversy that is difficult to resolve because of the rarity of the neoplasm and the lack of consistently applied diagnostic criteria.

Multicenter investigations of different therapies to osteosarcoma of long bones have led to an improved prognosis that now appears superior to that associated with gnathic neoplasms. These protocols involve neoadjuvant (preoperative) chemotherapy followed by radical surgical excision with careful pathologic examination of the specimen to evaluate the chemotherapeutic effects on the tumor. Adjuvant (postoperative) chemotherapy is used and may be modified if poor histopathologic **response to the neoadjuvant regimen is noted. Four-year survival rates exceeding 80% have been demonstrated** with this approach by some investigators. Limited numbers **of patients with jaw osteosarcomas have been treated with these protocols, and superior results have** been claimed compared with surgical treatment alone. **In addition, a systematic literature review of 20\ patients with craniofacial osteosarcoma demonstrated that** patients treated with chemotherapy exhibited an improved long-term survival regardless of the ability to **achieve complete surgical removal.**

In **spite of the improved prognosis in patients receiving** chemotherapy, radical surgical excision remains the mainstay of therapy. Because the tumor may extend for some distance beyond the apparent clinical and radiographic **margins, local recurrence after surgery is a major** problem. Local uncontrolled disease is more often the cause of death for patients with jaw osteosarcoma than are the effects of distant metastases. Most deaths from **uncontrolled local disease occur within 2 years of the initial treatment. Jaw osteosarcomas have less tendency to metastasize than do osteosarcomas of long bones.** Although regional lymph nodes may be infrequently involved. metastases most often affect the lungs and brain. When comparing mandibular and maxillary **osteosarcomas, metastasis is noted more frequently from mandibular neoplasms, whereas** local **recurrence** is associated more frequently with maxillary tumors.

The prognosis remains serious. Various studies indicate a 30% **to** 50% **survival rate. Survival rates of up to 80% have been reported for patients receiving initial radical** surgery. the best hope for permanent cure. Additional **prospective investigations of gnathic osteosarcoma** treated by neoadjuvant chemotherapy followed by surgical removal and adjuvant chemotherapy are necessary in an attempt to confirm the most appropriate approach.

PERIPHERAL OUXTACORTICAL) OSTEOSARCOMA

in contrast to the usual forms of intramedullary osteosar**coma, several varieties originate adjacent to the cortex** of the bone. initially grow outward from the surface. and do not involve the underlying medullary cavity. The terminology used for these lesions by different authors is somewhat confusing. These peripheral (juxtacortIcal) **osteosarcomas usually occur in the long bones, but** examples involvlng the jaws have been reported.

The parosteal type of osteosarcoma is a lobulated nodule attached to the cortex by a short stalk (Figure 14-79). There is no elevation of the periosteum and no peripheral periosteal reaction. Histopathologically. the exophytic mass demonstrates a spindle-cell fibroblast-like proliferation that contains well-developed trabeculae of bone. With time, the trabeculae often coalesce and form a large mass of solid bone. Parosteal osteosarcoma is a low-grade sarcoma that has a small risk of **recurrence and metastasis if treated by radical excision.** With inadequate surgery, the tumor may eventually develop into a higher-grade osteosarcoma, with a **resultant poor prognosis.**

The periosteal form of osteosarcoma is a sessile **lesion that arises within the cortex and elevates the overlying** periosteum. which provokes the production of sig**nificant peripheral periosteal new bone formation (see** Figure 14-79). Often, the leading edge of the tumor mass perforates the surface of the periosteum and extends into the surrounding soft tissue. Histopathologically, the **tumor demonstrates primitive sarcomatous cells within** a tumor that demonstrates significant chondroblastic **differentiation. Close inspection will reveal foci of tumor osteoid and immature bone formation. Radical surgical** excision with wide margins is the therapy of choice.

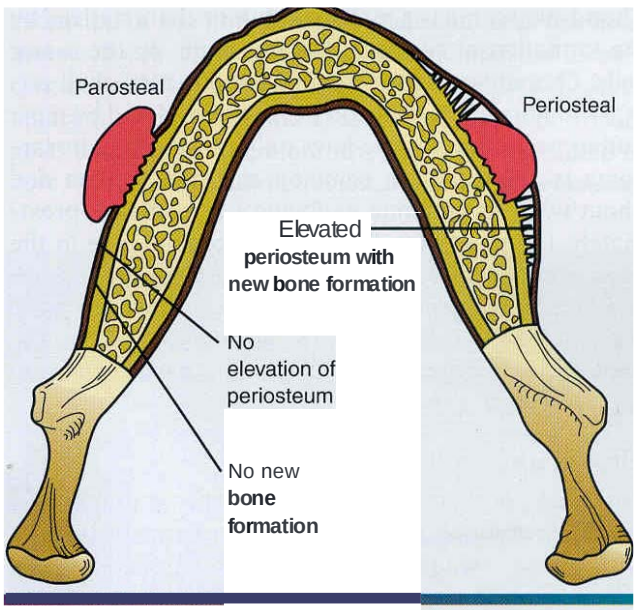

Figure 14-79 • Peripheral (juxtacortical) osteosarcoma. Illustration comparing different types of peripheral osteosarcoma. *Parosteal osteosarcoma* presents as a lobulated nodule without a peripheral periosteal reaction. *Periosteal osteosarcoma* presents as a sessile mass associated with significant periosteal new bone formation.

Although the prognosis is better than that associated with intramedullary tumors, periosteal osteosarcoma has a poorer outcome than the parosteal variant. In reviews of patients with periosteal osteosarcomas, approximately 25% died from metastatic disease.

POSTIRRADIATION BONE SARCOMA

Sarcoma arising in a bone that has been previously subjected to radiation therapy is a well-recognized phenomenon. The jaws are situated closely to tissues that commonly receive therapeutic radiation and are a common site for postirradiation bone sarcomas. Postirradiation sarcomas may develop as early as 3 years after radiation, but the average latent period is about 14 years. The frequency of development of sarcoma is related to radiation dose. Postirradiation sarcoma develops in about 0.2% of patients receiving 7000 cGy (rad): there is no increased prevalence of sarcoma for those receiving less than 1000 cGy.

Osteosarcoma is the most common type of postirradiation sarcoma, accounting for 50% of all cases. About 40% of postirradiation sarcomas are fibrosarcomas, with chondrosarcomas and other histopathologic types making up the rest. Postirradiation bone sarcomas have no distinctive histopathologic features that allow them to be distinguished from other bone sarcomas of the same type that arise *de novo*.

The prognosis for postirradiation sarcomas is about the same as for *de novo* tumors of the same type.

CHONDROSARCOMA

Chondrosarcoma is a malignant tumor characterized by the formation of cartilage, but not bone, by the tumor cells. Chondrosarcomas comprise about 10% of all primary tumors of the skeleton but are considered by most authorities to involve the jaws only rarely. Chondrosarcoma is about half as common as osteosarcoma and about twice as common as Ewing's sarcoma. Approximately 1% to 3% of all chondrosarcomas arise in the head and neck area. Some institutions report a somewhat greater frequency of chondrosarcomas in the jaws. This may be because of differing criteria used by the pathologists for distinguishing chondroblastic osteosarcomas from chondrosarcomas.

Clinical and Radiographic Findings

In extragnathic bones, chondrosarcoma is primarily a neoplasm of adulthood with a peak prevalence in the sixth and seventh decades of life. Although chondrosarcoma arises over a wide age range, the majority of affected patients are over 50 years of age; tumors arising in patients under the age of 45 are uncommon. No significant sex or race predilection is noted. The most frequently involved bones are the ileum, femur, and humerus. Involvement of the head and neck is seen infrequently.

When occurring in the head and neck, chondrosarcomas arise most frequently in the maxilla; less common sites of involvement are the mandibular body, ramus, nasal septum, and paranasal sinuses. Because of the rarity of the neoplasm, large series of chondrosarcomas of the jaws and facial bones are uncommon. In one of the larger series, the Mayo Clinic reviewed 86 patients with chondrosarcoma of the jaws and facial bones, and a pattern of occurrence similar to the extragnathic bones was observed. In this series. the peak prevalence was noted in the seventh decade, but the age at initial diagnosis had a wide range, with approximately 20% noted in patients younger than 20 years of age. The mean patient age at the time of diagnosis was 41.6 years. No sex or race predilection was noted. Involvement of the maxilla and maxillary sinus outnumbered those in the mandible by four to one.

Review of prior publications presents a conflicting picture in which the mean age is variable and often reveals a peak prevalence as early as the third decade. Some investigators have suggested that such conflicting results may be because of difficulty in performing literature reviews that may contain chondroblastic osteosarcomas intermixed with true chondrosarcomas.

A painless mass or swelling is the most common presenting sign. This may be associated with separation or loosening of teeth. In contrast to osteosarcoma, pain is an unusual complaint. Maxillary tumors may cause nasal obstruction, congestion, epistaxis, photophobia, or visual loss.

Radiographically, the tumor usually shows features suggestive of a malignancy, consisting of a radiolucent process with poorly defined borders. The radiolucent area often contains scattered and variable amounts of radiopaque foci, which are caused by calcification or ossification of the cartilage matrix (Figure 14-80). Some chondrosarcomas show extensive calcification and

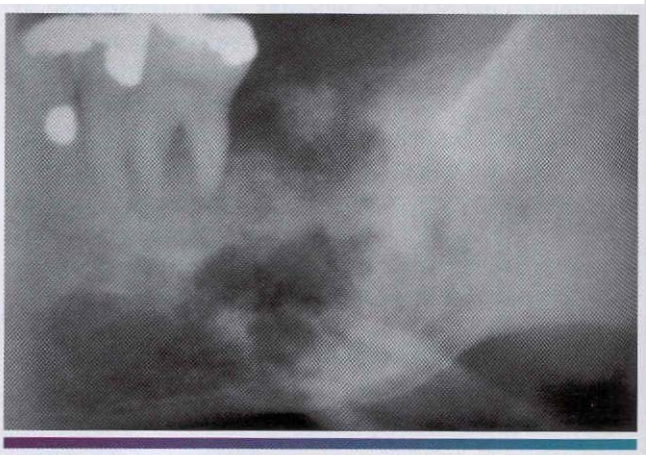

Figure 14-80 • Chondrosarcoma. Ill-defined radiolucent lesion of posterior mandible containing radiopaque foci. (Courtesy of Dr. Ben B. Henry.)

radiographically appear as a densely calcified mass with irregular peripheral margins. Penetration of the cortex can result in a sunburst pattern similar to that seen in some osteosarcomas.

Chondrosarcomas often demonstrate extensive infiltration between the osseous trabeculae of the preexisting bone without causing appreciable resorption. in such cases, the extent of the tumor is difficult to determine by radiographic examination. Root resorption or symmetric widening of the periodontal ligament space of the teeth involved by the tumor also may be noted. Chondrosarcomas may grow in a lobular pattern with minimal or no foci of calcification. in such instances, the lesion can appear as a multilocular radiolucency and mimic a benign process.

Histopathologic Features

chondrosarcomas are composed of cartilage showing varying degrees of maturation and cellularity. In most cases, typical lacunar formation within the chondroid matrix is visible, although this feature may be scarce in poorly differentiated tumors. The tumor often shows a lobular growth pattern, with tumor lobules separated by thin fibrous connective tissue septa. The central areas of the lobules demonstrate the greatest degree of maturation. The peripheral areas consist of 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.

Chondrosarcomas may be divided into three histopathologic grades of malignancy. This grading system correlates well with the rate of tumor growth and prognosis for chondrosarcomas of the extragnathic skeleton.

Grades. Grade I chondrosarcomas closely mimic the appearance of a chondroma, composed of chondroid matrix and chondroblasts that show only subtle variation from the appearance of normal cartilage. The distinction between benign and well-differentiated malignant cartilaginous tumors is notoriously difficult. Many believe that a tumor should be considered malignant when large, plump chondroblasts and binucleated chondrocytes are present, even in only scattered microscopic fields. Calcification or ossification of the cartilaginous matrix often is prominent, and mitoses are rare.

Grade II chondrosarcomas show a greater proportion of moderately sized nuclei and increased cellularity, particularly about the periphery of the lobules. The carnlaginous matrix tends to be more myxoid with a less prominent hyaline matrix. The mitotic rate, however, is low {Figure i4-8ii.

Grade III chondrosarcomas are highly cellular and may show a prominent spindle cell proliferation. Mitoses may be prominent. Easily recognizable cartilaginous matrix containing cells within lacunae may be scarce.

Chondrosarcomas of the jaws are predominantly of the histopathologic grades I and Ii. Grade III tumors are very uncommon. In the 56 cases reviewed by the Mayo Clinic, over 75% were grade I with the remainder being grade II; no grade III chondrosarcomas were noted in this series.

Variants. Several uncommon microscopic variants of chondrosarcoma are also recognized.

The clear cell chondrosarcoma shows cells with abundant clear cytoplasm; this may lead to problems in differentiation from a metastatic clear cell carcinoma. The clear cell chondrosarcoma is considered to be a low-grade lesion.

Dedifferentiated chondrosarcoma is a high-grade malignancy that shows an admixture of well-differentiated chondrosarcoma and a malignant mesenchymal tumor resembling fibrosarcoma. If these variants occur in the jaws, they are exceedingly rare.

Treatment and Prognosis

The prognosis for chondrosarcoma is related to the size, location, and grade of the lesion. The most important factor is the location of the tumor because this has the greatest influence on the ability to achieve complete resection. The **most effective** treatment for **chondrosarcoma is radical surgical excision.** Radiation and chemotherapy are less effective when compared with osteosarcoma and are primarily used for unresectable high-grade chondrosarcomas.

Although aggressive tumors are occasionally seen, gnathic chondrosarcomas are usually slowly growing neoplasms with a lower potential for metastasis than osteosarcoma. Local recurrence leads to death by direct extension of the tumor into vital structures of the head and neck. Maxillary and antral tumors often are located centrally, obtain a larger size before diagnosis, occur adjacent to the CNS, and create more difficulty in surgical eradication; therefore, they are less amenable to cure. In the Mayo Clinic review, no distant metastases

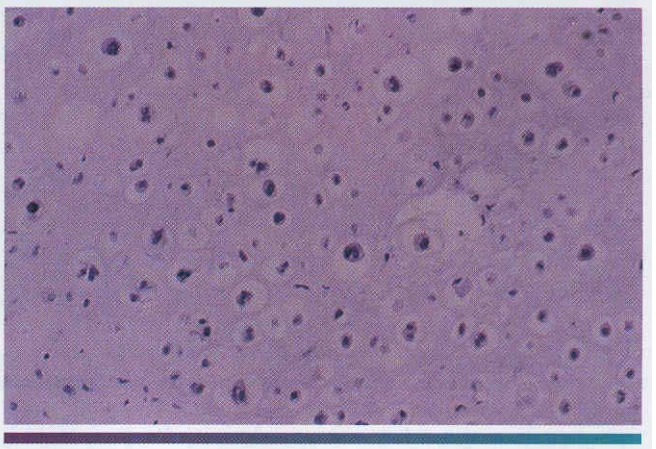

Figure 14-81 • Chondrosarcoma. This grade II chondrosarcoma shows a variation in size of chondrocyte nuclei. Occasional double nuclei are seen in the lacunae.

occurred in the 56 reported patients: the 5-, 10-, and 15-year survivals were 67.6%, 53.7%, and 43.9% respectively. As is obvious from this data, the importance of 5-year survival is minimal because recurrence often is a late sequela. Patients must be followed for their lifetime. Although the Mayo Clinic series suggested the prognosis of gnathic and craniofacial chondrosarcoma was better than that associated with osteosarcoma, disagreements exist and numerous investigators believe the prognosis of chondrosarcoma is worse. As adjuvant chemotherapy continues to improve the prognosis of osteosarcoma, this disagreement may resolve.

MESENCHYMAL CHONDROSARCOMA

The mesenchymal chondrosarcoma, an uncommon and distinctive tumor of bone and soft tissue, shows a biphasic histopathologic pattern. This aggressive form of chondrosarcoma represents only 3% to 9% of all chondrosarcomas.

Clinical and Radiographic Features

In contrast to other types of chondrosarcoma, the mesenchymal variant is unusual in that it most frequently affects individuals In the second or third decade of life and the jaws are among the most frequently involved bones (25% to 30%). Other commonly affected sites are the ribs, shoulder, pelvic girdle, and vertebrae. About one third to one fourth of all examples arise in the soft tissues rather than in bone.

Swelling and pain, often of fairly short duration, are the most common symptoms. Radiographically, the tumor demonstrates a circumscribed radiolucency with infiltrative margins (Figure 14-82). Stippled calcification may be present within the radiolucent area.

Histopathologic Features

Microscopically, the mesenchymal chondrosarcoma reveals sheets or patternless masses of small, undifferentiated spindle or round cells surrounding discrete nodules of cartilage (Figure 14-83). The chondroid tissue is well differentiated, and its degree of cellularity and atypia may vary from that of a benign chondroma to a low-grade chondrosarcoma. The noncartilaginous component of the tumor is difficult to differentiate from, and may be confused with, a variety of small cell tumors of bone, such as Ewing's sarcoma, lymphoma, and metastatic small cell carcinoma. In some cases, a prominent, branching vascular pattern is present in the soft tissue component of a mesenchymal chondrosarcoma. If cartilaginous foci are sparse, the tumor may be misdiagnosed as a hemangiopericytoma.

Treatment and Prognosis

Surgical excision with wide margins is the most appropriate therapy. Radiation and chemotherapy have not prolonged survival in a predictable manner. Local recurrence and metastasis are not rare. When metastasis occurs, hematogenous spread is seen more frequently than lymphatic involvement, with the lung being a favored site for metastatic deposits. Recurrent or metastatic disease may be discovered as long as 20 years after initial therapy. The 10-year survival rate is approximately 28%.

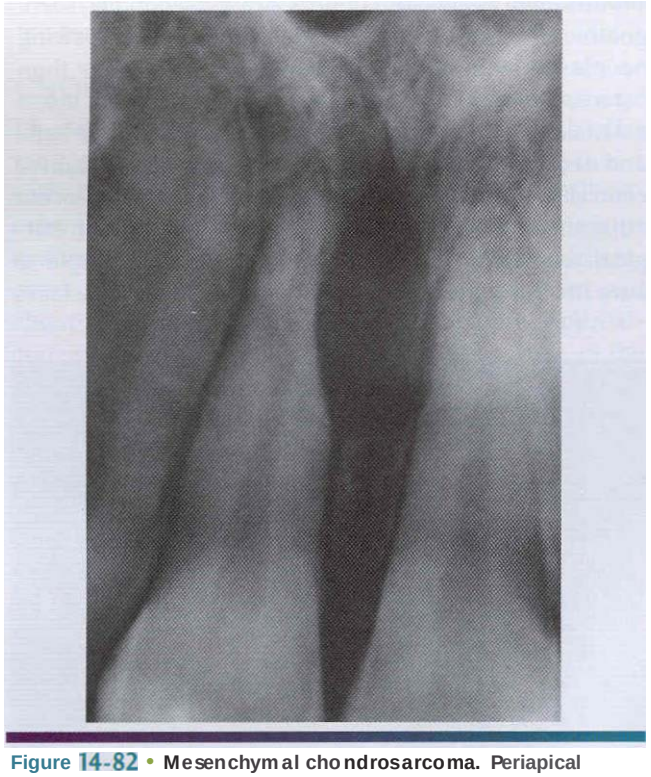

Figure 14-82 • **Mesenchymal chondrosarcoma.** Periapical radiograph showing a radiolucent lesion between the roots of the central incisors in a 29-year-old woman. The roots of the incisors show resorption. At surgery, the lesion was considerably larger than indicated on the radiograph. (Courtesy of Dr. Gary Baker.)

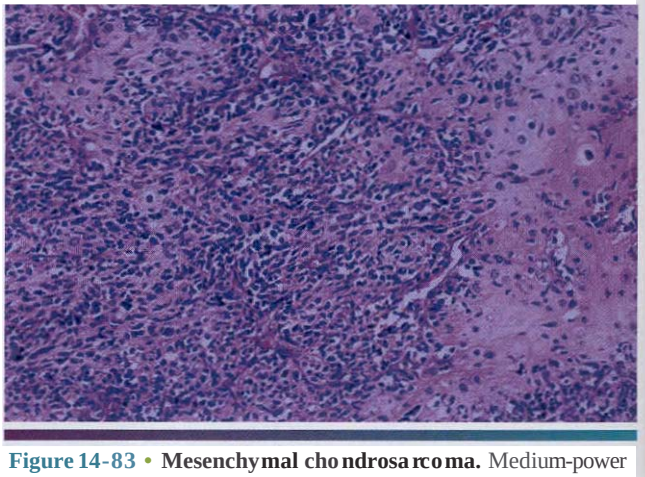

Figure 14-83 • **Mesenchymal chondrosarcoma.** Medium-power photomicrograph showing sheets of small basophilic cells with focal areas of cartilaginous differentiation *(right)*.

EWING'S SARCOMA

Ewing's sarcoma is a distinctive primary malignant tumor of bone that is composed of small undifferentiated round cells of uncertain histogenesis. Recent studies have provided data showing that most cases of Ewing's sarcoma **exhibit features consistent with neuroectodermal origin.** In 85% to 90% of the cases, the *tumor* cells demonstrate **a reciprocal translocation between chromosomes 11 and** 22 *[t(* 11;22) (q24;q12)]. Ewing's sarcoma constitutes 6% to 8% of all primary malignant bone tumors and represents **the third most common osseous neoplasm after osteosarcoma and chondrosarcoma. In addition,** extraskeletal examples have been well documented.

Clinical and Radiographic Features

The peak prevalence of Ewing's sarcoma is in the second decade of lite, with approximately 80% of patients being younger than 20 years of age at the time of diagnosis and 50% of these tumors being detected in the second decade. A slight male predominance is noted. The vast majority of affected patients are white, with blacks almost never developing this tumor. The long bones, pelvis, and ribs areaffected most frequently, but almost any bone can be **affected. Jaw involvement is uncommon, with only 1% to** 2% occurring in the gnathic or craniofacial bones.

Pain, often associated with swelling, is the most common symptom. It Is usually Intermittent and varies from dull to severe. Fever, leukocytosis, and an elevated erythrocyte sedimentation rate also may be present and may lead to an erroneous diagnosls of osteomyelitis. The tumor commonly penetrates the cortex, resulting in a soft tissue mass overlying the affected area of the bone (Figure 14-84). Jaw involvement is more common in the mandible than the maxilla. Paresthesia and loosening of teeth are **common findings in EWing's sarcomas of the jaws.**

Radiographically, there is irregular lytic bone destruc**tion with ill-defined margins. Cortical destruction or** expansion mayor may not be present. The character**istic "onionskin" periosteal reaction. commonly observed in Ewing's sarcoma of long bones. is seldom seen in jaw lesions.**

Histopathologic Features

EWing's sarcoma is composed of small round cells wlth well-delineated nuclear outlines and ill-defined cellular borders (Figure 14-85). The tumor cells often are arranged in broad sheets without any distinct pattern. In **some cases, variable-sized nests of tumor cells are sep**arated by fibrovascular septa, creating a lobular pattern. **Large areas of necrosis and hemorrhage are commonly** present. Ewing's sarcomas are not as morphologically **homogeneous as once was believed. Some examples** contain focl or may be composed mostly of larger cells. These are designated as large **cell** (atypical) Ewing's **sarcomas.**

About 75% of cases contain glycogen granules in the cytoplasm of the tumor cells. This is a helpful diagnostic feature, but it is not specific because glycogen also *can* **be demonstrated in some other primitive tumors. About** 25% of well-documented EWing's tumors do not show glycogen.

Diagnosis of EWing's sarcoma may be very difficult. The tumor must be differentiated from other primitive small cell tumors involving bone and soft tissues in young **patients. These include metastatic neuroblastoma,** malignant lymphoma, small cell osteosarcoma, embry**onal rhabdomyosarcoma. and the primitive neuroecto**dermal tumor. Metastatic small cell carcinoma also must be considered in the differential diagnosis of a suspected **Ewing's sarcoma in an older patient.**

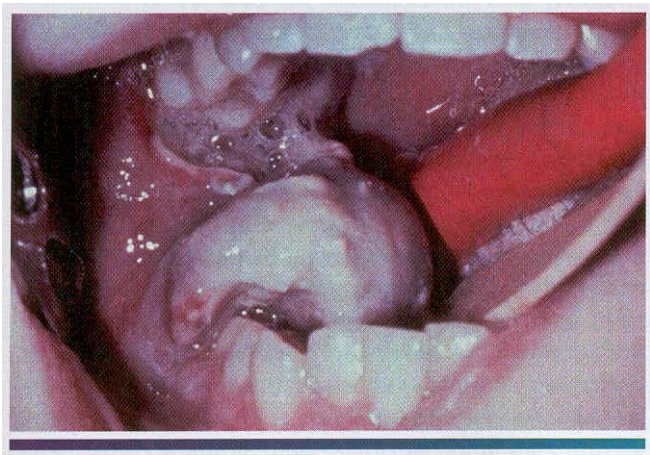

Figure 14-84 . Ewing's sarcoma. A rapidly growing, ulcerated tumor of the right posterior mandible. (Courtesy of Dr. George Biozis.)

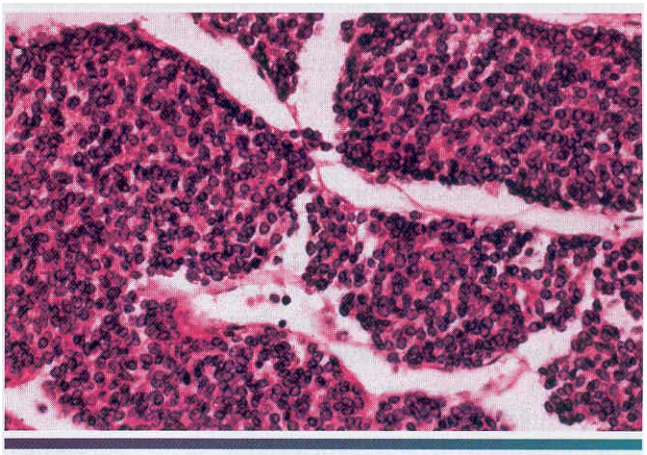

Figure 14-85 • Ewing's sarcoma. Broad sheets of small round cells with well-defined nuclear outlines and ill-defined cytoplasmic borders.

A battery of immunohistochemical reactions and electron microscopy may be required for confirmation of the diagnosis of Ewing's sarcoma in some cases. EWing's sarcoma expresses high levels of an antigen determined by the MIC2 gene. The product of MIC2 is a glycoprotein designated CD99 that can be detected by the immunoperoxidase technique. Although useful in confirmation of Ewing's sarcoma, positive reactivity to C099 also is noted in other tumors and some normal tissues. In questionable cases, the presence of the genetic alterations associated with EWing's sarcoma can be investigated to provide a sensitive and specific diagnostic marker.

Treatment and Prognosis

The prognosis for patients with EWing's sarcoma has improved dramatically in recent years. Formerly, less than 5% of patients survived more than 5 years. Current treatment, eonsisting of combined surgery, radiotherapy, and multidrug chemotherapy, has led to 40% to 80% survival rates. Because of the risk for postradiation sarcomas, some clinicians do not recommend radiation except when surgical resection of the primary site is not possible.

At the time of initial diagnosis, seemingly localized disease often is associated with occult micrometastases. making systemic therapy appropriate in most cases. EWing's sarcomas frequently metastasize to the lungs, liver, lymph nodes, and other bones. The anatomic location of the tumor is a critical factor in prognosis. Pelvic lesions are associated with the poorest prognosis. Distal lesions *have* a better prognosis than those in a proximal location. With modern therapy, patients with Ewing's sarcoma of the jaws probably have an improved prognosis; however, there is a scarcity of good information because of the small number of cases.

METASTATIC TUMORS TO THE JAWS

Metastatic carcinoma is the most common form of cancer involving bone. Autopsy studies have shown that more than two thirds of breast carcinomas, one half of all prostate carcinomas, and one third of all lung and kidney carcinomas spread to one or more bones before a patient dies. Although metastasis to a jaw bone may arise from primary carcinomas of any anatomic site, carcinomas of the breast, lung, thyroid, prostate, and kidney give rise to the majority of gnathic metastases. Metastatic spread of a carcinoma to the jaws usually occurs by the hematogenous route. Sarcomas arising in soft tissues or other bones may metastasize to the jaws. but this is very rare.

Clinical and Radiographic Features

Most patients with metastatic carcinoma are older; children are affected rarely. This finding is a reflection of the greater prevalence of carcinoma in the elderly. Although metastatic lesions may be observed in any bone, the vertebrae, ribs, pelvis, and skull are the most frequent sites for metastasis.

The jaws are usually considered to be uncommon sites for metastasis but may be involved more often than generally appreciated. A study of carcinomas arising in various extraoral sites demonstrated that 10 (16%) of 62 autopsied cases of carcinoma showed histopathologic evidence of metastasis to the mandible, even though radiographic study of the mandibles removed at autopsy in these cases failed to show evidence of metastatic disease. Metastasis to the maxilla is uncommon. and more than 80% of reported metastases to the jaws have occurred in the mandible.

Metastatic involvement of the jaws exhibits a wide variety of symptoms. Often, the patient experiences pain, swelling, loosening of teeth, a mass, or paresthesia. Metastasis to the mandible with involvement of the inferior alveolar nerve occasionally produces a distinctive pattern of anesthesia termed numb-chin syndrome in which there is an unexplained loss of sensation in the lower lip and chin. These symptoms, however, are not specific for metastatic disease and may be associated with primary inflammatory or neoplastic diseases of the jaws. In some instances, the patient may be completely asymptomatic, and the diagnosis of metastatic carcinoma occurs only after microscopic study of a lesion noted on radiographic examination. Not uncommonly. an osseous metastasis is discovered in a nonhcaling extraction site from which the tooth was recently removed because of complaints of local pain or significant mobility.

Of particular interest are those cases in which diagnosis of a jaw metastasis is the first indication that the patient has a primary malignancy at some other anatomic site. On occasion, the oral lesion is the first indication of an undiscovered and distant malignancy. Location of the occult primary tumor may be difficult, requiring extensive evaluation.

Radiographically, metastatic deposits in the jaws usually appear as radiolucent defects. The defect may be well circumscribed, resembling a cyst, but more often it isill defined with a "moth-eaten" appearance. Involvement of the alveolus may resemble periodontal disease clinically and radiographically (Figure 14-86). On occasion. a metastatic tumor may cause widening of the periodontal ligament (Figure 14-87). Some carcinomas, particularly from the prostate and breast, may stimulate new bone formation in the metastatic site. resulting in radiopaque or mixed radiolucent and radiopaque lesions.

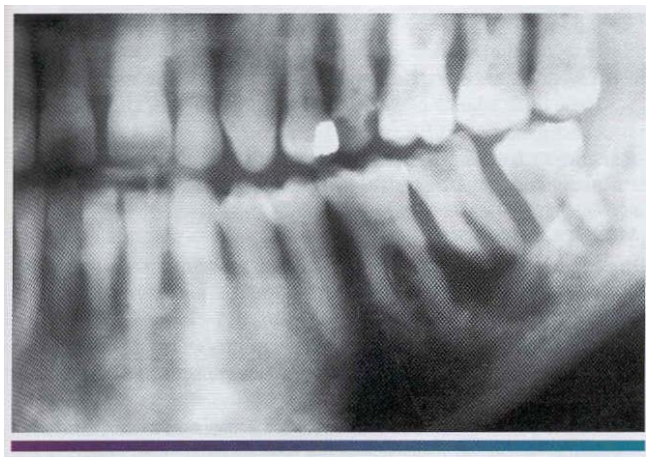

Figure 14-86 • **Carcinoma metastatic to the jaws.** Panoramic radiograph showing destruction of the alveolar bone surrounding the roots of the mandibular second molar. Such changes may mimicadvanced periodontal disease. In this patient. the lesion originated from an occult carcinoma of the lung. (Courtesy of Or. I.M. Sarnovsky.)

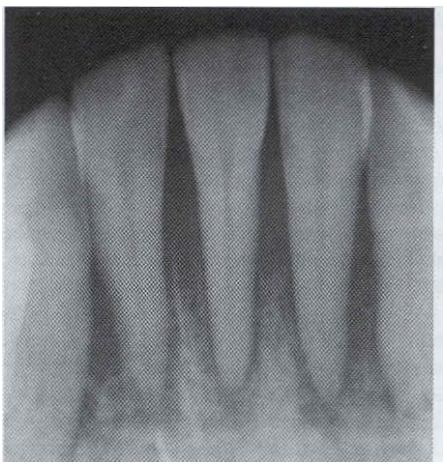

Figure 14-87 • **Carcinoma metastatic to the jaws.** Periapical radiograph showing widening of the periodontal ligament spaces.

Not uncommonly, patients with gnathic metastases will have symptoms at a time when conventional radiographs fail to demonstrate detectable alterations. Ill these instances, bone scintigraphy is occasionally used because it has a higher sensitivity and a greater ability to detect subtle osseous metastases. Some investigators recommend this technique for patients with prolonged, unexplained pain who have a history of cancer that is frequently associated with osseous metastases.

Histopathologk Features

The microscopic appearance of metastatic carcinoma in bone varies. In some instances, the metastatic tumor is well differentiated and closely resembles a carcinoma of a specific site, such as the kidney, colon, or thyroid. In such instances, the pathologist can say with reasonable **certainty that a given metastatic tumor comes from a** specific primary site (Figure 14-88). More often, how**ever, metastatic carcinomas are poorly differentiated and** histopathologic study of the metastatic deposit gives little clue as to the primary site of the tumor. Poorly differentiated metastatic carcinoma may be difficult to differentiate from anaplastic small cell sarcomas, malignant lymphomas, and malignant melanoma. Immunohisto**chemical reactions are usually necessary in such cases** to establish the diagnosis. Although the diagnosis of metastatic carcinoma can usually be determined by microscopic examination, the final diagnosis depends mostly on a careful medical history and complete physical examination with appropriate laboratory studies.

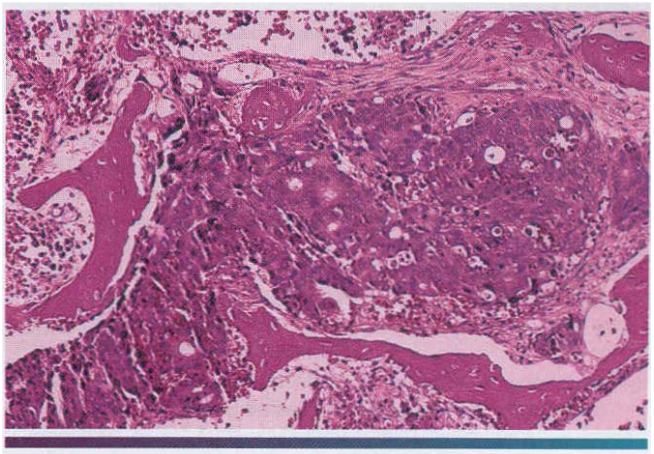

Figure 14-88 • **Carcinoma metastatic to the jaws. Islands of malignant cells can be seen filling the marrow spaces.**

Treatment and Prognosis

The prognosis for metastatic carcinoma of the jaws is **poor because. by definition, osseous metastasis auto**matically places the patient in Stage *IV* disease, Although a solitary metastatic focus may be treated by excision or radiation therapy, jaw involvement almost always is associated with widely disseminated disease, Five-year **survival after detection of metastatic carcinoma** Involving the jaws is exceedingly rare, and most patients do not **survive more than 1 year.**

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CHAPTER 15

Odontogenic Cysts and Tumors*

CHAPTER OUTLINE

*Dr. Charles A. Waldron wrote the original version of this chapter in the first edition of this book.

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 11.)

Odontogenic cysts are subclassified as developmental or inflammatory in origin. Developmental cysts are of unknown origin, but they 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 1992 World Health Organization (WHO) classification. (The periapical cyst is discussed in Chapter 3.)

Box **15-1** ***Classification of Odontogenic Cysts***

DEVELOPMENTAL

1. Dentigerous cyst
2. Eruption cyst
3. Odontogenic keratocyst
4. Orthokeratinized odontogenic cyst
5. Gingival (alveolar) cyst of the newborn
6. Gingival cyst of the adult
7. Lateral periodontal cyst
8. Calcifying odontogenic cyst*
9. Glandular odontogenic cyst

INFLAMMATORY

1. Periapical (radicular) cyst
2. Residual periapical (radicular) cyst
3. Buccal bifurcation cyst

*The term *calcifying odontogenic cyst* includes both nonneoplastic cysts and true neoplasms. Although the calcifying odontogenic cyst is included with odontogenic tumors in the 1992 WHO classification, it is discussed with the odontogenic cysts in this chapter.

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 (Figure 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*.

Clinical and Radiographic Features

Although dentigerous cysts may occur in association with any unerupted tooth, most often they involve mandibular third molars. Other relatively frequent sites include max-

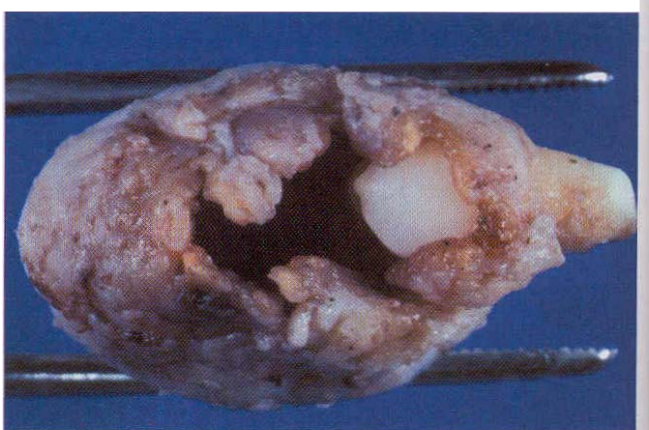

Figure 15-1 • **Dentigerous cyst. Gross specimen of a dentigerous cyst involving a maxillary canine tooth. The cyst has been cut open to show the cyst-to-crown relationship.**

illary canines, maxillary third molars, and mandibular second premolars. Dentigerous cysts rarely *involve* unerupted deciduous teeth. Occasionally, they are associated with supernumerary teeth or odontomas.

Although dentigerous cysts may be encountered in patients over 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 aretaken 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 arc considered to be large dentigerous cysts on radiographic examination will prove to be odontogenic keratocysts or arneloblastomas. Dentigerous cysts may become infected and beassoclated with 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 adjac ent tooth.

Radiographic ally, 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 sclerotic 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. Dentigerous cysts, however, are grossly and histopathologically unilocular processes and probably never are tru ly multil ocular lesions.

The cyst-to-crown relationship shows several radiographic variations. In the central variety, which is the most common, the cyst surro unds the crown of the tooth and the crown projects into the cyst (Figure 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 (Figure 15-3). In the circ umferential *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 (Figure 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.

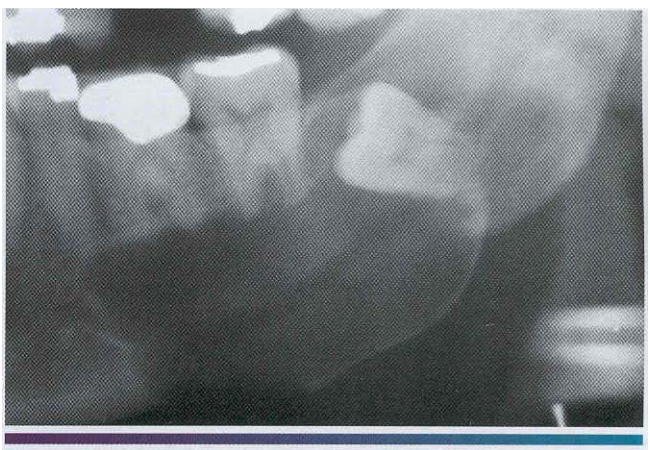

Figure 15-3 • Dentigerous cyst. Lateral variety showing a large cyst along the mesial root of the unerupted molar. This cyst exhibited mucous cell prosoplasia. (Courtesy of Dr. John R. Cramer)

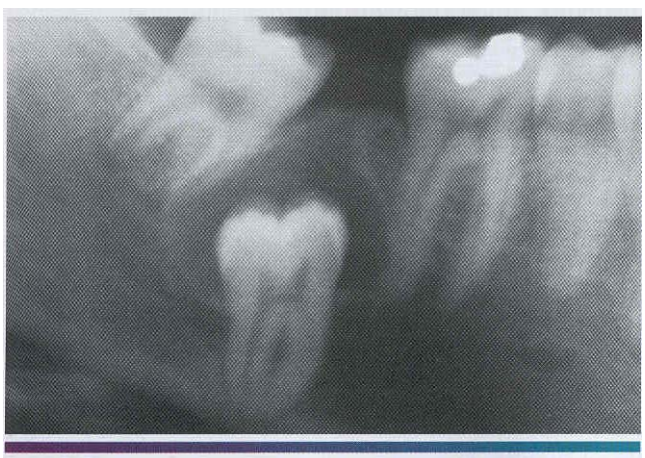

Figure 15-2 • Dentigerous cyst. Central type showing the crown projecting into the cystic cavity. (Courtesy of Dr. Stephen E. Irwin.)

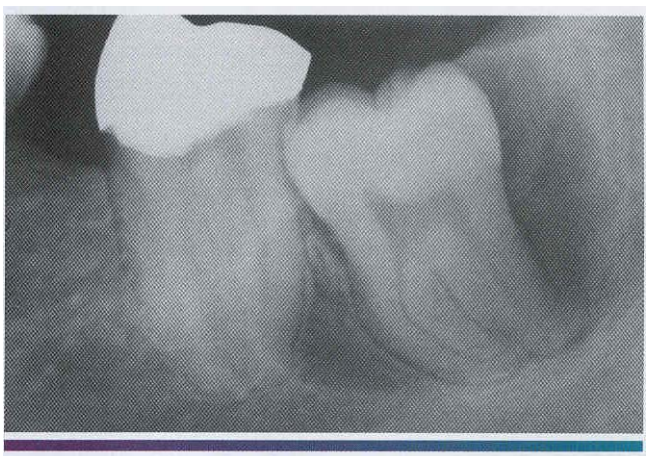

Figure 15-4 • Dentigerous cyst. Circumferential variety showing cyst extension along the mesial and distal roots of the unerupted tooth. (Courtesy of Dr. Richard Marks.)

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 (Figure 15-51. For the lesion to be considered a dentigerous cyst, some investigators believe that the radiolucent space surrounding the tooth crown shouid be at least 3 to 4 mm in diameter. Radiographic findings are **not diagnostic for a dentigerous cyst, however,** because odontogenic keratocysts, unilocular ameloblastomas, **and many other odontogenic and nonodontogenic** tumors may have 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. The epithelial lining consists of two to four layers of flattened nonkeratinizing cells, and the epithelium and *connective* tissue interface is flat (Figure 15-61.

In the fairiy 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 of rete ridges and more definite squamous features (Figure 15-71. A keratinized surface is sometimes seen, but these changes must be differentiated from those observed in the odontogenic keratocyst. Focal areas of mucous cells may be found in the epithelial lining of dentigerous cysts (Figure 15-81. Rarely, ell-

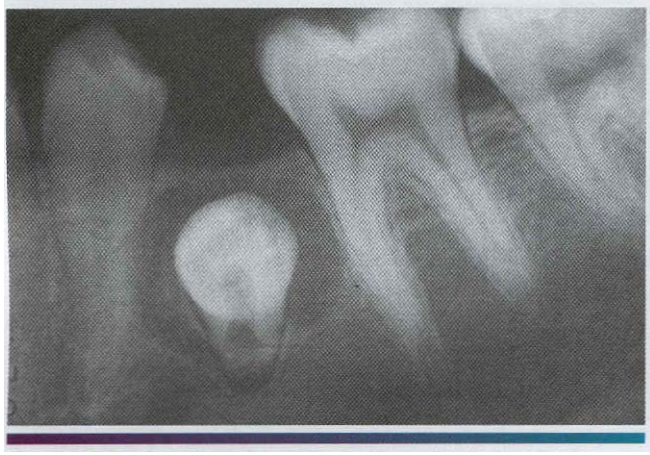

Figure 15-5 • Dentigerous cyst or enlarged follicle. Radiolucent lesion involving the crown of an unerupted mandibular premolar. Distinction between a dentigerous cyst and an enlarged follicle for a lesion of this size by radiographic and even histopathologic means is difficult. if not impossible. (Courtesy of Dr. Wally Austelle.)

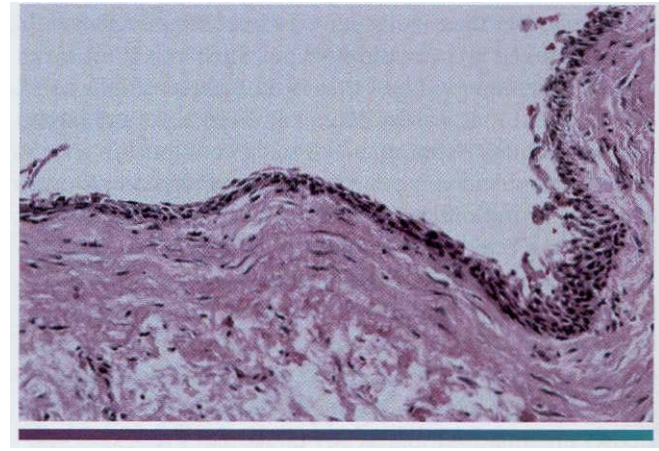

figure 15-6 • Dentigerous cyst. This noninflamed dentigerous cyst shows a thin. nonkeratinized epithelial lining.

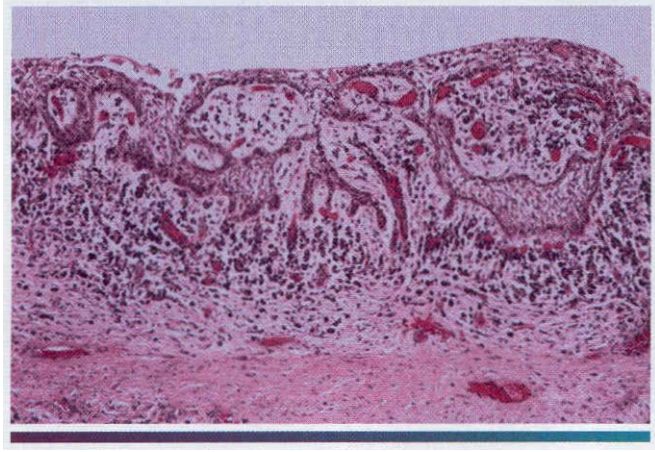

Figure 15-7 • Dentigerous cyst. This inflamed dentigerous cyst shows a thicker epithelial lining with hyperplastic rete ridges. The fibrous cyst capsule shows a diffuse chronic inflammatory infiltrate.

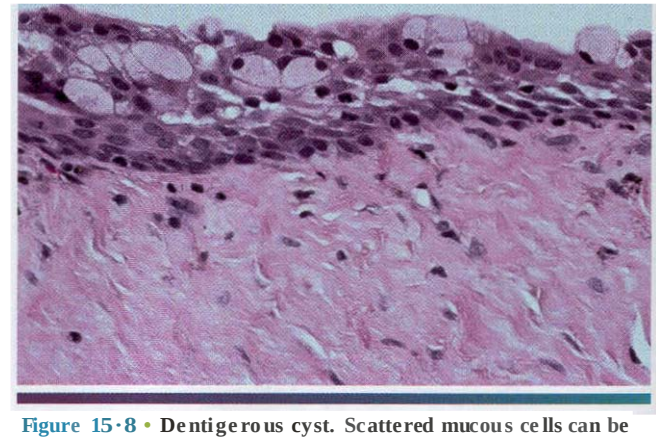

Figure 15-8 • Dentigerous cyst. Scattered mucous cells can be seen within the epithelial lining.

iated 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 enamei 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 assuring that the lesion does not represent a more significant pathologic process (e.g.. odontogenic keratocyst or ameloblastoma).

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, 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 at 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 609). It is likely that some intraosseous mucoepidermoid carcinomas (see page 422) 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 tram 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 associated with the first permanent molars and the maxillary incisors. Surface trauma may result in a considerable amount of blood in the cystic fluid, which imparts a blue to purplish-brown color. Such lesions sometimes are referred to as eruption hematomas (Figure 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 tacilitate 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 at nonkeratinizing squamous epithelium (Figure 15-10).

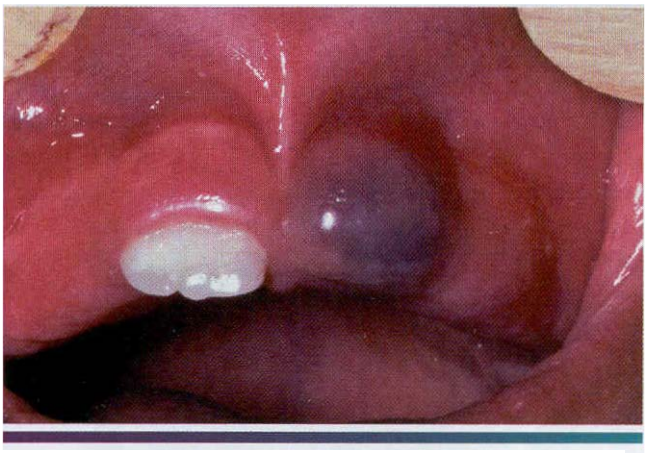

Figure 15-9 • Eruption cyst. This soft gingival swelling contains considerable blood and can also be designated as an eruption hematoma.

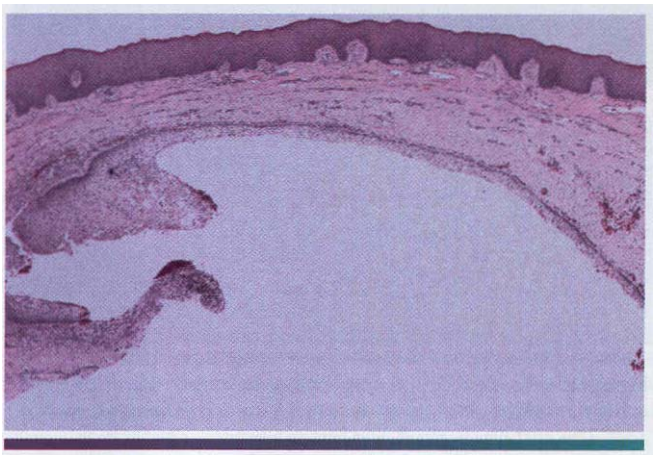

Figure 15-10 • Eruption cyst. A cystic epithelial cavity can be seen below the mucosal surface.

Treatment and Prognosis

Treatment may not be required because the cyst usually ruptures spontaneously, permitting the tooth to erupt. If this does not occur, 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 widely 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 occurs in place of a tooth.

In the mid-1950s, oral pathologists in Europe introduced the term odontogenic keratocyst 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, lists odontogenic keratocyst as the preferred designation.

Whether there is a primordial cyst that is not microscopically an odontogenic keratocyst is still unsettled. Many believe that all primordial cysts are odontogenic keratocysts, although some recognize the existence of a primordial cyst that does not have the histopathologic features of the odontogenic keratocyst. If such a lesion exists, it must be exceedingly rare. Reference to this lesion **is almost nonexistent in the current literature. and no** reported series include a significant number of cases. In the authors' experience, a cyst clinically considered to represent a primordial cyst, in the older meaning of the **term. almost always is an odontogenic keratocyst after** microscopic study (Figure 15-11).

ODONTOGENIC KERATOCYST

The odontogenic keratocyst 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 **odontogenic keratocyst 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 dentig**erous 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 odontogenic keratocysts. and their growth may be related to unknown factors inherent in the epithelium itself or enzymatic activity in the fibrous wall. Several investigators suggest that odontogenic keratocysts be regarded as benign cystic neoplasms rather than cysts. Although there are wide variations in the reported frequency of odontogenic keratocysts compared with that of other types of **odontogenic cysts. *several* studies that include large** series of cysts indicate that odontogenic keratocysts make up 3% to 11% of all odontogenic cysts.

Clinical and Radiographic Features

Odontogenic keratocysts 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 ascending ramus (Figure 15-12).

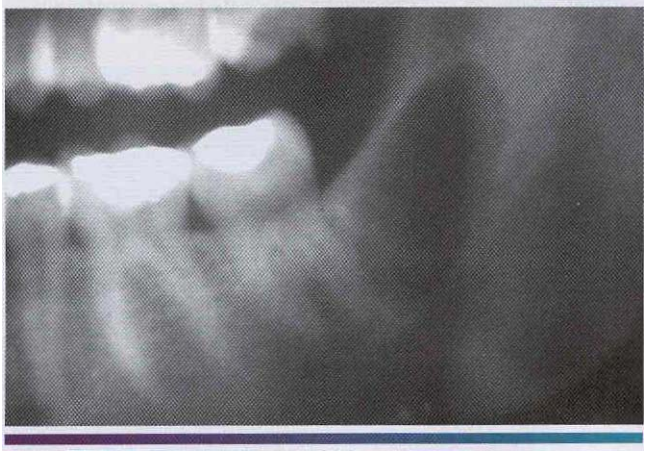

figure 15-11 • **Primordial cyst. This patient gave no history of** extraction **of the third molar. A cyst is located in the third molar area. The cyst was excised, and histopathologic examination revealed an odontogenic** keratocyst.

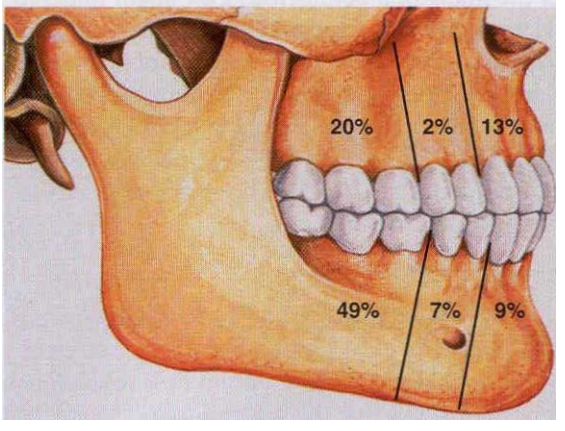

figure 15-12 • **Odontogenic keratocyst. Relative distribution of odontogenic** keratocysts **in the jaws.**

Small odontogenic keratocysts are usually asymptomatic and discovered only during the course of a radiographic examination. Larger odontogenic kerarocysrs may be associated with pain, swelling. or drainage. Some extremely large cysts. however, may cause no symptoms.

Odontogenic keratocysts tend to grow in an anteroposterior direction within the medullary cavity of the bone with out 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 odontogenic keratocysts may be present, and such patients should be evaluated for other manifestations of the nevoid basal cell carcinoma (Gorlin) syndrome (see page 598).

Odontogenic keratocysts demonstrate a well-defined radiolucent area with smooth and often corticated margins. Large lesions, particularly in the posterior body and ascending ramus of the mandible, may appear multilocular (Figure 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 (Figures 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 odontogenic keratocysts is less common than that noted with dentigerous and radicular cysts.

The diagnosis of odontogenic keratocyst is based on the histopathologic features. The radiographic findings, although often highly suggestive, are not diagnostic. The radiographic findings in an odontogenic keratocyst may simulate those of a dentigerous cyst, a radicular cyst, a residual cyst, a lateral periodontal cyst (Figure 15-16), or the so-called "giobuiomaxiiiary cyst" (which is no longer considered to be a true entity). Odontogenic keratocysts of the anterior midline maxillary region can mimic nasopalatine duct cysts. For unknown reasons, this particular subset of keratocysts usuaiiy occurs in older individuals with a mean age of nearly 70 years. Rare examples of peripheral odontogenic keratocysts within the gingival soft tissues have been reported.

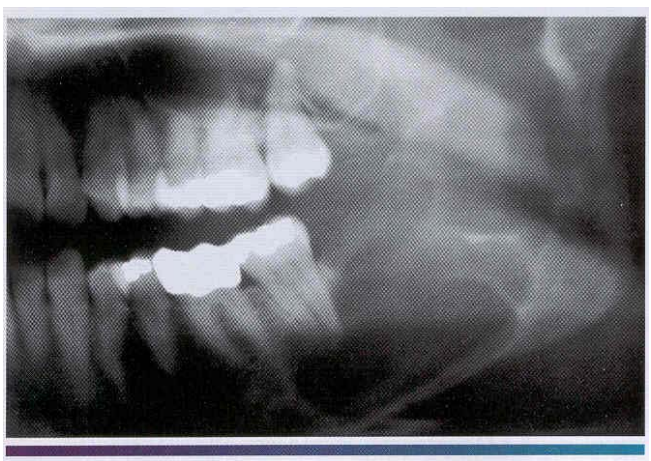

Figure 15-13 . Odontogenic keratocyst, Large, multilocular cyst involving most of the ascending ramus. (Courtesy of Dr. S.c. Roddy.)

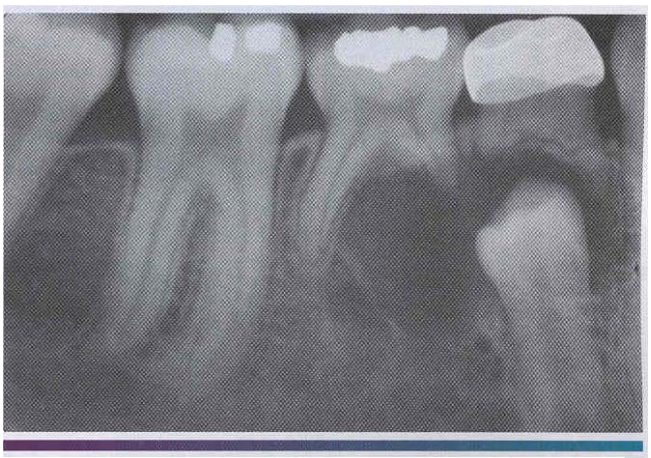

Figure 15-14 • Odontogenic keratocyst. This cyst involves the crown of an unerupted premolar. Radiographically, this lesion cannot be differentiated from a dentigerous cyst.

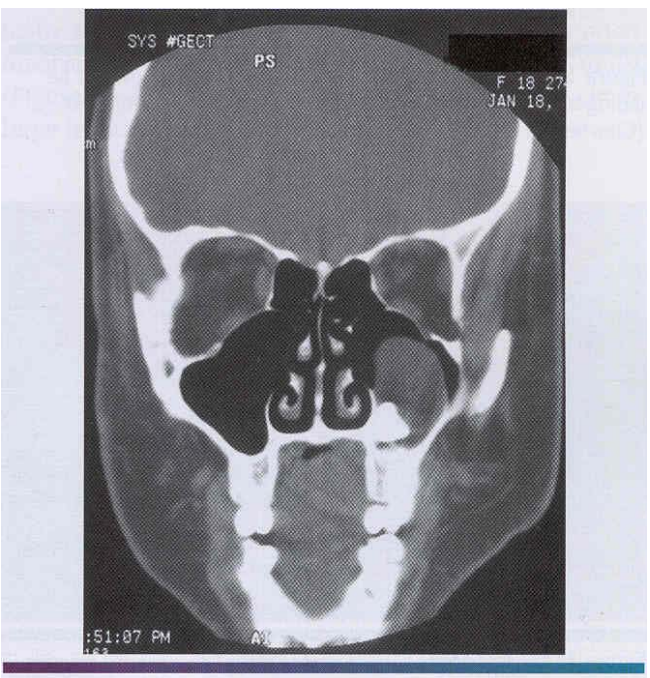

Figure 15-15 . Odontogenic keratocyst. Computed tomography (CT) scan showing a large cyst involving the crown of an unerupted maxillary third molar. The cyst largely fills the maxillary sinus. (Courtesy of Dr. E.B. Bass.)

Histopathologic Features

The odontogenic keratocyst 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 essentially devoid of any inflammatory infiltrate, 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 (Figure IS-17). 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 odontogenic keratocyst.

In the presence of inflammatory changes, the typical features of the odontogenic keratocyst 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 (Figure IS-18). When these changes involve most of the cyst lining, the diagnosis of odontogenic keratocyst cannot be confirmed unless other sections show the typical features described earlier.

Some investigators recognize a microscopic orthokeratotlc variant and include this lesion as a subtype of the odontogenic keratocyst. However, these cysts do not demonstrate a hyperchromatic and palisaded basal cell layer, which is so characteristic of true odontogenic keratocysts. 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).

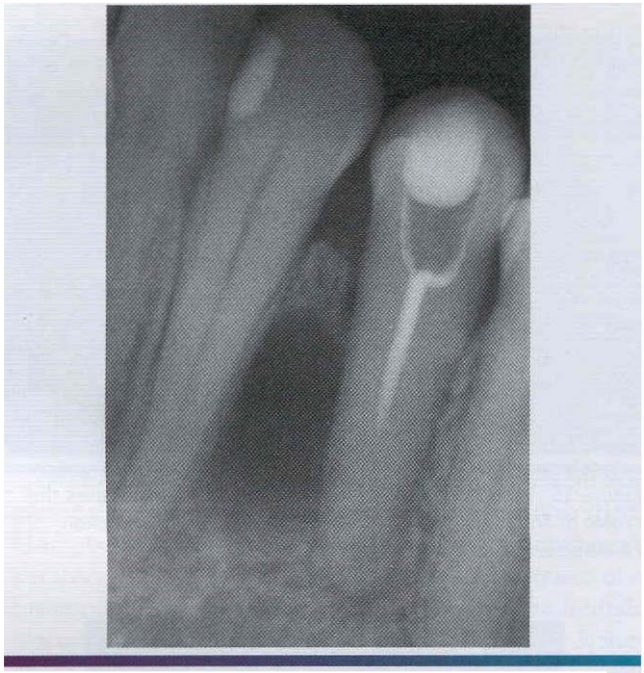

Figure 15-16 • Odontogenic keratocyst. This cyst cannot be radiographically differentiated from a lateral periodontal cyst. (Courtesy of Dr. Keith Lemmerman.)

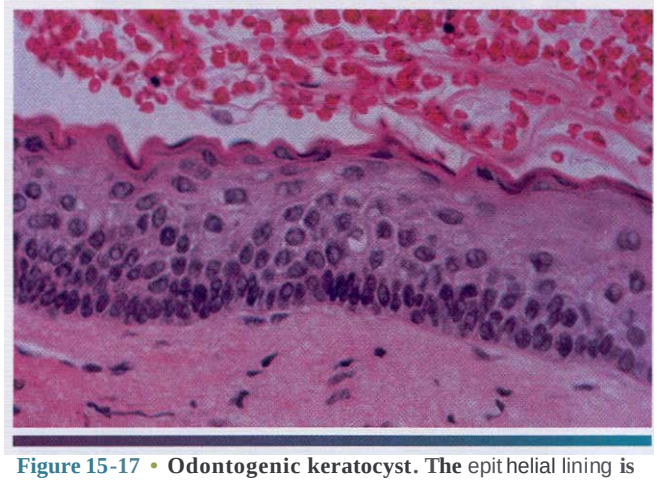

Figure 15-17 • Odontogenic keratocyst. The epithelial lining is 6 to 8 cells thick, with a hyperchromatic and palisaded basal cell layer. Note the corrugated parakeratotic surface.

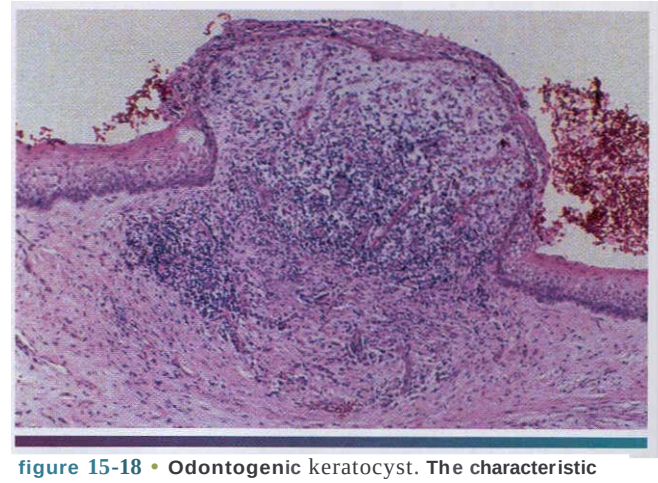

figure 15-18 • Odontogenic keratocyst. The characteristic microscopic features have been lost in the central area of this portion of the cystic lining because of the heavy chronic inflammatory cell infiltrate.

Treatment and Prognosis

Although the presence of an odontogenic keratocyst may be suspected on clinical or radiographic grounds, histopathologic confirmation is required for the diagnosis. Consequently, most odontogenic keratocysts arc treated similarly to other odontogenic cysts, that is, 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, odontogenic keratocysts 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 to 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 odontogenic keratocysts, particularly those in the posterior body and ascending ramus. Multiple recurrences are not unusual. Although many odontogenic keratocysts 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*. 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 odontogenic keratocysts by insertion of a polyethylene drainage tube to allow decompression and subsequent reduction in size of the cystic cavity. 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 odontogenic keratocysts is good. Occasionally, a locally aggressive odontogenic keratocyst 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 odontogenic kerarocyst have been reported. but the propensity for an odontogenic keratocyst to undergo malignant alteration is no greater and is possibiy less than that for other types of odontogenic cysts. Patients with odontogenic keratocysts should be evaluated for manifestations of the nevoid basal cell carcinoma syndrome (see page 598).

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 ciinicopathologically different from the more common parakeratinized odontogenic keratocyst 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 a 2:I male-to-female ratio. The lesion occurs twice as frequently in the mandible than the maxilla. 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 (Figure 15-19). The size can vary from less than I em to large lesions greater than 7 cm in diameter.

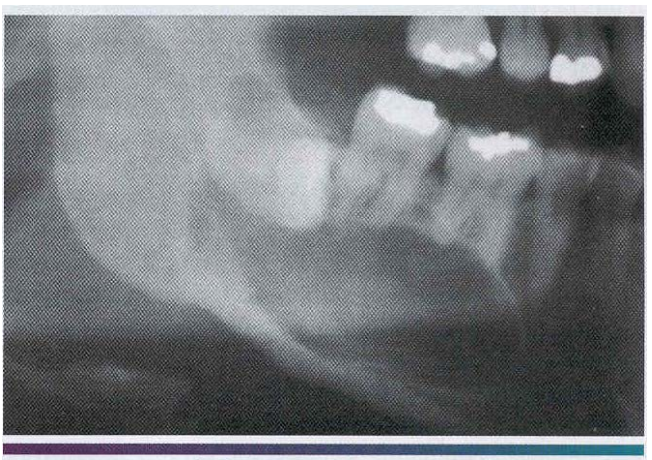

Figure 15-19 . Orthokeratinized odontogenic cyst. A large cyst involving a horizontally impacted lower third molar. On microscopic examination, this was an orthokeratinized odontogenic cyst. (Courtesy of Dr. Carroll Gallagher.)

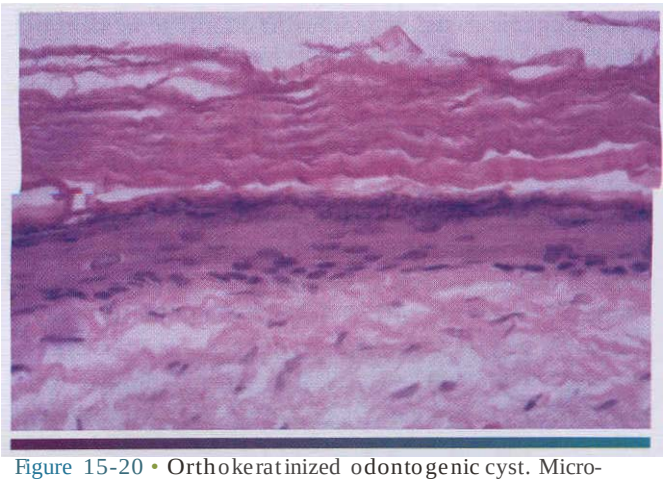

Figure 15-20 • Orthokeratinized odontogenic cyst. Microscopic features showing a thin epithelial lining. The basal epithelial layer does not demonstrate palisading. Prominent keratohyaline granules are present beneath the orthokeratotic surface. Flakes of orthokeratin are present in the lumen.

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 odontogenic keratocyst, is not present (Figure 15-20).

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 odontogenic kcratocysts. 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 have not been associated with nevoid basal cell carcinoma syndrome.

NEVOID BASAL CELL CARCINOMA SYNDROME (CORLIN SYNDROME)

Nevoid basal cell carcinoma syndrome (Gorlin syndrome) is an autosomal dominant inherited condition that exhibits high penetrance and variable expresslvitv. It is caused by mutations In **patched** (PTCH), a tumor suppressor gene that has been mapped to chromosome 9q22,3-q31, The chief components are multiple basal cell carcinomas of the skin, odontogenic keratocysts, intracranial calcification, and rib and vertebral anomalies. Many other anomalies have been reported in these patients and probably also represent manifestations of the syndrome, The prevalence of Gorlin syndrome is estimated to be about 1 in 60,000.

Box 15-2 ***Major*** *Clinicnl Features of* ***the*** *Nevoid* ***Basal*** *Cell Ctlrcit/omtl Syt/drome*

50% OR GREATER FREQUENCY

- Multiple basal cell carcinomas
- Odontogenic keratocysts
- Epidermal cysts of the skin
- Palmar/plantar pits
- Calcified falx cerebri
- Enlarged head circumference
- Rib anomalies (splayed. fused, partially missing, bifid)
- **Mild** ocular hypertelorism
- Spina blfida 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
- Mental retardation

From Gorlin R): Nevoid basal-cell carcinoma syndrome, *Medicine* 66:98-11 3,1987.

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, The eyes may appear widely separated, and many patients have true mild ocular hypertelorism. Mild mandibular prognathism is also commonly present (Figure 15-21).

Basal cell carcinomas of the skin are a major component of the syndrome. They usually begin to appear at puberty or in the second and third decades of life, although they can develop in young children. The tumors may vary *trom* flesh-colored papules to ulcerating plaques. They are often appear on non-sun exposed skin but are most commonly located in the midface area (Figure 15-22). The number of skin tumors may vary from only a few to many hundreds. Blacks with the syndrome tend to have fewer basal cell carcinomas than whites, probably because of protective skin pigmentation.

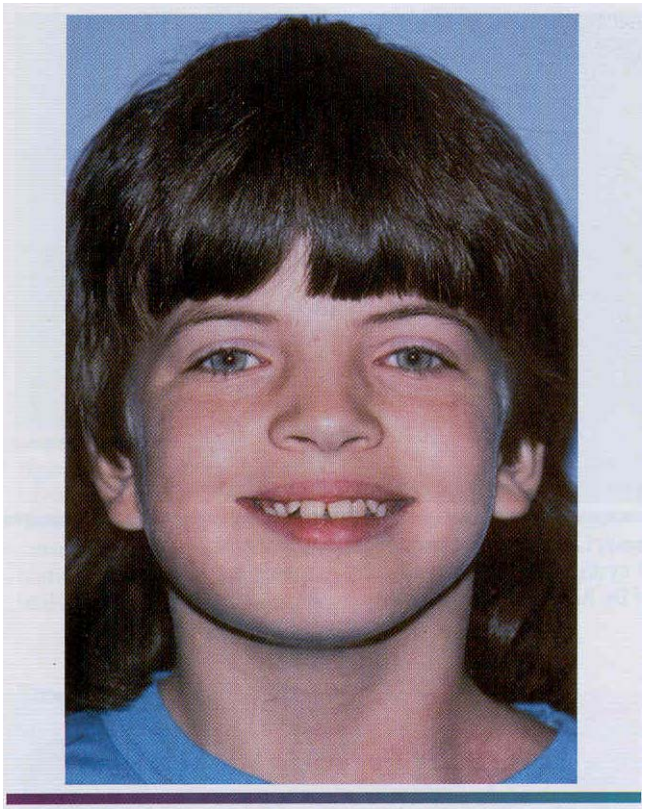

Figure 15-21 • Nevoid basal cell carcinoma syndrome. This 1-year-old girl shows hypertelorism and mandibular swelling. (Courtesy of Dr. Richard DeChamplain.)

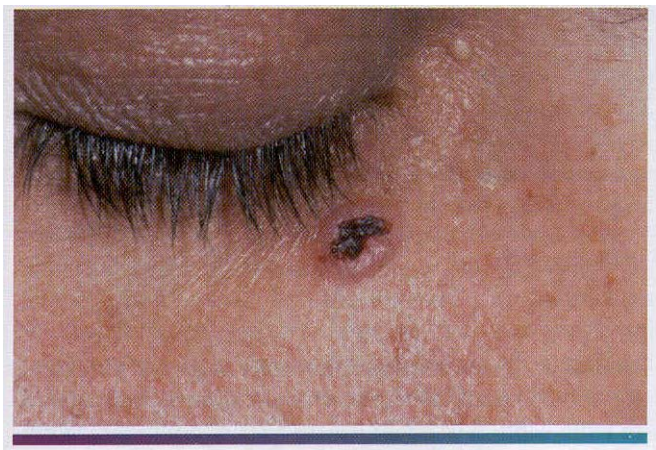

Figure 15-22 • Nevoid basal call carcinoma syndrome. An ulcerating basal cell carcinoma is present on the upper face.

Palmar and plantar pits are present in about 65% of patients (Figure 15-23). These punctate lesions represent a localized retardation of the maturation of basal epithelial cells. Basal cell carcinomas may develop at the base of the pits.

Ovarian fibromas have been reported in 14% to 24% of women with this syndrome. A number of other tumors also have been reported to occur with lesser frequency. These

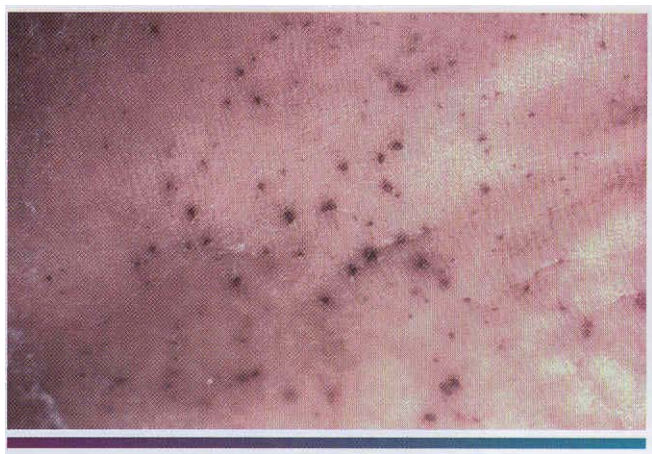

Figure 15-23 • Nevoid basal cell carcinoma syndrome. Plantar pits.

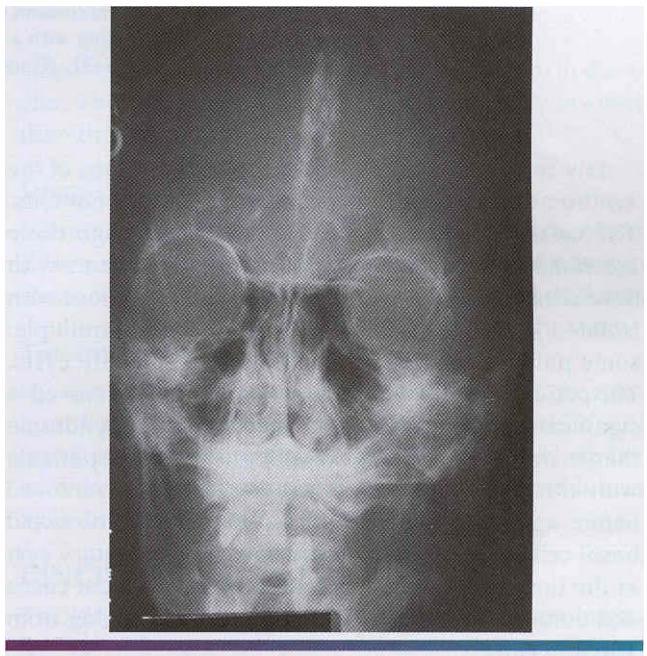

Figure 15-24 • Nevoid basal cell carcinoma syndrome. Anteroposterior skull film showing calcification of the falx cerebri. (Courtesy of Dr. Ramesh Narang.)

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. 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) imaging, is a common finding and is present in most affected patients (Figure 15-24).

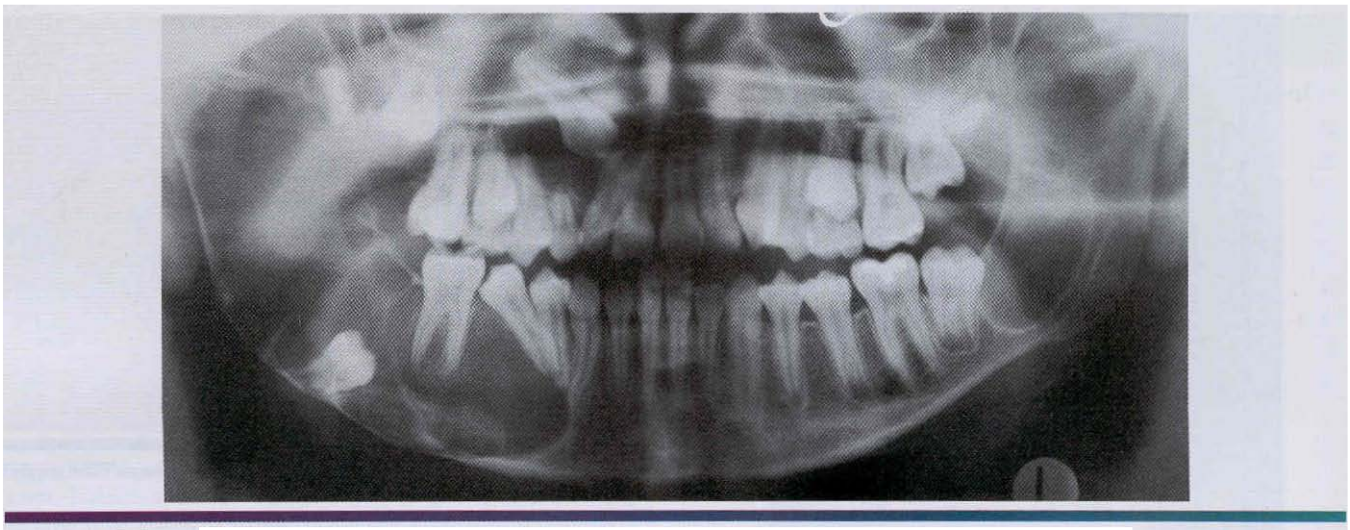

Figure 15-25 • Nevoid basal cell carcinoma syndrome. Large cysts are present in the right and left mandibular molar regions, together with a smaller cyst involving the right maxillary canine in the same patient shown in Figure 15-21. (Courtesy of Dr. Richard DeChamplain.)

law cysts are one of the most constant features of the syndrome and are present in at least 75% of the patients. The cysts are odontogenic keratocysts, although there are some differences between the cysts in patients with nevoid basal cell carcinoma syndrome and in those with isolated keratocysts. The cysts are frequently multiple; **some patients have had as many as ten separate cysts.** The patient's age when the first keratocyst is removed is significantly younger in those affected by this syndrome than in those with isolated keratocysts. For most patients with this syndrome. their first keratocyst 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 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 kcratocysts. The cysts in patients with this syndrome are often associated with the crowns of unerupted teeth; on radiographs they may mimic dentigerous cysts (Figure 15-25).

Histopathologic Features

The cysts in the nevoid basal cell carcinoma syndrome histopathologically are invariably odontogenic keratocysts. The keratocysts in patients with this syndrome tend to have more satellite cysts. solid islands of epithelial proliferation. and odontogenic epithelial rests within the fibrous capsule than do isolated keratocysts (Figure 15-26l. Foci of calcification also appear to be more

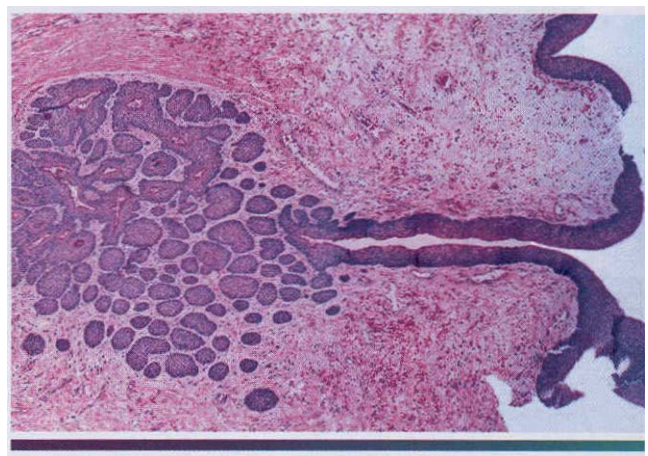

Figure 15-26 • Nevoid basal cell carcinoma syndrome. Odontogenic keratocyst showing numerous odontogenic epithelial rests in the cyst wall.

common. These features, however. are not diagnostic for nevoid basal cell carcinoma syndrome because they may be seen in isolated keratocysts. Odontogenic keratocysts **associated with this syndrome have been shown** to demonstrate overexpression of p5J and cyclin Dl (bel- L) 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.

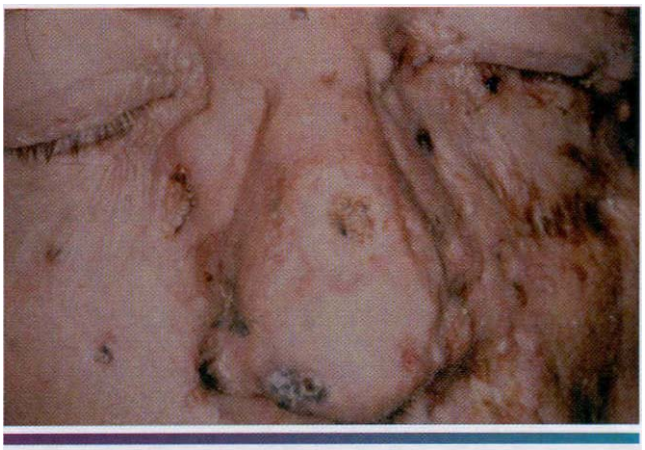

Figure 15·27 • Nevoid basal cell carcinoma syndrome. This 52-year-old man had more than 100 basal cell carcinomas removed from his face over a 30-year period. Several basal cell carcinomas are present in this photograph. The lesion at the inner canthus of the left eye was deeply invasive and was eventually fatal as a result of brain invasion.

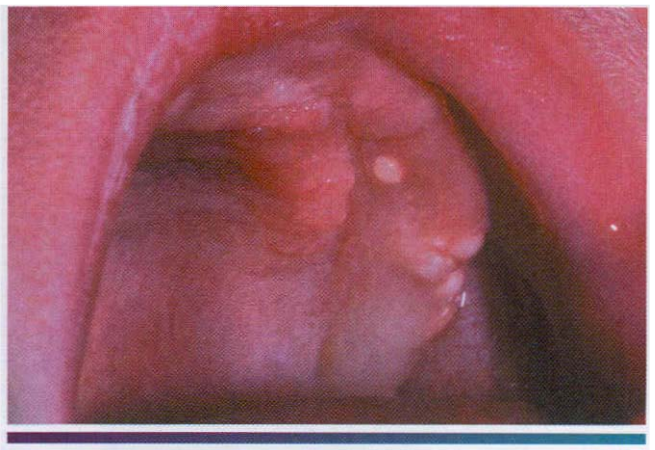

Figure 15-28 • Gingival cyst of the newborn. Multiple whitish papules on the alveolar ridge of a newborn infant.

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 (Figure 15-27). The jaw cysts are treated by enucleation. 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 this syndrome is also relatively common. Geneticcounseling 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 Bohns nodules) are also found in the midline of the palate or laterally on the hard and soft palate (see page 25).

Clinical Features

Gingival cysts of the newborn appear as small, usually multiple whitish papules on the mucosa overlying the alveolar processes of neonates (Figure 15-28). The individual cysts are usually no more than 2 to 3 mm in diameter. The maxillary alveolus is more commonly involved than the mandibular.

Histopathologic Features

Examination of an intact gingival cyst of the newborn shows a thin, flattened epithelial lining with a parakeratotic 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 arc 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 arc most commonly

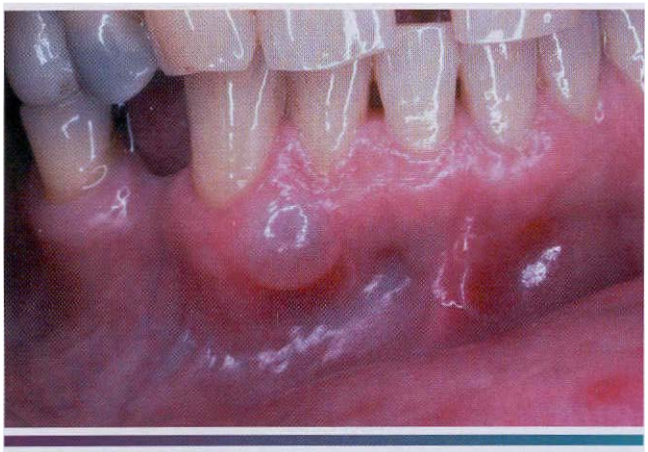

Figure 15-29 • Gingival cyst of the adult. Tense, fluid-filled swelling on the facial gingiva.

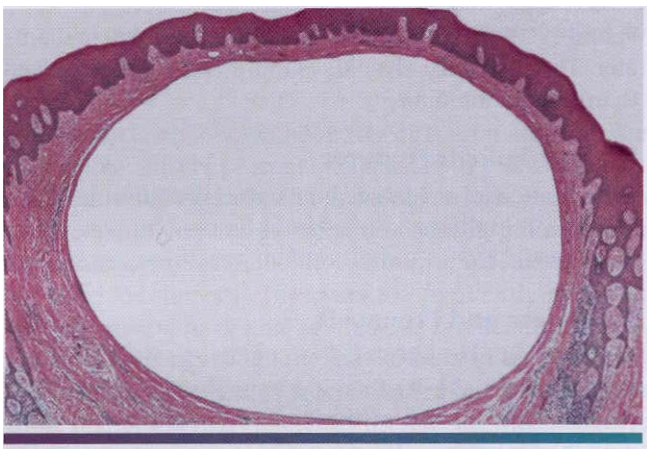

Figure 15-30. Gingival cyst of the adult. Low-power photomicrograph showing a thin-walled cyst in the gingival soft tissue.

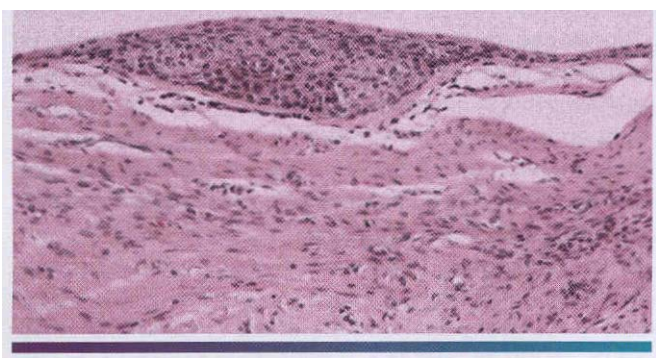

Figure 15-31 • Gingival cyst of the adult. High-power photomicrograph showing a plaquelike thickening of the epithelial lining. Note the focal clear cells.

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.

Clinically, the cysts appear as painless, domelike swellings, usually less than 0.5 cm in diameter, although rarely they may be somewhat larger (Figure 15-29). They are often bluish or bluish-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 (Figures 15-30 and 15-31). 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.

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 116) and odontogenic keratocysts (see page 594). 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

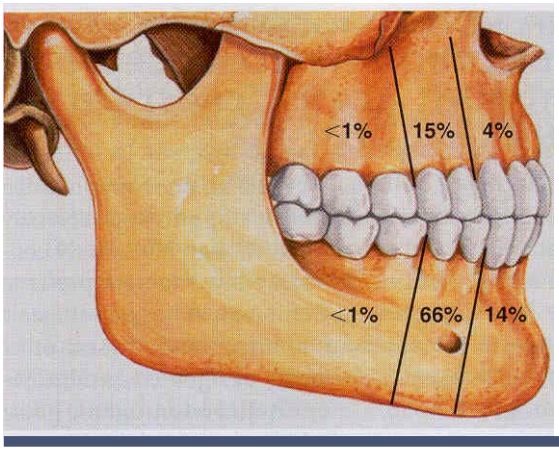

Figure 15-32 • Lateral periodontal cyst. Relative distribution of lateral periodontal cysts in the jaws.

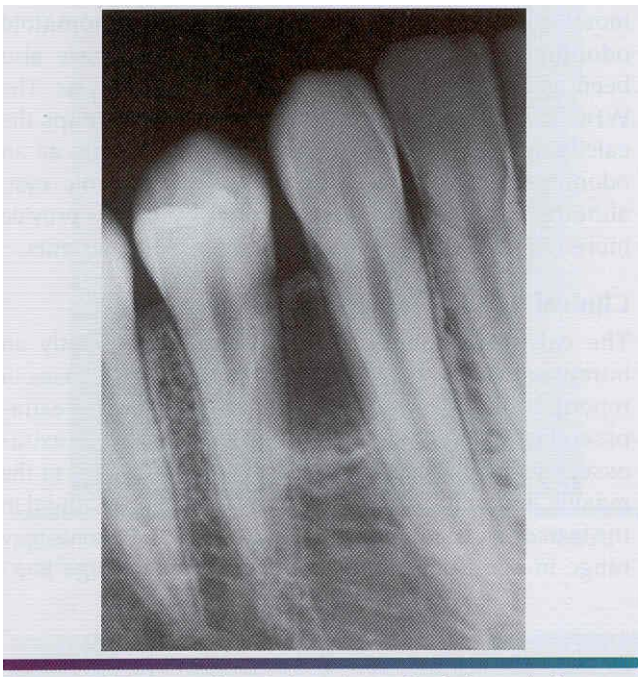

Figure 15-33 • Lateral periodontal cyst. Radiolucent lesion between the roots of a vital mandibular canine and first premolar.

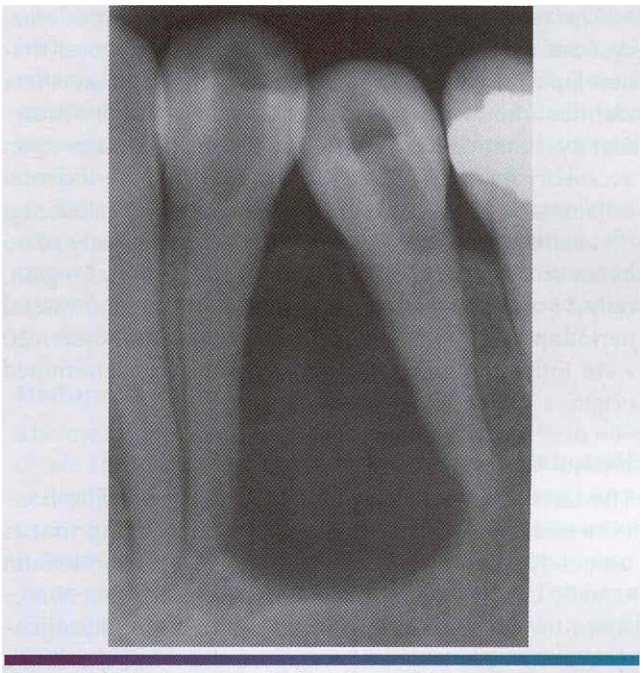

Figure 15-34 • Lateral periodontal cyst. A larger lesion causing root divergence.

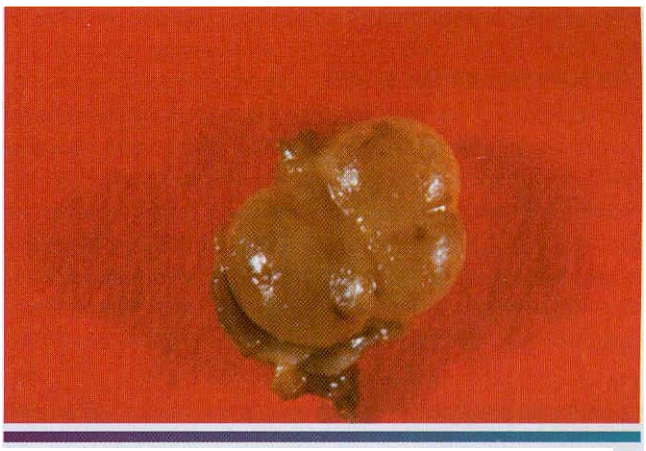

Figure 15-35 • Lateral periodontal cyst. Gross specimen of a botryoid variant. Microscopically, this grapelike cluster revealed three separate cavities.

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 (Figure 15-32).

Radiographically, the cyst 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 (Figures 15-33 and 15-34).

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 (Figure 15-35). 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 odontogenic keratocyst 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 Jl8). 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; 8 were odontogenic keratocysts, 20 were inflammatory cysts, and 5 were of undetermined origin.

Histopathologic Features

The lateral periodontal cyst has a thin, generally noninflamed, fibrous wall with an epithelial lining that is only 1 to 3 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 epithelium, which are composed chiefly of clear cells (Figure 15-36). Clear cell epithelial rests sometimes are seen within the fibrous wall.

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 (GORLIN CYST; DENTINOGENIC GHOST CEII TUMOR; CALCIFYING GHOST CEII ODONTOGENIC CYST)

The calcifying odontogenic cyst is an uncommon lesion that demonstrates considerable histopathologic diversity and variable clinical behavior. Although it is Widely considered to represent a cyst, some investigators prefer to e1asslfy it as a neoplasm. Some calcifying odontogenic cysts appear to represent nonneoplastic cysts; other members of this group, variously designated as dentinogenic ghost cell tumors or epithelial odontogenic ghost cell tumors, have no cystic features, may be infiltrative or even malignant, and are regarded as neoplasms.

In addition, the calcifying odontogenic cyst may be associated with other recognized odontogenic tumors, most commonly odontomas. However. adenomatoid odontogenic tumors and amcloblastomas have also been associated with calcifying odontogenic cysts. The WHO Classification of Odontogenic Tumors groups the calcifyi ng odontogenic cyst with all Its variants as an odontogenic tumor rather than an odontogenic cyst. although it admits that further experience may provide more reliable criteria for classification of the variants.

Clinical and Radiographic Features

The calcifying odontogenic cyst is predominantly an intraosseous lesion, although 13% to 30% of cases In reported series have appeared as peripheral (extraosseous) lesions. Both the intraosseous and extraosseous forms occur with about equal frequency in the maxilla and mandible. About 65% of cases are found in the incisor and canine areas (Figure 15-37). Patients may range in age from infant to elder. The mean age is 33

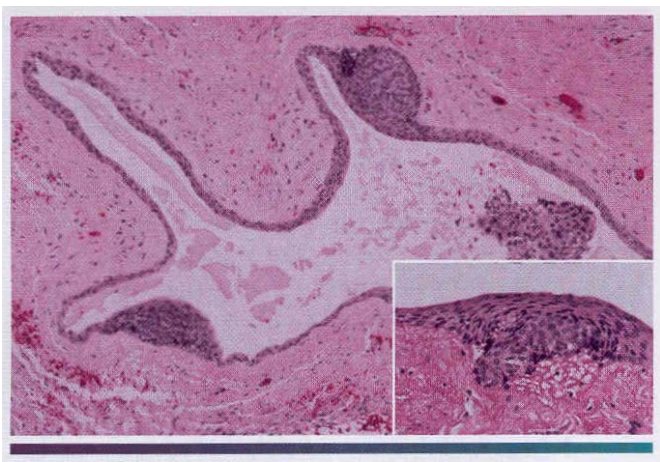

Figure 15-36 . lateral periodontal cyst. This photomicrograph shows a thin epithelial lining with focal nodular thickenings. These thickenings often show a swirling appearance of the cells *(inset)*.

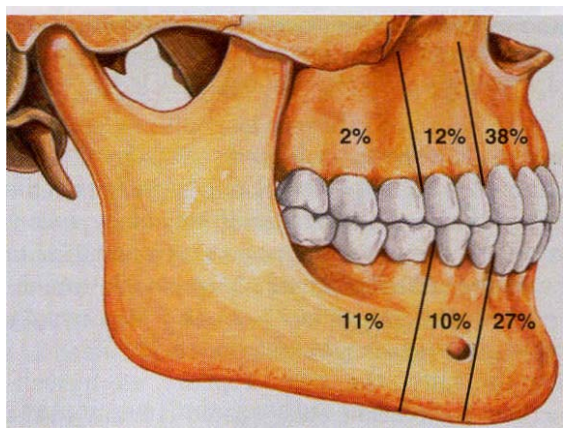

Figure 15·37 • Calcifying odontogenic cyst. Relative distribution of calcifying odontogenic cysts in the jaws.

years, and most cases are diagnosed in the second and third 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 rare neoplastic variants of the calcifying odontogenic cyst appear to occur in older patients; because of the paucity of reported cases, however, this may not be significant.

The central calcifying odontogenic cyst is usually a unilocular, well-defined radiolucency, although the lesion may occasionally appear multilocular. Radiopaque structures within the lesion, either irregular calcifications or toothlike densities, are present in about one third to one half of cases (Figure 15-38). 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 em in greatest diameter, but lesions as large as 12.0 em have been noted. Root resorption or divergence of adjacent teeth is seen with some frequency (Figure 15-39L

Extraosseous calcifying odontogenic cysts are localized sessile or pedunculated gingival masses with no distinctive clinical features (Figure 15-40). They can resemble common gingival fibromas, gingival cysts, or peripheral giant cell granulomas.

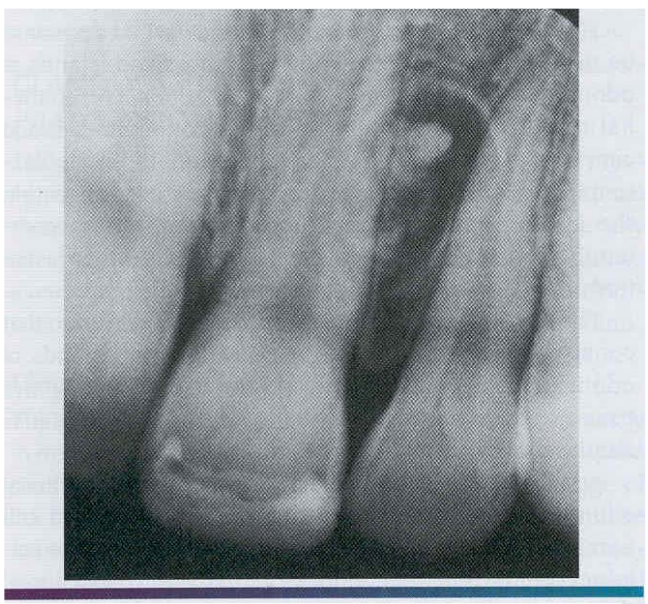

Figure 15-38 • Calcifying odontogenic cyst. Maxillary radiolucent lesion containing calcified structures.

Histopathologic Features

The cystic (nonneoplastic) forms comprise 86% to 98% of all calcifying odontogenic cysts in various reported series. These may occur both Intraosseously and extraosseously. Most commonly, a well-defined cystic lesion is found with a fibrous capsule and a lining of odontogenic epithelium of 4 to 10 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 (Figure 15-41).

The nature of the ghost cell change is controversial. Some believe that this change represents coagulative necrosis; 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

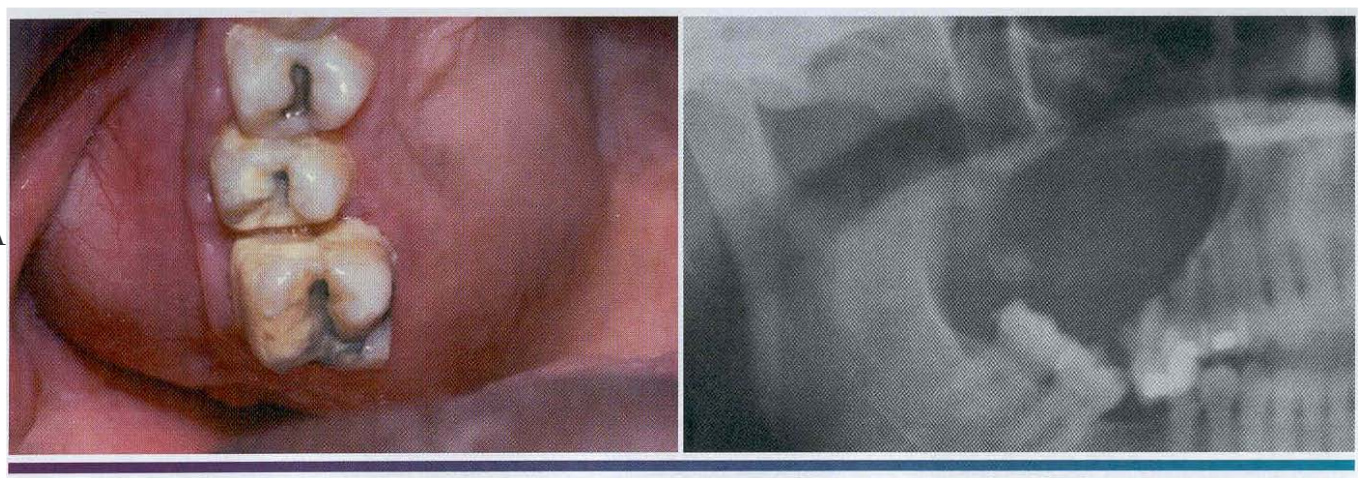

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Figure 15-39 • Calcifying odontogenic cyst. A, Expansion of the posterior maxillary alveolus caused by a large calcifying odontogenic cyst. B, Panoramic radiograph of the same patient showing a large radiolucency in the posterior maxilla. A small calcified structure is seen in the lower portion of the cyst. (Courtesy of Dr. Tom Brock.)

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 materia) 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 odontogenic epithelium on the adjacent mesenchymal tissue (Figure 15-42).

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.

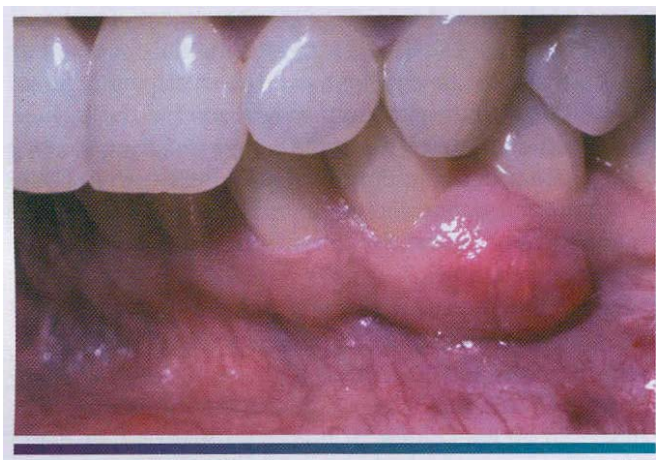

Figure 15-40 • Peripheral calcifying odontogenic cyst. Nodular mass of the mandibular facial gingiva.

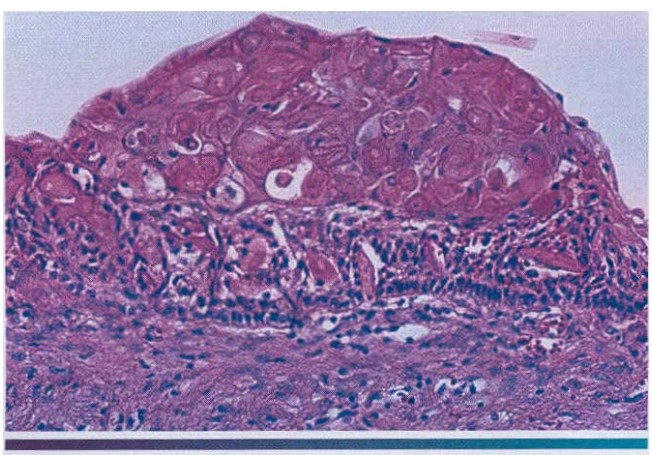

Figure 15·41 • Calcifying odontogenic cyst. The cyst lining shows ameloblastoma-like epithelial cells, with a columnar basal layer. Large eosinophilic ghost cells are present within the epithelial lining.

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 cystic calcifying odontogenic cysts are associated with odontomas. This variant is usually a unicystic lesion that shows the features of calcifying odontogenic cyst together with those of a small complex or compound odontoma.

Neoplastic (solid) calcifying odontogenic cysts are uncommon, accounting for 2% to 16% of all calcifying odontogenic cysts in reported series. These may occur intraosseously or extraosseously.

The extraosscous forms of the solid variant 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 intraosscous 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 juxtacpithelial dentinoid are present.

A small number of aggressive or malignant epithelial odontogenic ghost cell tumors (odontogenic ghost cell carcinoma) have been reported. These lesions have cellular pleomorphism and mitotic activity with invasion of the surrounding tissues.

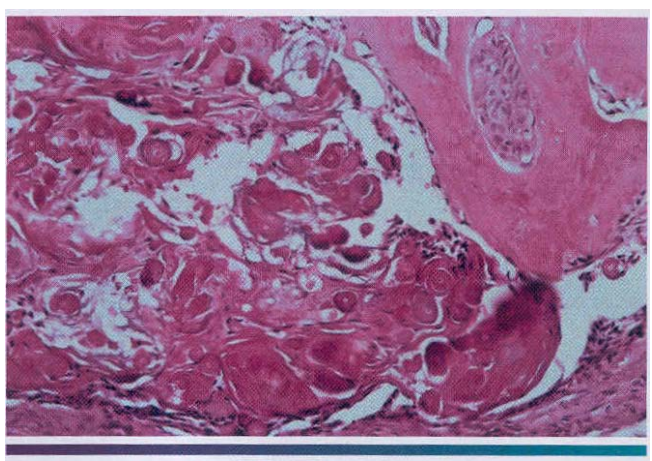

figure 15-42 • Calcifying odontogenic cyst. Eosinophilic dentinoid material is present adjacent to a sheet of ghost cells.

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. The peripheral neoplastic calcifying odontogenic cyst appears 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. odontogenic ghost cell carcinomas appear to have an unpredictable behavior. Recurrences are **common, and a few patients have died from either uncon**trolled 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 and recently recognized 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 49 years at the time of diagnosis; rarely does it occur before the age of 20. Nearly 85% 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 I ern in diameter to large destructive lesions thai 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 (Figure 15-43).

Radiographically, the lesion may appear as a uniloc-ular or. more commonly. a multilocular radiolucency. The margins of the radiolucency are usually well defined with **a sclerotic 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 and have an irregular and sometimes papillary surface (Figure 15-44). Occasionally. cilia may be noted. **Pools of mucicarminophilic material are often present** within the epithelium. Cuboidal cells usually line these pools. Mucous cells mayor may not be present within the epithelium. 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 422). In selected microscopic fields. the microscopic features may be identical. Examination of multiple sections, however, usually permits the differentialion of these **lesions.**

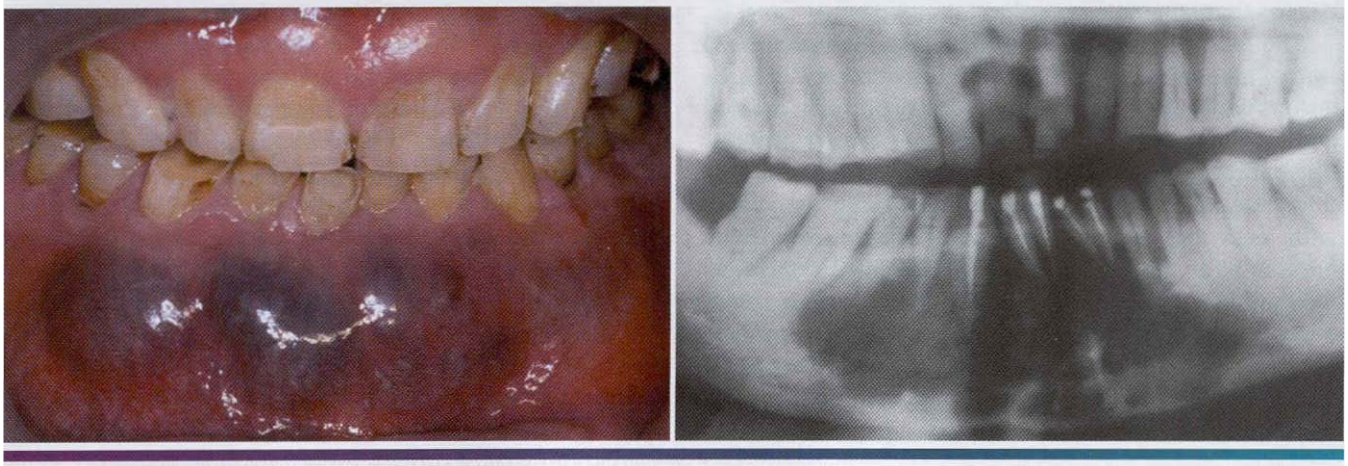

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Figure 15-43 • Glandular odontogenic cyst. A. Expansile lesion of the anterior mandible. B, The panoramic radiograph shows a large multilocular radiolucency. (Courtesy of Dr. Cheng-Chung Lin.]

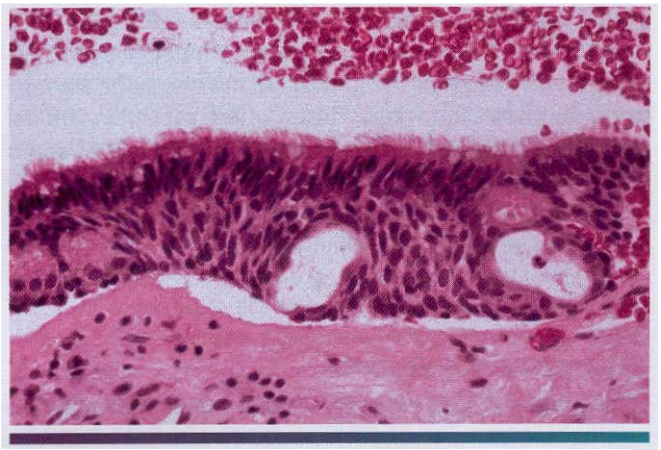

Figure 15-44 • Clandular odontogenic cyst. The cyst is lined by stratified squamous epithelium that exhibits surface columnar cells with cilia. Small microcysts and clusters of mucous cells are present.

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 30% or more of all cases. Because of its potentially aggressive nature and tendency for recurrence, some authors have advocated *en bloc* resection for many of these lesions.

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. The pathogenesis of this cyst is uncertain. 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. Some of these lesions have been associated with teeth that demonstrate buccal enamel extensions into the bifurcation area (see page 82). Such extensions may predispose these teeth to buccal pocket formation, which could then enlarge to form a cyst in response to pericoronitis. However, the distinction of paradental cysts from secondarily inflamed dentigerous cysts is difficult, if not impossible, in many instances (see page 590).

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 molar, which may be in the process of erupting.

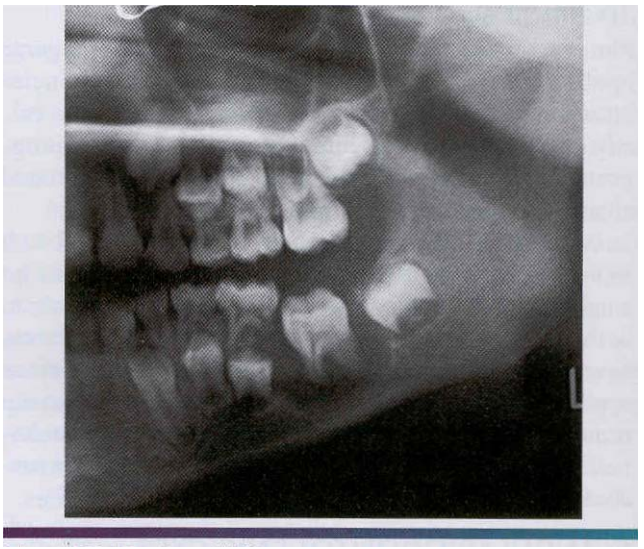

Figure 15-45 • Buccal bifurcation cyst. Well-circumscribed unilocular radiolucency superimposed on the roots of the mandibular first permanent molar. (Courtesy of Dr. Michael Pharoah.)

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 furcation and root area of the involved tooth (Figure 15-45). 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 (Figure 15-46). Many cases are associated with proliferative periostitis (see page 131) 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. One recent report described three cases that resolved without surgery—either with no treatment at all or by daily irrigation of the buccal pocket with saline and hydrogen peroxide.

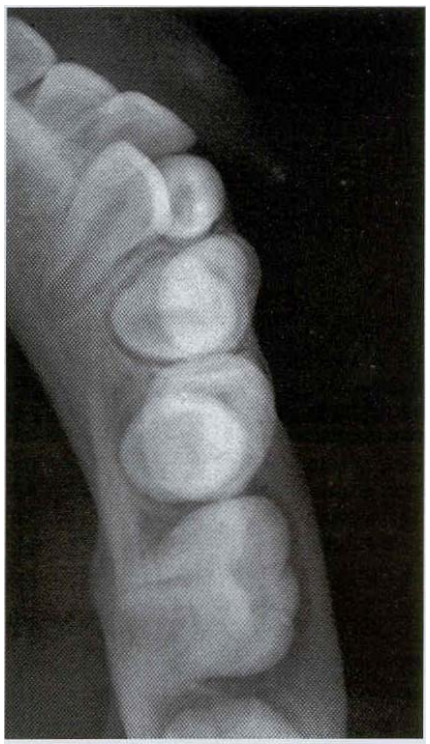

Figure 15-46 . **Buccal bifurcation cyst. Occlusal radiograph of the lesion shown in Figure 15-45. Note the lingual displacement of the roots of the first permanent molar. (Courtesy of Dr. Michael** Pharoah.)

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 422) also may arise from mucous cells lining a dentigerous cyst.

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 I% to 2% of all oral cavity carcinomas seen in some oral and maxillofacial pathology services may originate from odontogenic cysts. The pathogenesis of carci**nomas arising in odontogenic cysts is unknown. Occa**sionally, areas within the lining of odontogenic cysts histopathologically demonstrate varying degrees of epithelial dysplasia, and such changes likely give rise to **the carcinoma.**

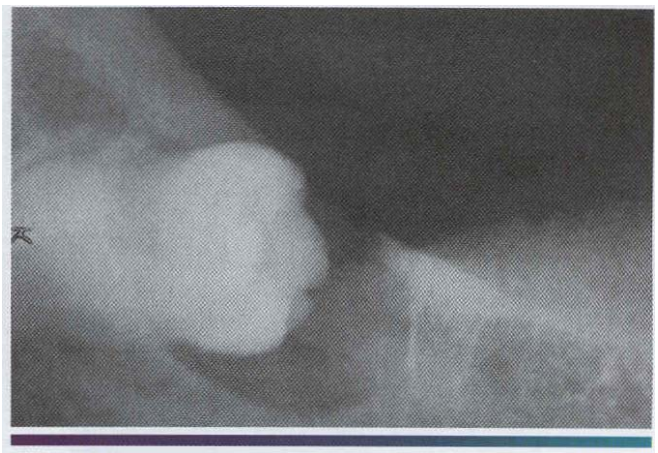

Figure 15-47 • **Carcinoma arising in a dentigerous cyst. Radiolucent lesion surrounding the crown of an impacted third molar in a 56-year-old woman. This was clinically considered to be a dentigerous cyst. (Courtesy of Dr. Richard Ziegler.)**

Clinical and Radiographic Features

Although carcinomas arising in cysts may be seen in **patients over a wide age range, they are encountered most** often in older patients. The mean reported age is 57 to 61 **years. This lesion is about twice as common in men as in women. Pain and swelling are the most common com**plaints. 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. A lesion consid*ered* to *be* a residual periapical cyst is apparently the **most common type associated with carcinomatous** transformation. In about 25% of reported cases, the car**cinoma appeared to have arisen in a dentigerous cyst** (Figure 15-47). In one patient, the carcinoma appeared **to originate in a lateral periodontal cyst.**

A few examples of carcinoma **arising in an odontogenic** keratocyst also have been documented (Figure 15-48). However, some reported examples do not appear to have **arisen in true** parakeratinized **odontogenic keratocysts,** but rather in orthokeratinized odontogenic cysts.

Histopathologic Features

Most carcinomas arising in cysts have histopathologically been well-differentiated squamous cell carcinomas. It is sometimes possible to identify a transition **from a normal-appearing cyst lining to invasive squa**mous cell carcinoma (Figures 15-49 and IS-SOl.

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 chemo**therapy. The prognosis is difficult to evaluate because

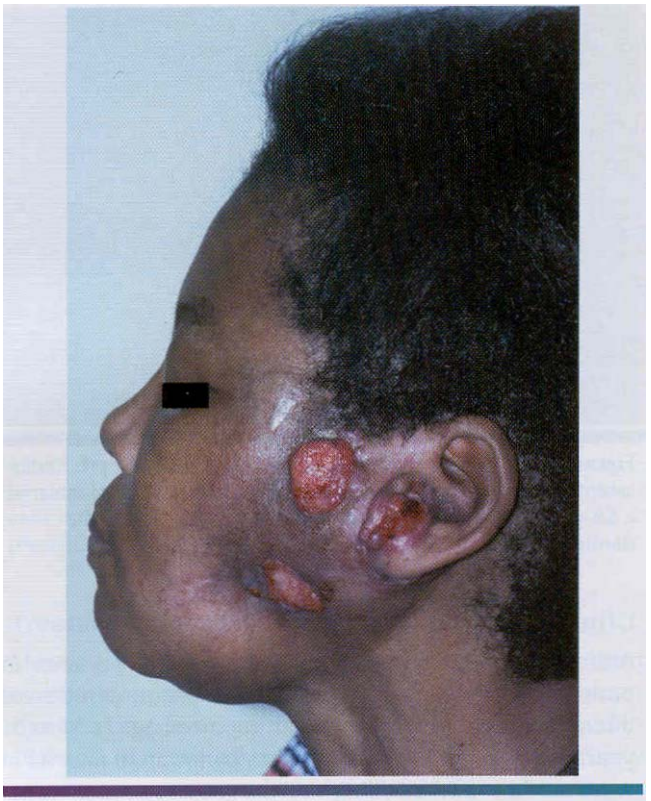

Figure 15-48 . Carcinoma arising in a cyst. There is a massive carcinoma of the mandible, with extension into the parotid gland. the face, and the base of the brain. Nineteen years previously, a large odontogenic keratocyst with areas of epithelial dysplasia had been removed from the ascending ramus. The patient had suffered multiple recurrences, with eventual change into invasive carcinoma.

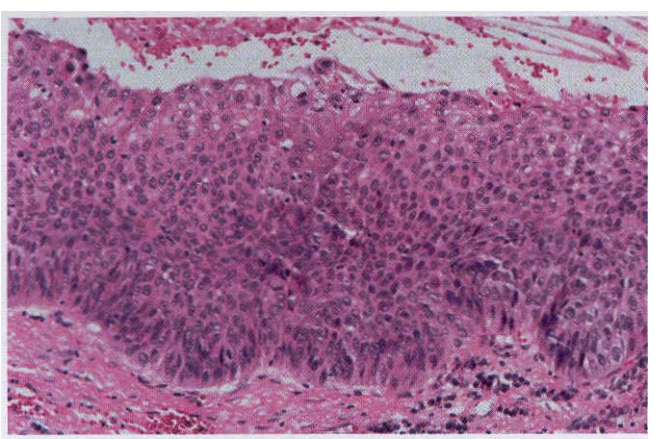

Figure 15-49 • Carcinoma arising in a cyst. High-power view of a dentigerous cyst from a 53-year-old man. The lining demonstrates full-thickness epithelial dysplasia.

most reports consist of isolated cases: often , the follow-up is inadequate. Several larger studies indicate an **approximate 50 % 5-year survival rate after treatment.** Metastases to regional lymph nodes have been demonstrated in a few cases.

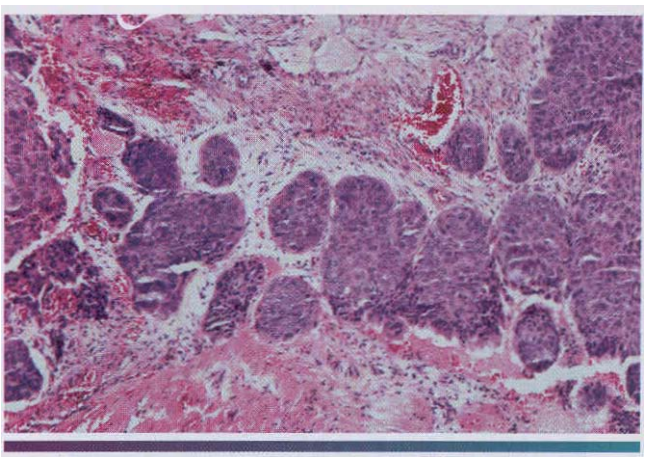

Figure 15-50 • Carcinoma arising in a cyst. Same case as Figure 15-49 showing islands of invasive epithelial cells in the cyst wall.

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.

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 tumor-like malformations (hamartomas).

Odontogenic tumors, like normal odontogenesis, **demonstrate varying inductive interactions between** odontogenic epithelium and odontogenic ccrornes-enchyme. 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 ecto-dermal 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 odonto-**genic epithelium and ectomesenchymal elements. Dental hard tissue mayor may not be formed in these lesions.

A third group, tumors of odontogenic ectornes-enchyrnc, 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 15-3 presents categories of odontogenic tumors modified from the 1992 WHO classification .

Box 15-3 *Classification of Odontogenic* n mlOrs

A. Tumors of odontogenic epithelium
   1. Ameloblastoma
      a. Malignant ameloblastoma
      b. Ameloblastic carcinoma
   2. Clear cell odontogenic carcinoma
   3. Adenomatoid odontogenic tumor"
   4. Calcifying epithelial odontogenic tumor
   5. Squamous odontogenic tumor

B. Mixed odontogenic tumors
   1. Ameloblastic fibroma
   2. Ameloblastic fibro-odontoma
   3. Ameloblastic fibrosarcoma
   4. Odontoameloblastoma
   5. Compound odontoma
   6. Complex odontoma

C. Tumors of odontogenic ectomesenchyme
   1. Odontogenic fibroma
   2. Granular cell odontogenic tumor
   3. Odontogenic myxoma
   4. Cementoblastoma

*Although the adenometold odontogenic tumor is included with [he mixed odontogenic tumors in the 1992 WHO classification. the authors prefer to include it with the epithelial odontogenic tumors in this chapter.

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 elinically significant odontogenic tumor. Its relative frequency equals the combined frequency of all other odontogenic tumors. exeluding 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 occur in three different clinicoradiographic situations. which deserve separate consideration because of differing therapeutic considerations and prognosis.

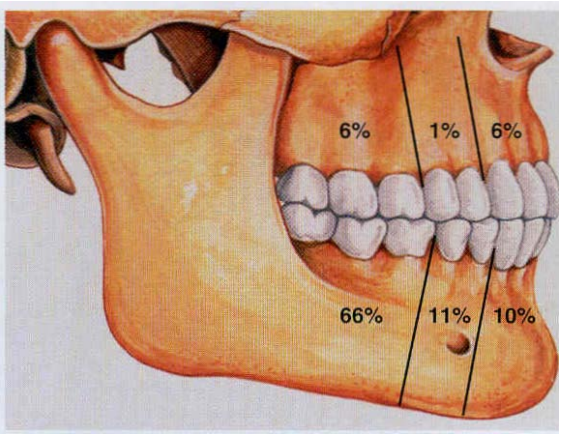

Figure 15-51 • Ameloblastoma. Relative distribution of ameloblastomas in the jaws.

These are:
1. Conventional solid or multIcystic (about 86% of all casesl.
2. Unicystic (about 13% of all cases), and
3. Peripheral (extraosseous) (about I% of all eases).

CONVENTIONAL SOLID OR MULTICYSTIC INTRAOSSEOUS AMELOBLASTOMA

Clinical and Radiographic Features

Conventional solid or multicystic intraosscous ameloblastoma is encountered in patients over a wide age range. It is rare in children younger than age 10and 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 gender predilection. Some studies indicate a greater frequency in blacks; others show no racial predilection. About 85% of conventional arncloblastornas occur in the mandible. most often in the molar-ascending ramus area. About IS% of arneloblastomas occur in the maxilla, usually in the posterior regions (Figure IS-51). 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 (Figures IS-52 and IS-53). If untreated. the lesion may grow slowly to massive or grotesque proportions (Figure I5-54l. Pain and paresthesia are uncommon. even with large tumors.

The most typical radiographic feature is that of a multilocular radiolucent lesion. The lesion is often described as havlng a "soap bubble" appearance when the radiolucent loculations are large and as *being* "honeycombed" when the loculations are small (Figures IS-55 to I5-57). 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,

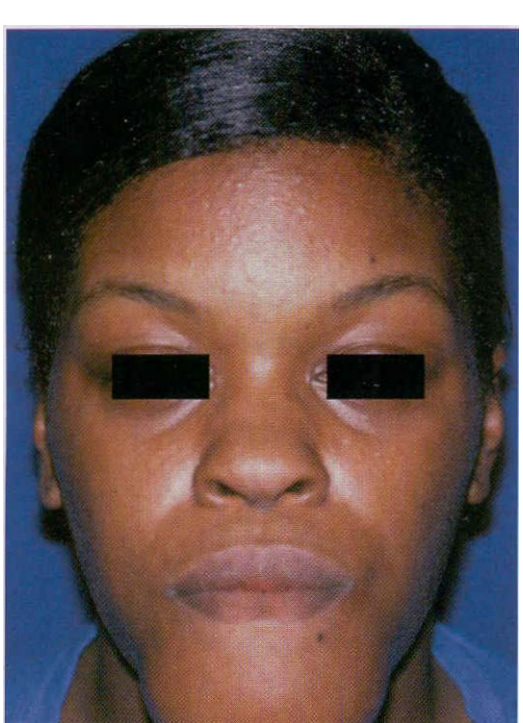

Figure 15-52 • Ameloblastoma. la rge expansile mass of the anterior mandible. (Courtesy of Dr. Michael Tabor.)

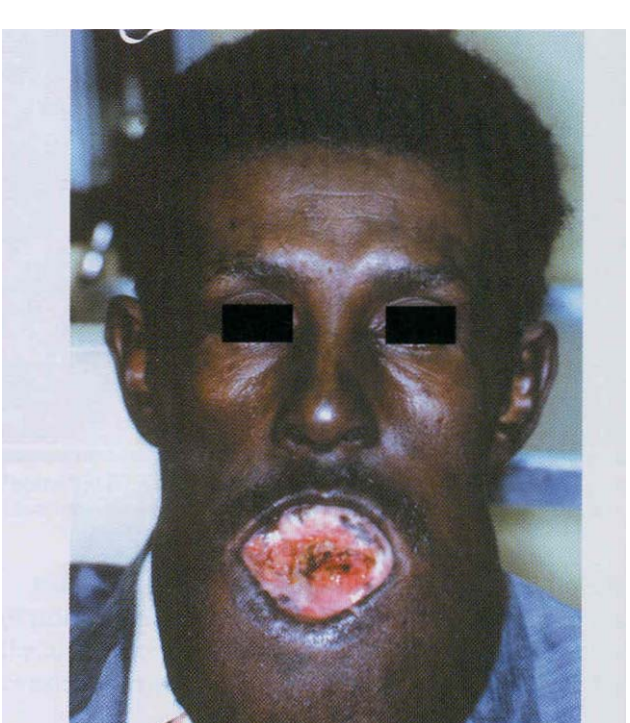

Figure 15-54 • Ameloblastoma. Massive tumor of the anterior mandible. (Courtesy of Dr. Ronald Baughman.)

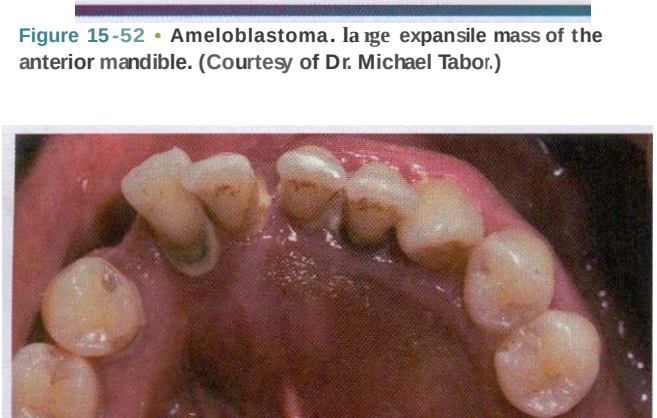

Figure 15-53 • Ameloblastoma. Prominent expansion of the lingual alveolus caused by a large ameloblastoma of the mandibular symphysis. The radiograph of the patient is shown in Figure IS-5Z

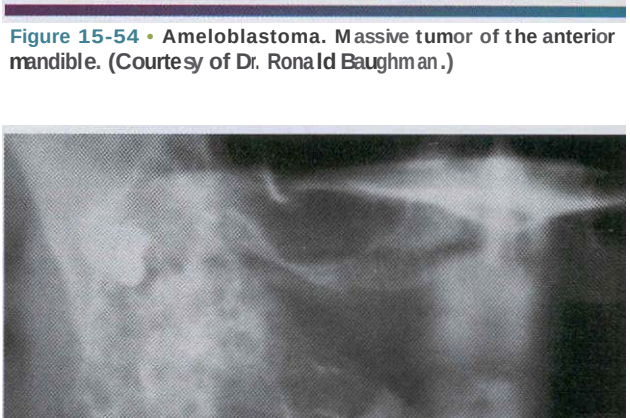

Figure 15-55 • Ameloblastoma. large multilocular lesion involving the mandibular angle and ascending ramus. The large loculations show the "soap bubble" appearance. An unerupted third molar has been displaced high into the ramus.

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 (Figure 15-58). 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 variety of odontogenic and nonodontogenic lesions may show similar radiographic features (see Appendix).

One form of amelobla stoma that does not have these characteristic features is the desmoplastic amelobiastorna, a variant that was initially documented in the literature in 1984 by Eversole and co-workers. The desmoplastic ameloblastoma has a marked predilection to occur in the anterior regions of the jaws. particularly the

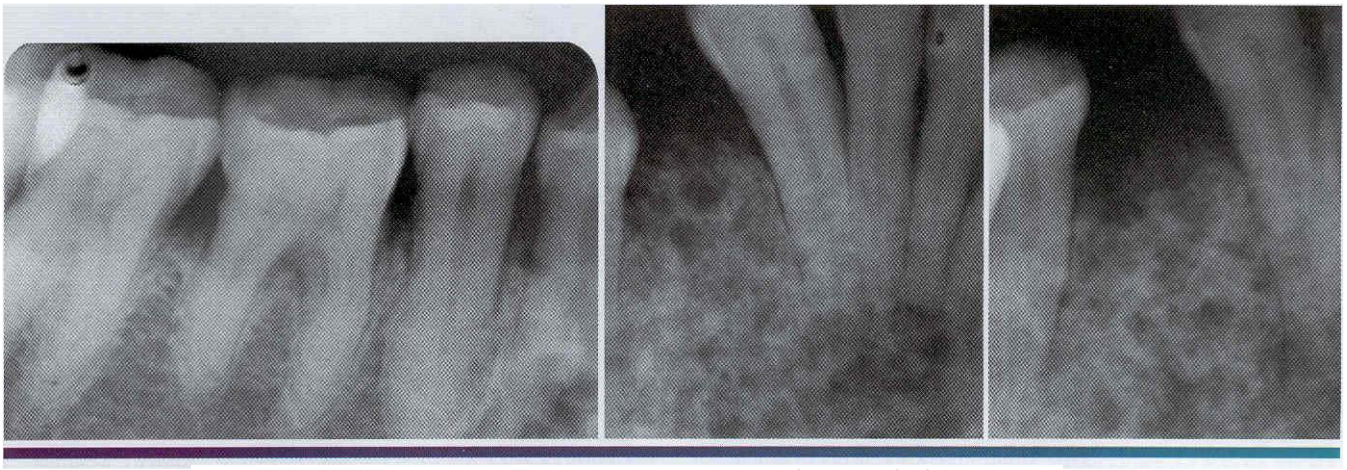

Figure 15-56 • Ameloblastoma. Periapical films showing the "honeycombed" appearance. (Courtesy of Dr. John Hann.)

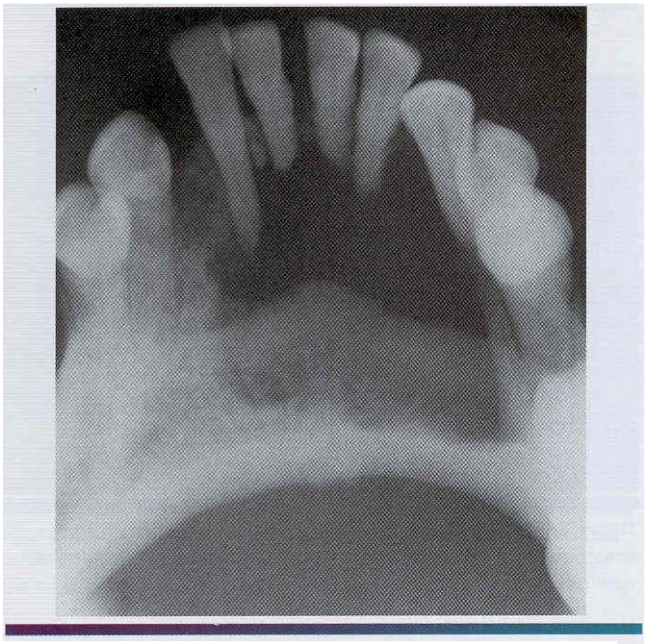

Figure 15-57 • Ameloblastoma. Destructive radiolucent lesion associated with root resorption of the anterior teeth. (Courtesy of Dr. Richard Brock.)

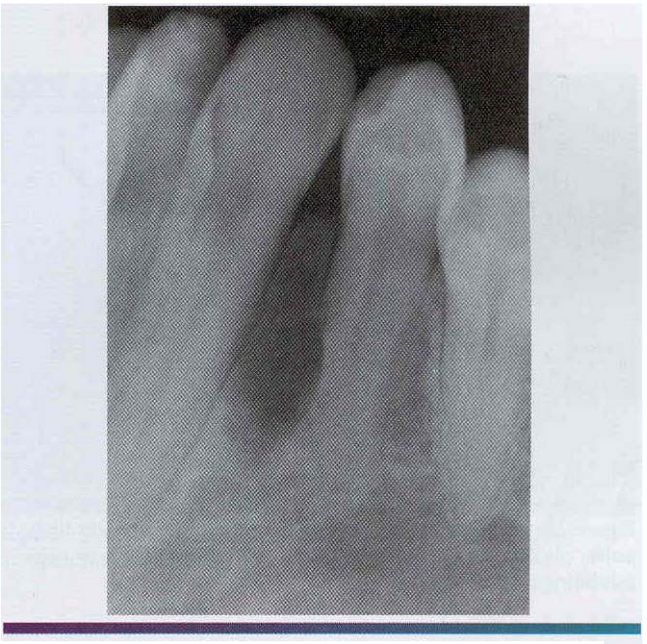

Figure 15-58 • Ameloblastoma. This small unilocular radiolucency lesion could easily be mistaken for a lateral periodontal cyst. (Courtesy of Dr. Tony Traynham]

maxilla. Radiographically, this type seldom suggests the diagnosis of ameloblastoma and usually resembles a fibro-osseous lesion because of its mixed radiolucent and radiopaque appearance (Figure 15-59). 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.

Histopathologic Features

Conventional solid or multicystic intraosscous 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 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.

Folltcular pattern. The follicular histopathologic pattern is the most common and recognizable. Islands of

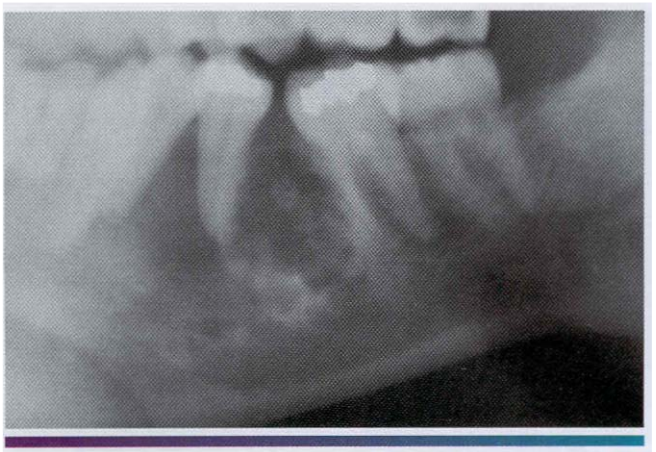

Figure 15-59 • Desmoplastic ameloblastoma. Large irregular radiolucency demonstrating focal radiopacities. (Courtesy of Dr. Gary P. Schopfer}

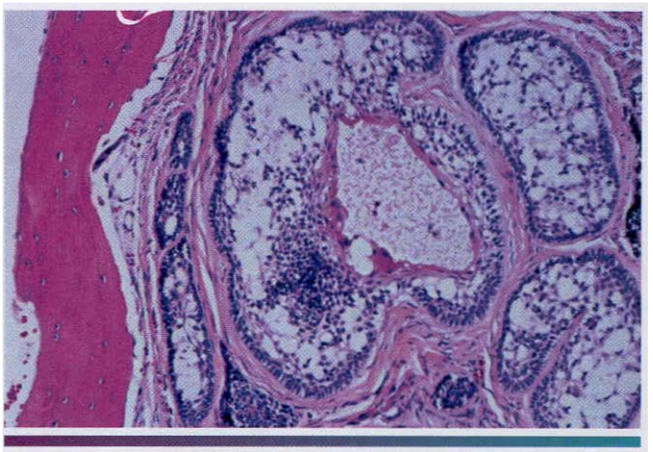

Figure 15-60 • Ameloblastoma (follicular pattern). Multiple islands of odontogenic epithelium demonstrating peripheral columnar differentiation with reverse polarization. The central zones resemble stellate reticulum and exhibit foci of cystic degeneration.

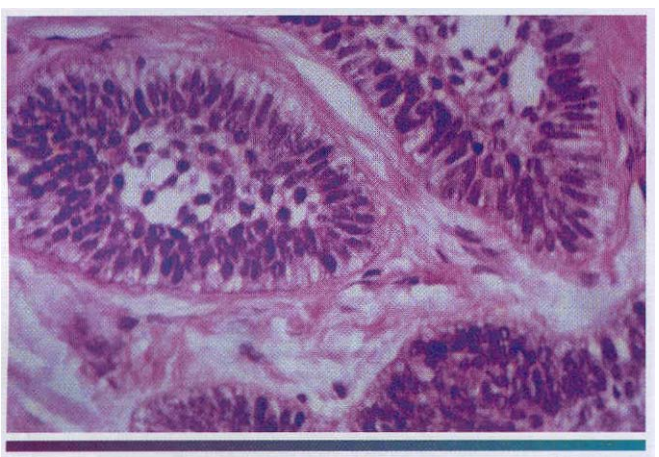

Figure 15-61 • Ameloblastoma (follicular pattern). This high-power photomicrograph highlights the peripheral columnar cells exhibiting reverse polarization.

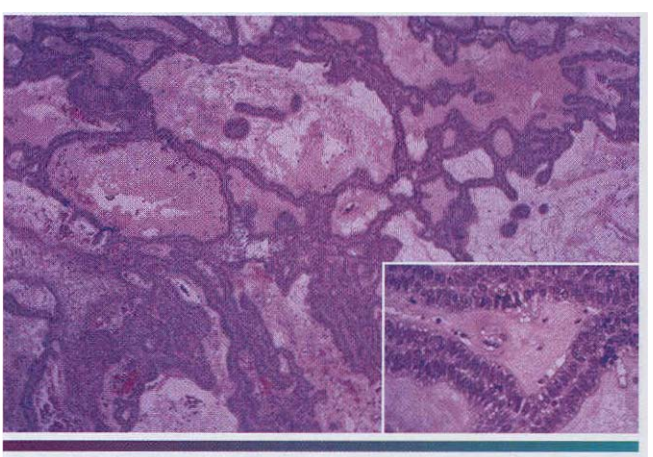

Figure 15-62 • Ameloblastoma (plexiform pattern). Large anastomosing cords of odontogenic epithelium. The high-power view *(inset)* reveals columnar cells with reverse polarization.

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 (Figures 15-60 and 15-611.

***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 arranged epithelial cells. The supporting stroma tends to be loosely arranged and vascular. CYSI 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 (Figure t5-62).

*Acanthomatous **patter".*** 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; histopathologicali y, however, such a lesion may be con-

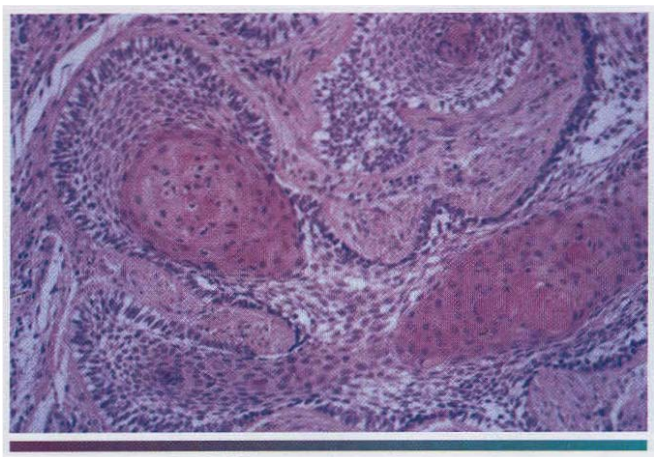

Figure 15-63 • **Ameloblastoma (acanthomatous pattern).** Islands of ameloblastoma demonstrating central squamous differentiation.

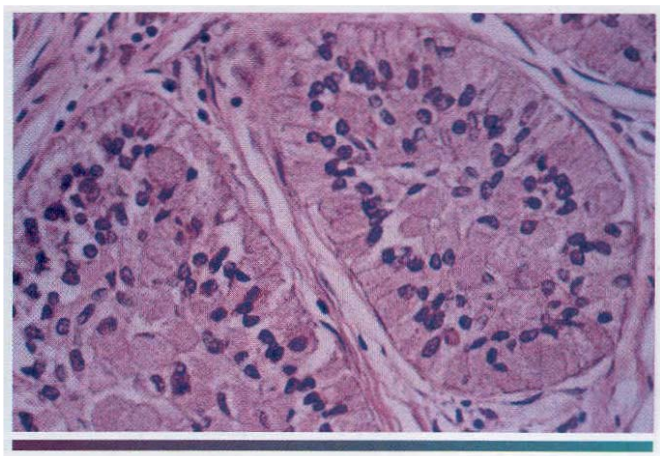

Figure 15-64 • **Ameloblastoma (granular cell variant).** Tumor islands exhibiting cells with prominent granular cytoplasm.

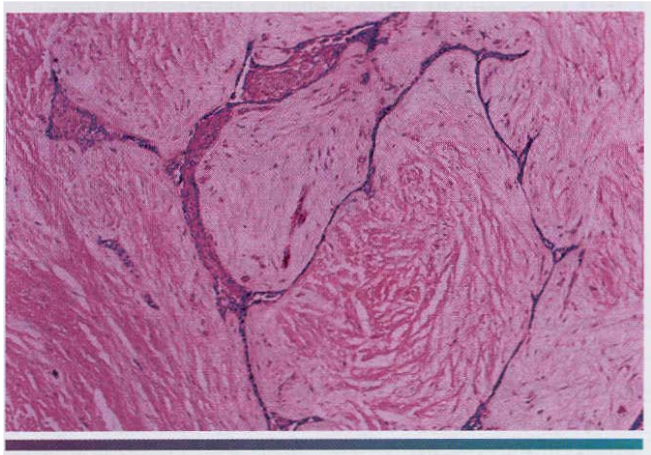

Figure 15-65 • **Ameloblastoma (desmoplastic variant).** Thin cords of ameloblastic epithelium within a dense fibrous connective tissue stroma.

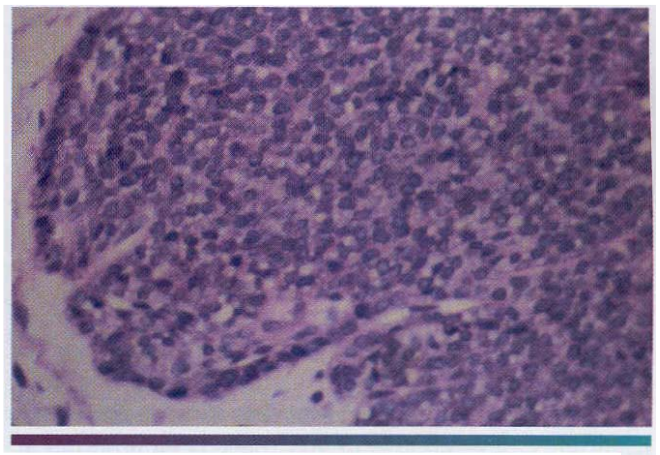

Figure 15-66 • **Ameloblastoma (basal cell variant).** Island of hyperchromatic basaloid cells.

fused with squamous cell carcinoma or squamous odontogenic tumor (Figure 15-63).

Granular ***cell patter".*** **Ameloblastomas may some**times 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 degener*ative* change in long-standing lesions. this variant has **been seen in young patients and in clinically aggressive tumors.** When **this granular cell change is extensive in** an ameloblastoma. the designation of granular cell **amelo blastoma** is appropriate (Figure 15-64).

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 **cytokinc known as** transforming growth **factor ß in asso**ciation with this lesion. suggesting that this may be responsible for the desmoplasia. Peripheral columnar ameloblast-like cells are inconspicuous about the epithelial islands (Figure 15-65).

B"s,,1cell 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 carci**noma 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 (Figure 15-66).

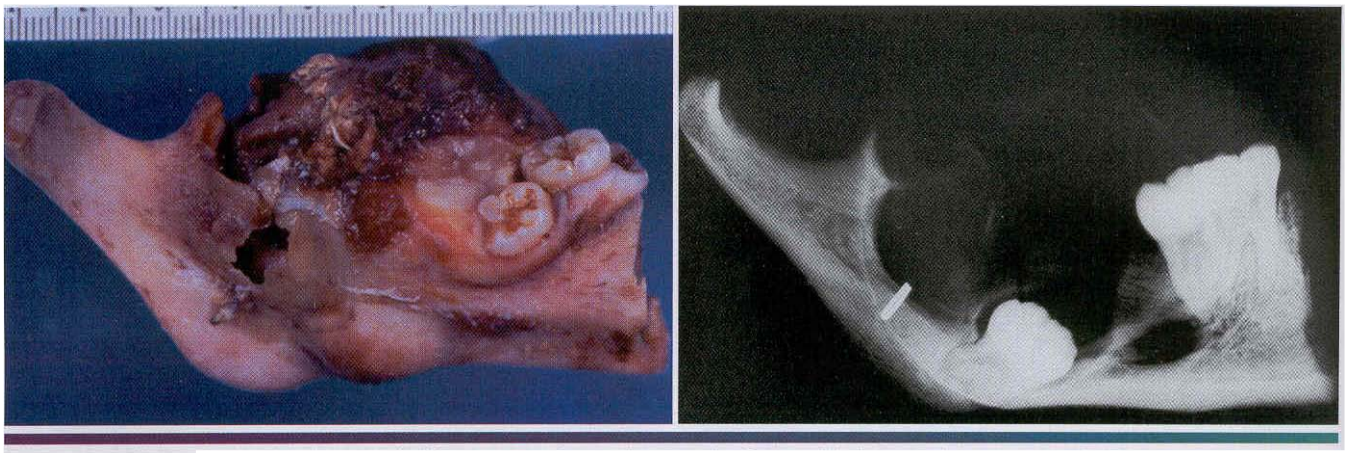

Figure 15-67 . Ameloblastoma. A, Cross photograph of a mandibular resection specimen. B, The radiograph of the specimen shows a large radiolucent defect associated with an inferiorly displaced third molar. (Courtesy of Dr. Mary Richardson.)

Treatment and Prognosis

Patients with conventional solid or multicystic intra-osseous ameloblastomas have been treated by a variety **of means. These range from simple enucleation and** curettage to *en bloc* resection (Figure 15-67). 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 iesion 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 clinicaliy manifest, and 5-year **disease-free periods do not indicate a cure.**

Marginai resection is the most wideiy used treatment, but recurrence rates of up to 15% have been reported after marginal or biock resection. Many surgeons advocate that the margin of the resection should be at least i.o 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. 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 secondary radiation-induced malignancy developing in a relatively young patient population.

The conventional ameloblastoma is a persistent, infil-trative neoplasm that may kill the patient by progressive **spread to involve vital structures. Most of these tumors, however, are not life-threatening lesions. Rarely, an ame-**loblastoma exhibits frank malignant behavior. These are discussed separately.

UNICYSTIC AMELOBLASTOMA

The unicystic ameloblastoma deserves separate consideration based on its clinical, radiographic, and pathologic features and its response to treatment. Unicystic ameloblastomas account for 10% to 15% of all intra-**osseous ameloblastomas in various studies. Whether the unicystic ameloblastoma originates *de novo* as a neo-**plasm 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 most often seen 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 (Figures 15-68 and 15-69), 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 arnelo-

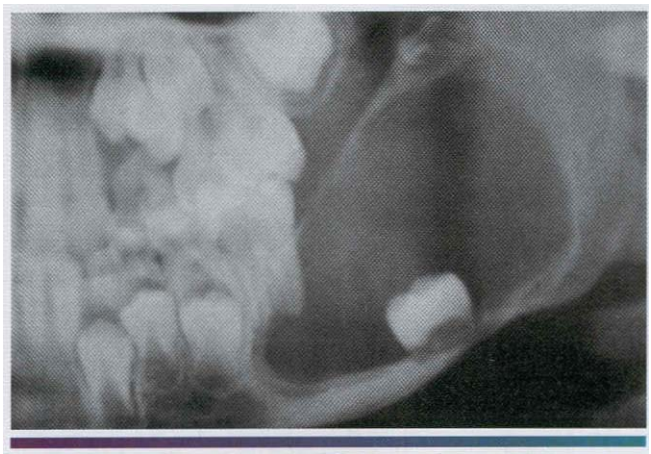

Figure 15-68 • Unicystic ameloblastoma. A large radiolucency in a 7-year-old boy with displacement of the developing second molar to the inferior border of the mandible. This was believed to be a large dentigerous cyst. (Courtesy of Dr. Larry Chewning.)

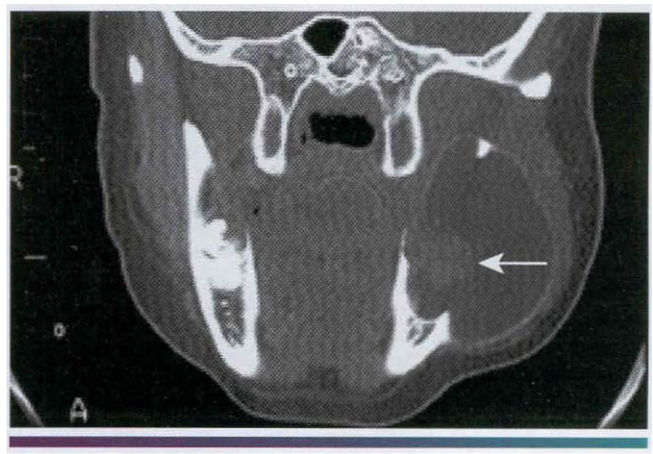

Figure 15-69 • Unicystic ameloblastoma (intraluminal plexiform type). Coronal computed tomography (CT) image that **shows a large cystic lesion with an intraluminal mass arising from** the cyst wall *(anuw)*.

blastoma 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 that consists totally or partially of ameloblastic epithelium. This demonstrates a basal layer of columnar or cuboidal cells with hyperchromatic nuclei that show reverse polarity and basilar cytoplasmic vacuolization {Figure 15-70>' The overlying epithelial cells are loosely cohesive and resemble stellate reticulum. This finding does not seem to be related to inflammatory edema.

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 arneloblastomas (Figure 15-71). These lesions are sometimes referred to as plexiform unicystic ameloblastomas. The intraluminal cellular proliferation does not always meet the strict histopathologic criteria for ameloblastoma. and this may be secondary to inflammation that nearly always accompanies this pattern. Typical amelobiastorna, however. may be found in other. less inflamed parts of the specimen.

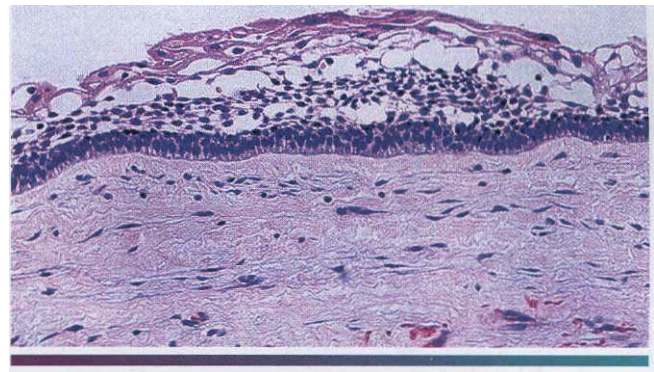

Figure 15-70 • Unicystic ameloblastoma (luminal type). The cyst is lined by ameloblastic epithelium showing a hyperchromatic. polarized basal layer. **The overlying epithelial cells are loosely cohesive and resemble stellate reticulum.**

In the third variant. known as mural unicvstic ameloblastoma. the fibrous wall of the cyst is infiltrated by typical follicular or plexiform ameloblastoma. The extent and depth of the ameloblastic intiltration may vary considerably. With any presumed unicystic ameloblastoma. multiple sections through many levels of the specimen are necessary to rule out the possibility *ot* mural invasion of tumor cells (Figure 15-72).

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 pre-

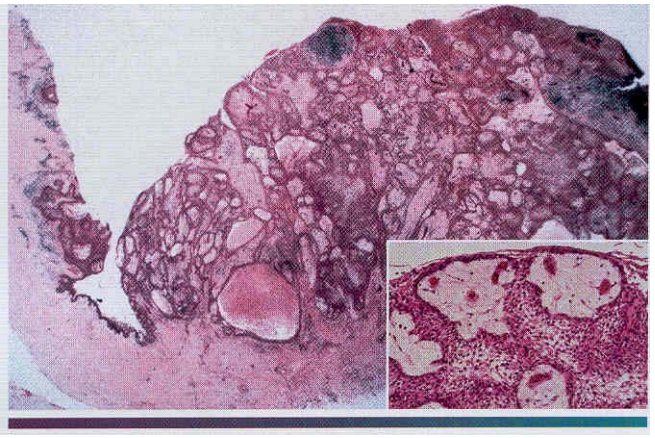

Figure 15-71 • Unicystic ameloblastoma (intraluminal plexiform type). Photomicrograph of the intraluminal mass arising from the cyst wall in the same patient shown in Figure 15-68. The inset shows the intraluminal mass at higher magnification.

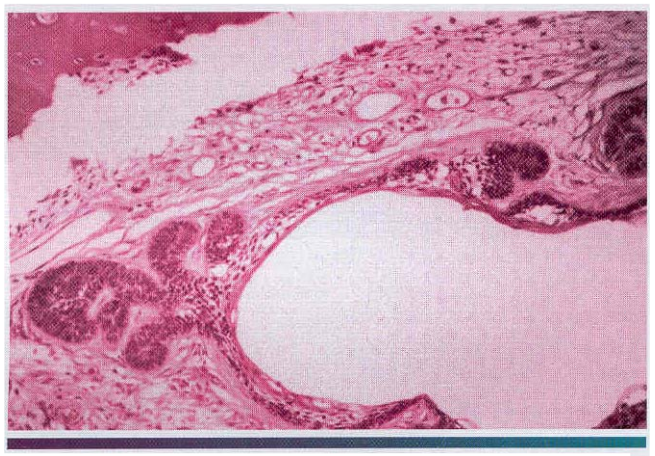

Figure 15-72 • Unicystic ameloblastoma (mural type). Islands of follicular ameloblastoma are infiltrating into the fibrous connective tissue wall.

sumed cyst. If the ameloblastic elements are confined to the lumen of the cyst with or without intraluminal tumor extension. 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, 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% have been reported after enucleation and curettage of unicystic ameloblastomas. This is considerably less than the 50% to 90% **recurrence rates noted after curettage of conventional solid and multicystic intraosseous ameloblastomas.**

PERIPHERAL (EXTRAOSSEOUS) AMEWBLASTOMA

The peripheral ameloblastoma is uncommon and accounts for about 1% 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.**

Clinical Features

The peripheral ameloblastoma is usually a painless, nonulcerated sessile or pedunculated gingival or alveolar mucosal lesion. The clinical features are nonspecific. and **most lesions are clinically considered to represent a** fibroma or pyogenic granuloma. Most examples are smaller than 1.5 em. but larger lesions have been reported (Figure 15-73). The tumor has been found in patients over 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 involve**ment does not occur. A few examples of a microscopi**cally identical lesion have been reported in the buccal **mucosa at some distance from the alveolar or gingival soft tissues.**

Hislopathologic Features

Peripheral ameloblastomas have islands of ameloblastic epithelium that occupy the lamina propria underneath the surface epithelium (Figure 15-74). 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. Whether this represents origin of the tumor from the basal layer of the epithelium or merging of the tumor with the surface epithelium has not **been ascertained.**

Basal cell carcinomas of the oral mucosa *have* been reported. but most authors consider them to represent 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.**

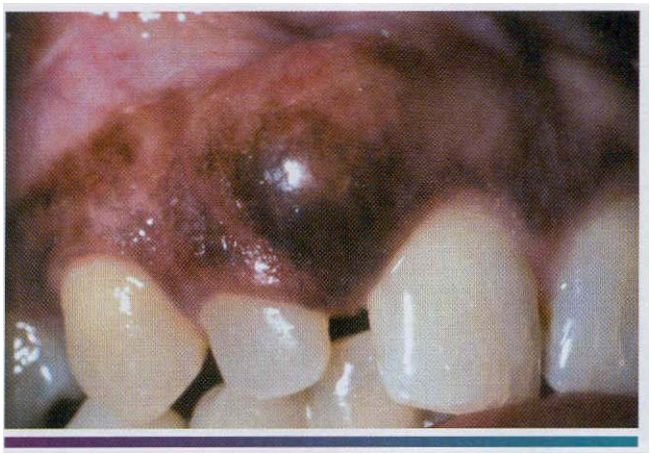

Figure 15-73 • Peripheral ameloblastoma. Sessile gingival mass. (Courtesy of Dr. Dean K. White.)

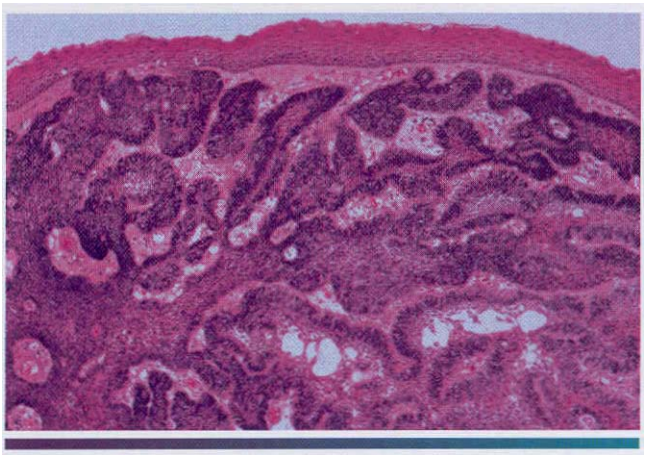

Figure 15-74 . Peripheral ameloblastoma. Interconnecting cords of ameloblastic epithelium filling the lamina propria.

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 ameloblastornas is difficult to determine but probably occurs in far less than 1% of all arnclobla srorna s.

The terminology for these lesions is somewhat controversial. The term malignant ameloblastoma should be used for a tumor that shows the histopathologic features of amelob lastoma. both in the primary tumor and in the metastatic deposits. 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. These lesions may follow a markedly aggressive local course. but metastases do not necessarily occur.

Clinical and Radiographic Features

Malignant arneloblastornas have been observed in patients who range in age from 4 to 75 years (mean age, 30 years). For patients with documented metastases. the interval between the initial treatment of the ameloblastoma and first evidence of metastasis varies from 1 to 30 years. In nearly one third of cases. metastases do not become apparent until 10 years after treatment of the primary tumor.

Metastases from arneloblastornas are most often found 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 ameloblastornas 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 (Figure J5-75).

Histopathologic Features

With malignant arncloblastomas, the primary jaw tumor and the metastatic deposits show no microscopic features that differ from those of arneloblastornas with a completely benign local course. With ameloblastic carcinomas. the metastatic deposits 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 (Figure 15-76). Necrosis in tumor islands and areas of dystrophic calcification may also be present.

Treatment and Prognosis

The prognosis of patients with malignant arneloblastornas 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 arneloblastic 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.

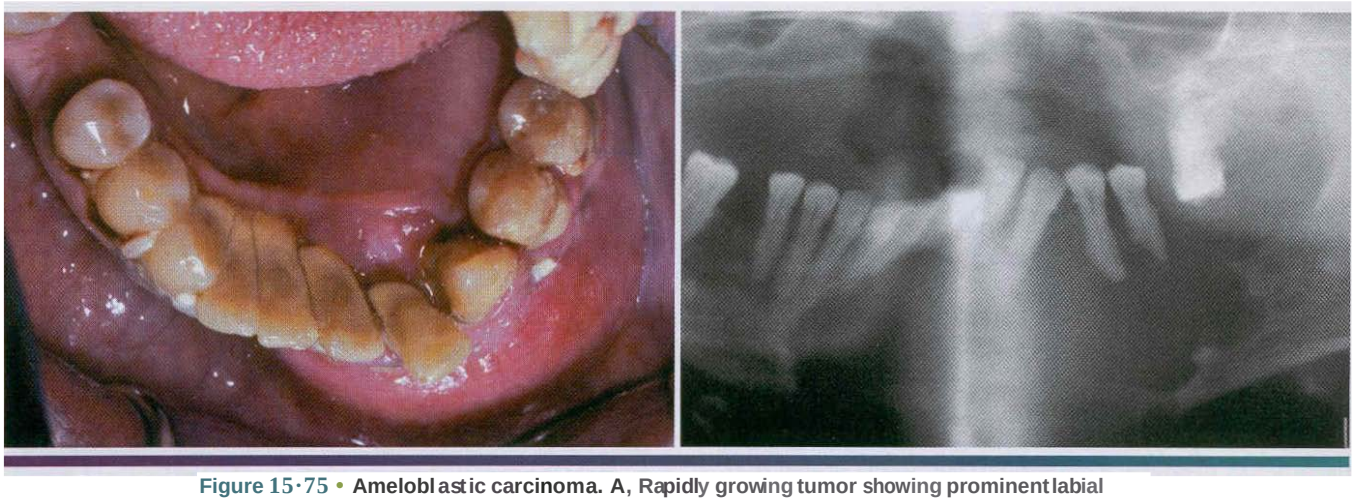

Figure 15·75 • Ameloblastic carcinoma. A, Rapidly growing tumor showing prominent labial expansion of the mandible in the incisor and premolar area. B, The panoramic radiograph shows irregular destruction of the mandible. (From Neville BW, Damm DD. White OK: *Coloratfas of clinical oral pathology*. ed 2, Baltimore. 1999. Williams & Wilkins.)

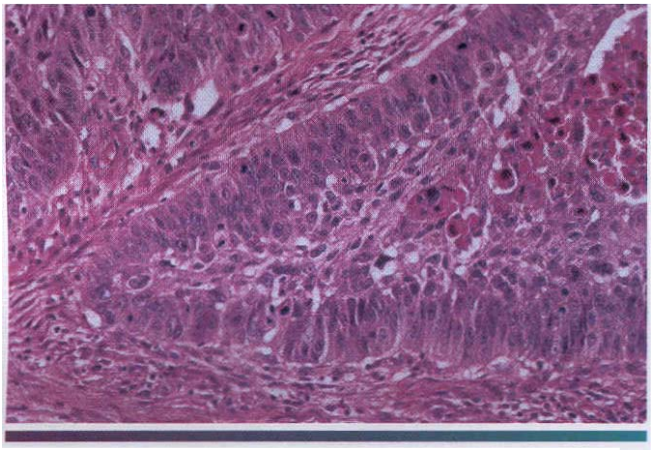

Figure 15-76 • Ameloblastic carcinoma. Ameloblastlc epithelium demonstrating hyperchromatism. pleomorphism, and numerous mitotic figures.

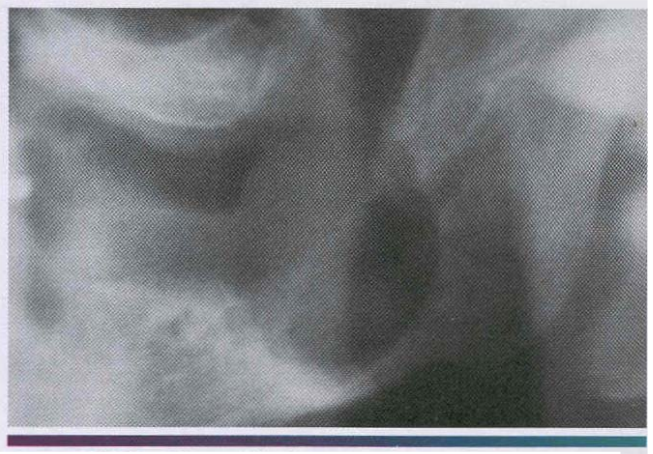

Figure 15-77 • Clear cell odontogenic carcinoma. Unilocular radiolucent defect.

CLEAR CELL ODONTOGENIC CARCINOMA (CLEAR CELL ODONTOGENIC TUMOR)

Clear cell odontogenic carcinoma is a rare jaw tumor that was first described in 1985. and to date. approximately 20 examples have been documented. The tumor appears to be of odontogenic origin. but its histogenesis **is uncertain. Histochemical and ultrastructural studies** show that the clear cells, which are the prominent feature of this neoplasm, have similarities to glycogen-rich presecretory ameloblasts.

Clinical and Radiographic Features

Because of the paucity of reported cases. there is little valid clinical information regarding the clear cell odontogenic carcinoma. **Most cases are diagnosed in patients** older than age 50, and both the mandible and maxilla have been involved. Some patients complain of pain and bony swelling; others arc relatively symptom-free.

Radiographically. the lesions appear as unilocular or multilocular radiolucencies. The margins of the radiolucency are often somewhat ill defined or irregular (Flgure 15-77).

Histopathologic Features

Several histopathologic patterns or combinations of patterns may be seen in the clear cell odontogenic carcinoma. **In some cases, the predominant pattern consists of** varying-sized nests of epithelial cells with a clear or faintly eosinophilic cytoplasm. Thin strands of hyalinized connective tissue separate the clear cell nests. The peripheral

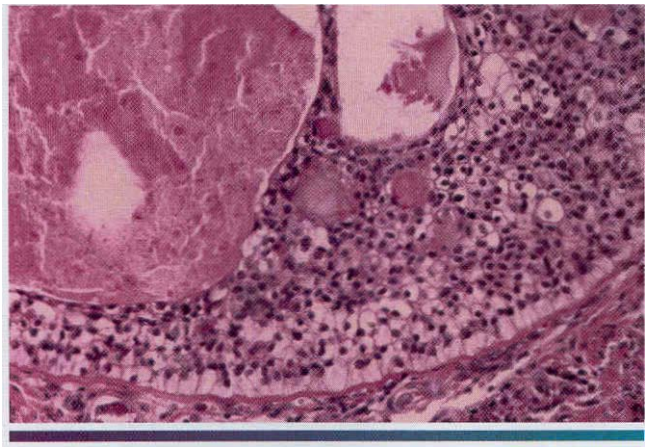

Figure 15-78 • **Clear cell odontogenic carcinoma. Tumor island demonstrating cells with a clear cytoplasm. Note the peripheral columnar differentiation.**

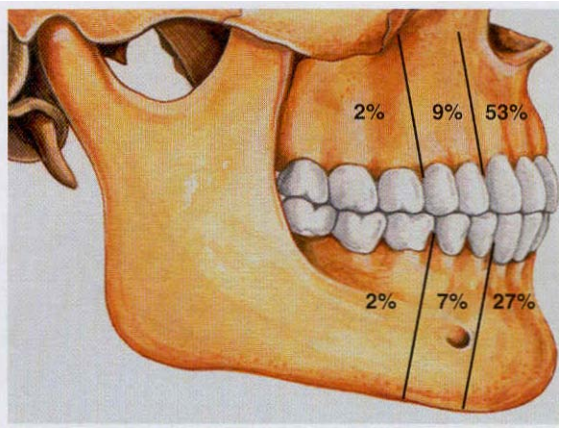

Figure 15-79 • **Adenomatoid odontogenic tumor. Relative distribution of adenomatoid odontogenic tumor in the jaws.**

cells of the clear cell islands may infrequently demonstrate palisading (Figure 15-78). In other instances, the dominant pattern consists of cords or small islands of hyperchromatic basaloid epithelial cells in a cellular fibrous stroma. The epithelial islands or cords contain varying numbers of clear cells.

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. Clear cell odontogenic carcinoma** 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. A clear cell variant of the calcifying epithelial odontogenic tumor may also present problems in the differential diagnosis. but amyloid stains should be negative in the case of clear cell odontogenic tumor. A metastatic clear cell neoplasm, such as a renal cell carcinoma. 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 tendency to recur. Most patients require** fairly radical surgery. Pulmonary or lymphatic metastases **may occur.**

ADENOMATOID ODONTOGENIC TUMOR

The adenomatoid odontogenic tumor represents 3% to 7% of all odontogenic tumors, and over 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 "adenoameloblasroma." its clinical features and biologic behavior indicate that it is a separate entity. Some authorities feel that, given the slow growth and circumscription of the lesion. it is best classified as a hamartoma rather than a true neoplasm. Although there is evidence that the tumor cells are derived from enamel organ epithelium, investigators have also suggested that the lesion arises from remnants of dental lamina.

In this text, the adenomatoid odontogenic tumor is classified as an epithelial odontogenic tumor; however, these lesions may infrequently produce dentinoid material, and rarely enamel matrix. Consequently, the WHO **classification of odontogenic lesions considers this process to represent a mixed odontogenic neoplasm, in** other words. an epithelial tumor with an inductive effect **on the odontogenic ectomesenchyme.**

Clinical and Radiographic Features

Adenomatoid odontogenic tumors are largely limited to younger patients. and two thirds of all cases are diagnosed when patients are 10to 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 (Figure 15-79). Females are affected about twice as often as males.

Most adenomatoid odontogenic tumors are relatively small. They seldom exceed 3.0 ern in greatest diameter, although a few large lesions have been reported. Peripheral (extraosseousl 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.

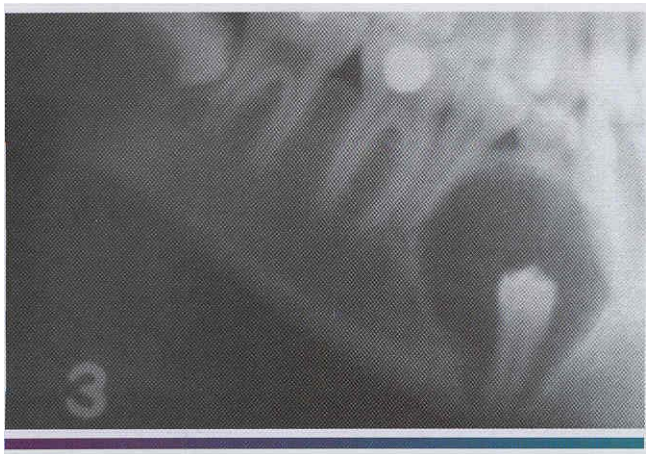

Figure 15-80 • **Adenomatoid odontogenic tumor (follicular type). Radiolucent lesion involving an unerupted mandibular first premolar. Fine snowflake calcifications are present in the radiolucent area. In contrast to the usual dentigerous cyst, the** radiclucency **extends almost to the apex of the tooth. (Courtesy of Dr. Tony Traynham.)**

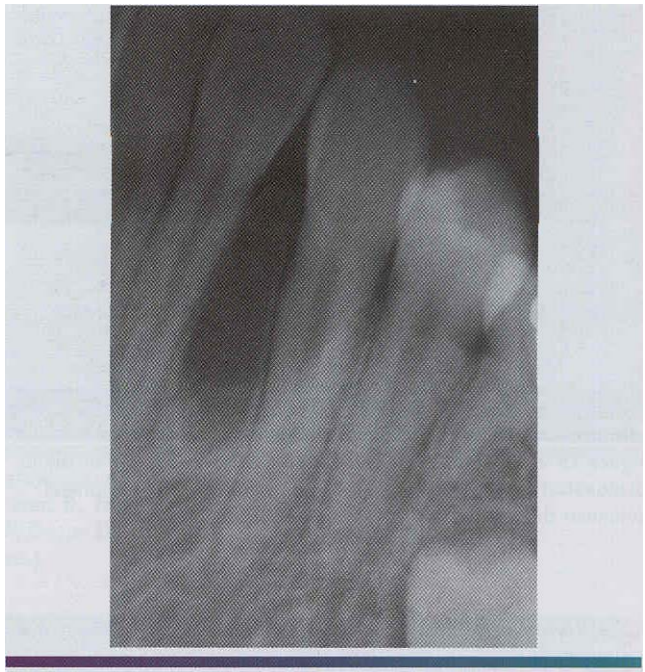

Figure 15-81 • **Adenomatoid odontogenic tumor** (extrafollicular type). **A small radiolucency is present between the roots of the lateral incisor and canine. (Courtesy of Dr. Ramesh Narang.)**

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 (Figure 15-80l.

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) (Figure 15-81i.

The lesion may appear completely radiolucent; often, however, it contains fine (snowflake) calcifications. This feature may be helpful in differentiating the adenomatoid odontogenic tumor from a dentigerous cyst.

Figure 15-82 • **Adenomatoid odontogenic tumor. A well-circumscribed solid mass can be seen enveloping the crown of this tooth.**

Histopathologic Features

The adenomatoid odontogenic tumor is a well-defined lesion that is usually surrounded by a thick, fibrous capsule (Figure 15-82l. When the lesion is bisected, the central portion of the tumor may be essentially solid or may show varying degrees of cystic change.

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 rosette like 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,

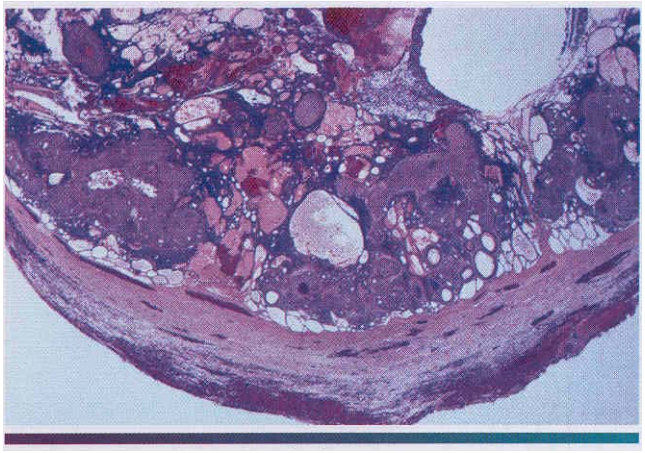

Figure 15-83 • Adenomatoid odontogenic tumor. Low-power view demonstrating a thick capsule surrounding the tumor.

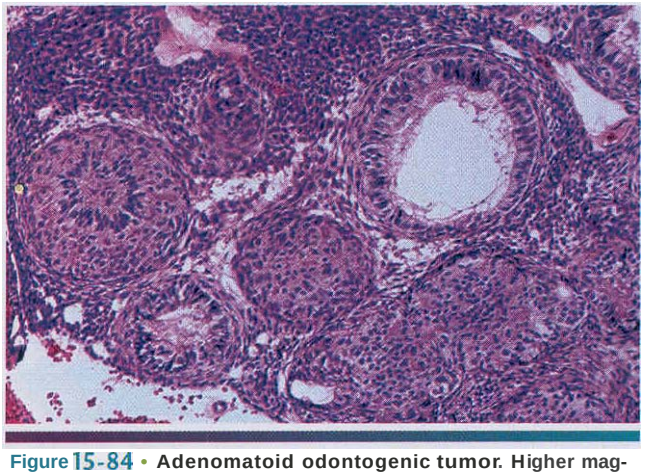

Figure 15-84 • Adenomatoid odontogenic tumor. Higher magnification showing the ductlike epithelial structures. The nuclei of the columnar calls are polarized away from the central spaces.

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 because of the secretory activity of the tumor cells, which appear to be prearneloblasts. In any event, these structures are not true ducts, and no glandular elements are present In the tumor (Figures 15-83 and 15-84).

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, particulariy 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 tumor. Interestingly, some adenornatoid odontogenic tumors have been described with focal areas that resemble calcifying epithelial odontogenic tumor, odontoma, or calcifyi ng odontogeniccyst. 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 I% of all odontogenic tumors. Fewer than 200 cases have been reported to date. 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 ot 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.

Clinical and Radiographic Features

Although the calcifying epithelial odontogenic tumor has been found in patients over 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 (Figure 15-85). A painless, slow-growing swelling is the most common presenting sign.

Radiographically, the tumor shows a unilocular or, more often, a multilocular radiolucent defect (Figure 15-86). The margins of the lytic defect are often scalloped. The lesion may be entirely radiolucent, but the defect may contain calcified structures of varying size and density. The tumor is frequently associated with an impacted tooth, most often a mandibular third molar.

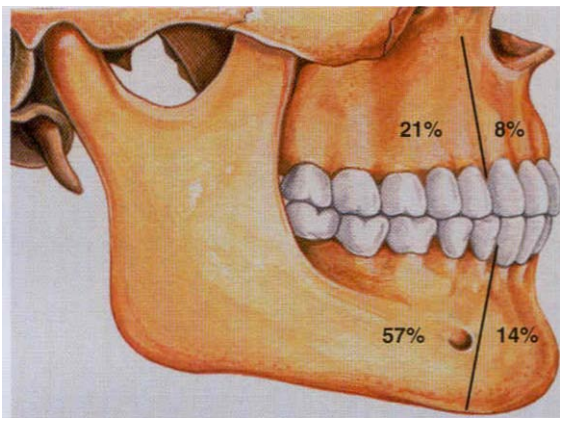

Figure 15-85 • Calcifying epithelial odontogenic tumor. Relative distribution of calcifying epithelial odontogenic tumor in the jaws.

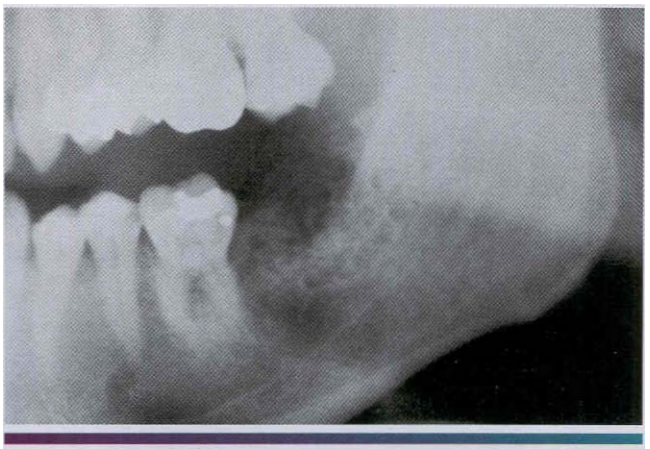

Figure 15-86 • Calcifying epithelial odontogenic tumor. Honeycombed multilocular radiolucency containing fine calcifications.

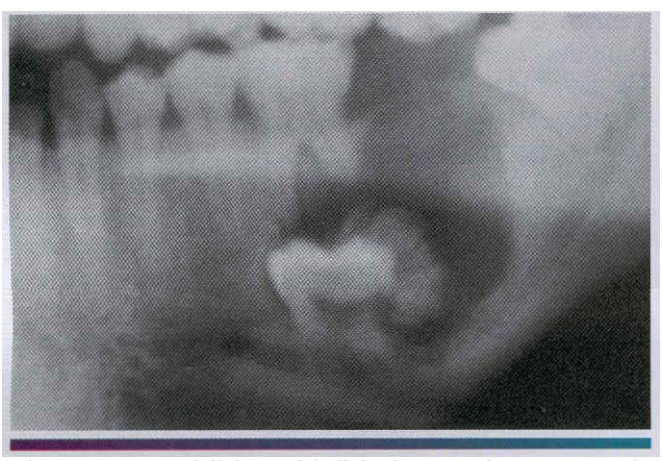

Figure 15-87 • Calcifying epithelial odontogenic tumor. Prominent calcification around the crown of an impacted second molar that is involved in the tumor. (Courtesy of Dr. Harold Peacock}

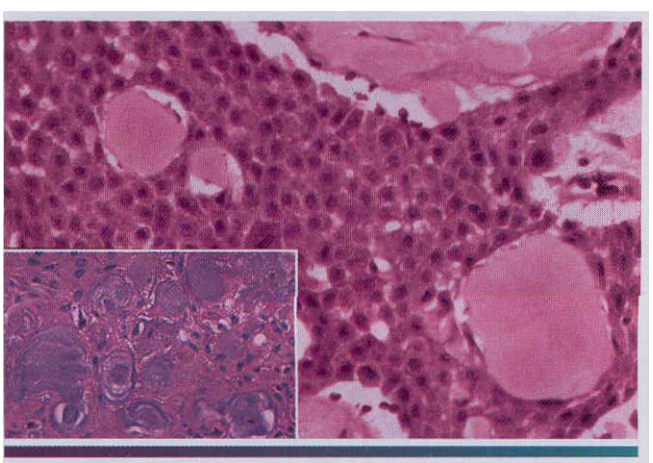

Figure 15-88 • Calcifying epithelial odontogenic tumor. Sheets of polyhedral tumor cells with prominent eosinophilic cytoplasm and intercellular bridging. Pools of amorphous eosinophilic amyloid are present. Multiple Uesegang ring calcifications are seen in the inset

Calcifications within the tumor are often most prominent around the crown of the impacted tooth (Figure 15-87).

A few cases of peripheral (extraosscous) 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 (Figure 15-88). 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 con-**siderable nuclear pleomorphism, but this feature is not **considered to indicate malignancy. Large areas of amor-**phous, eosinophilic, hyalinized (amyloid-like) extracellular material are also often present. The tumor islands frequently enclose masses of this hyaline material; this results 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). These tend to fuse together and form large, complex masses.

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

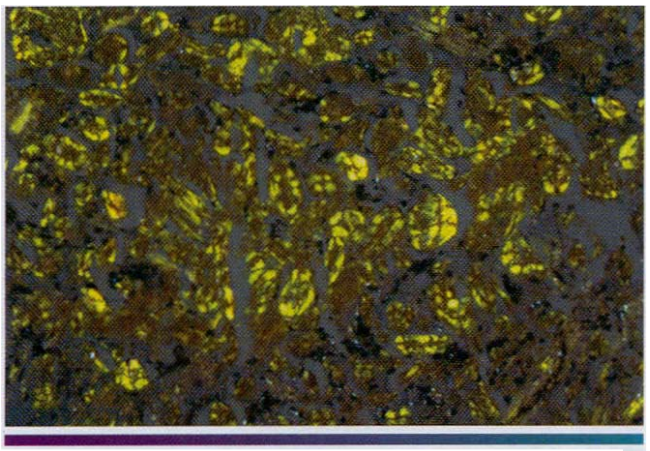

Figure 15-89 • Calcifying epithelial odontogenic tumor. With Congo red staining. the pools of amyloid exhibit an apple-green birefringence when viewed with polarized light.

amyloid-like material that contain only small nests or islands of epithelium. A clear cell variant has also been described. in which clear cells constitute a significant portion of the epithelial component.

The amyloid-like material in the Pindborg tumor has been extensively investigated by histochemical, immunohistochemical. and biochemical methods and by electron microscopy. Its precise nature, however, is still uncertain. Conflicting reports have suggested that this material represents either type IV collagen or keratin. but very few lesions have been studied. The material generally stains as amyloid (I.e.. positive staining results with Congo red or thioflavine T). After Congo red staining. the amyloid will exhibit apple-green birefringence when viewed with polarized light (Figure 15-89).

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 a single case with regional lymph node metastasis has been reported.

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. Fewer than 40 examples had been reported at the time of this writing. 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. 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 (Figure 15-90). In some instances, this suggests vertical periodontal bone loss. The radiolucent area may be somewhat ill defined or may show a well-defined. sclerotic margin. Most examples are relatively small lesions that seldom exceed 1.5 em in greatest diameter.

Histopathologic Features

The microscopic findings of squamous odontogenic tumor are distinctive and consist of varying-shaped islands *at* 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 arneloblastornas (Figure 15-91). Microcystic 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

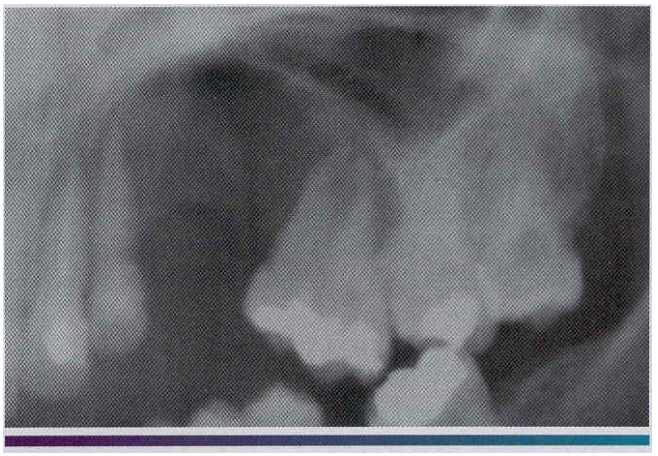

Figure 15-90 • Squamous odontogenic tumor. Lucent defect extending along the roots of the lateral incisor and first premolar teeth. (Courtesy of Dr. Ed McGaha.)

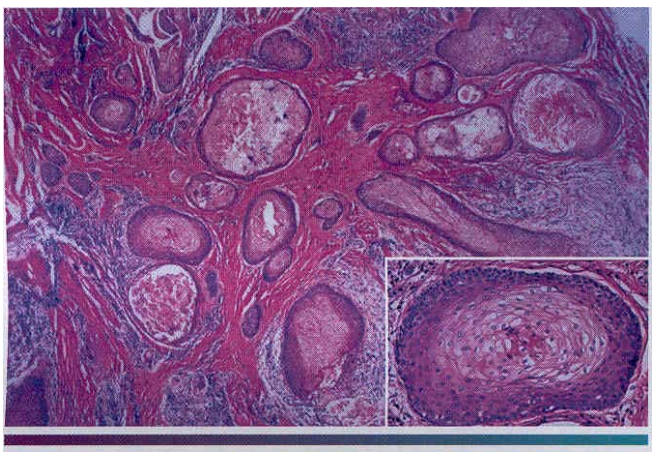

Figure 15-91 • Squamous odontogenic tumor. Islands of bland-appearing squamous epithelium in a fibrous stroma. Microcyst formation is seen. The inset shows one of the tumor islands at higher power.

cysts. These have been designated as *squamous odontogenic tumor-like 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 initially misdiagnosed 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 recently been reported.

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

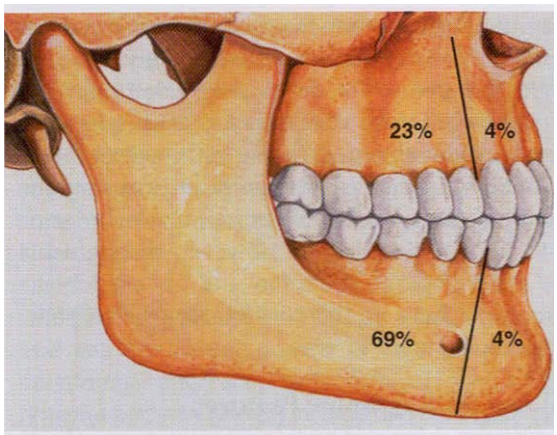

Figure 15-92 • **Ameloblastic fibroma.** Relative distribution of ameloblastic fibroma in the jaws.

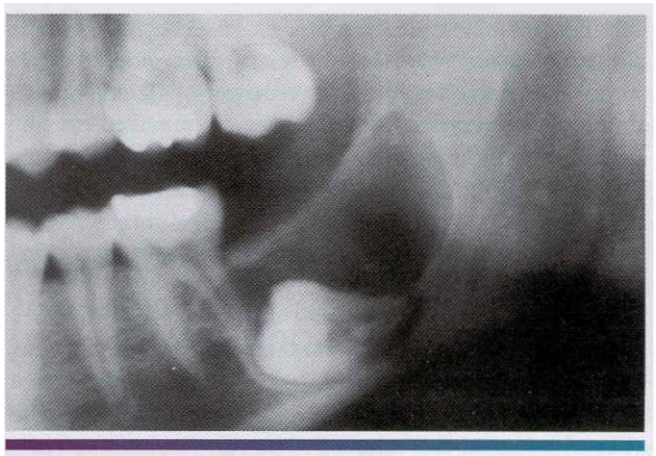

Figure 15-93 • **Ameloblastic fibroma.** Well-defined radiolucent defect associated with an unerupted second molar. (Courtesy of Dr. Robert Iauer.)

common site: about 70% of all cases are located in this area (Figure 15-92). Convincing examples of this tumor arising within the gingival soft tissue have not been described.

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 sclerotic. An unerupted tooth is associated with the lesion in about 75% of cases (Figure 15-93). The ameioblastic 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 (Figure 15-94). 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 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 arneloblastic 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. luxtaepithelial hyalinization of the mesenchymal portion of the tumor is sometimes seen, and occasionally diffuse areas of hyallnized acellular lesional tissue are evident.

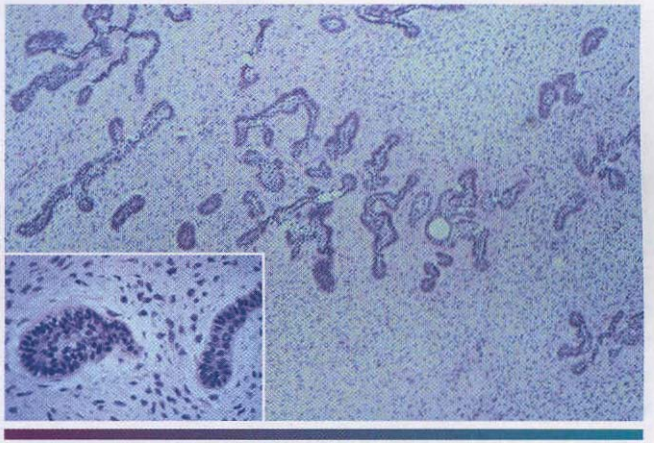

Figure 15-94 • **Ameloblastic fibroma.** long, narrow cords of odontogenic epithelium in a richly cellular, primitive mesenchymal stroma. Note the peripheral columnar differentiation *(inset).*

Treatment and Prognosis

The proper management of ameloblastic fibroma has been a recent topic of debate. Although initially it was believed that the arneloblastic 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 this data. recent recommendations have emphasized conservative initial therapy for ameloblastic fibroma, More aggressive surgical excision should probably be reserved for recurrent lesions, Approximately 45% of the cases of the rare ameloblastic fibrosarcoma develop in the setting of a recurrent amelobJastic fibroma,

AMELOBLASTIC FIBRO-ODONTOMA

The amelobJastic fibro-odontoma is defined as a tumor with the general features of an amelobJastic 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 ftbro-odontome. 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 libro-odontoma may be difficult based on histopathologic grounds alone,

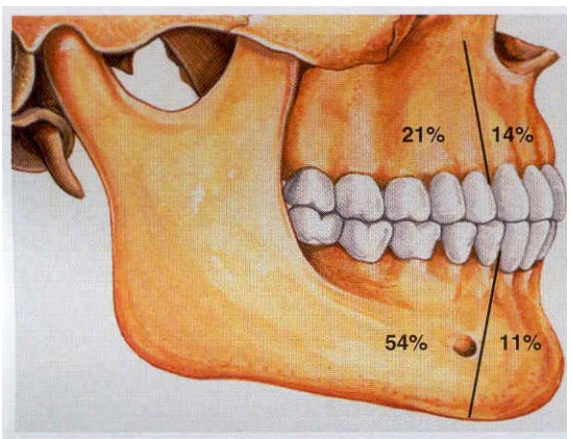

figure 15-95 • Ameloblastic fibro-odontoma. Relative distribution of ameloblastic fibro-odontoma in the *jaws*.

Clinical and Radiographic Features

The ameloblastic fibro-odontoma is usually encountered in children with an average age of 10 years, It is rarely encountered in adults. Like the ameloblastlc fibroma, arneloblastic ftbro-odontomas occur more frequently in the posterior regions of the jaws (Figure 15-95). There is no significant gender predilection. 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, rarely, 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 (Figure 15-96). 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. Some ameloblastic fibre-odontomas contain only a minimal

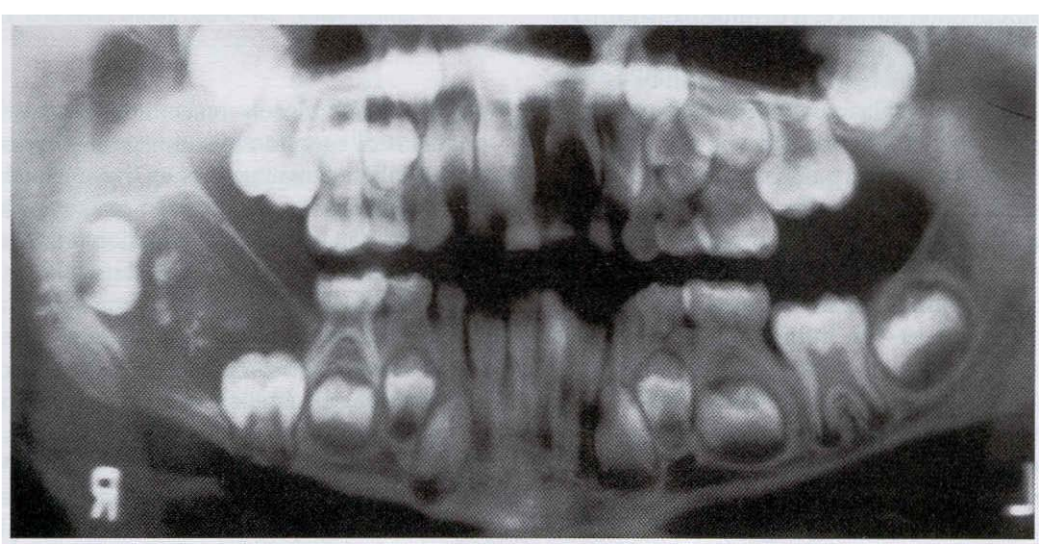

Figure 15-96 • Ameloblastic fibra-odontoma. Radiolucent defect in the ramus containing small calcifications having the radiodensity of tooth structure.

amount of calcifying enamel and dentin matrix and appear radiographically as radiolucent lesions (Figure 15-97). These cannot be differentiated from the wide variety of unilocular radiolucencies that may involve the jaws. At the other extreme, some ameloblastic fibre-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 flbro-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 (Figure 15-98). The more calcified lesions show mature dental structures in the form of rudimentary small teeth or conglomerate masses of enamel and dentin. A similar tumor in which the calcifying component consists only of dentin matrix and dentinoid material has been designated by some 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.

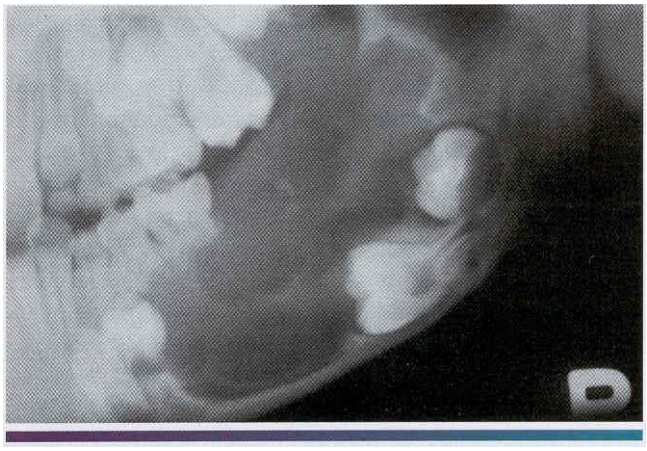

Figure 15-97 • Ameloblastic fibre-odontoma. **Radiolucent defect involving several unerupted teeth, Little calcified material is present in the radiolucent defect,**

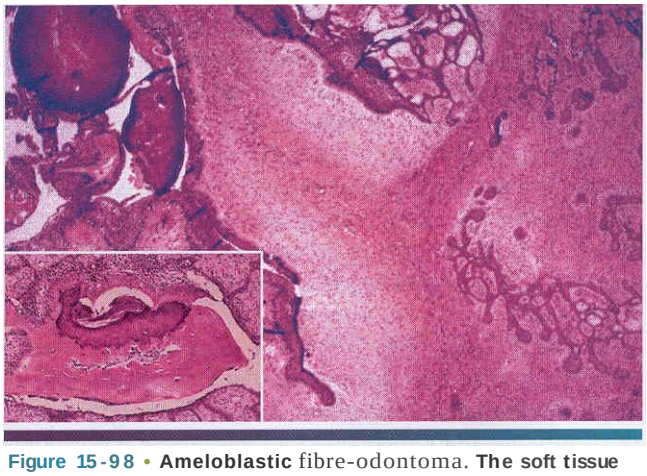

Figure 15-98 • Ameloblastic fibre-odontoma. **The soft tissue component of the tumor is indistinguishable from an ameloblastic fibroma. Developing rudimentary toothlike structures are shown** *(inset).*

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 recurrence after conservative removal is unusual. Development of an arneloblastic fibrosarcoma after curettage of an ameloblastic fibro-odontoma has been reported, but this is exceedingly rare.

AMEIOBLASTIC FIBROSARCOMA (AMELOBLASTIC SARCOMA)

The rare ameloblastic fibrosarcoma is considered to be the malignant counterpart of the ameloblastic fibroma, and slightly more than 50 cases have been documented in the literature. Interestingly, only the mesenchymal portion of the lesion shows features of malignancy; the epithelial component remains rather bland. The tumor may apparently arise *de novo,* although in approximately half of known cases, the malignant lesion represents a recurrence of a tumor previously diagnosed as an ameloblastic fibroma or an ameloblastic flbro-odontoma.

Clinical and Radiographic Features

Arneloblastic fibrosarcomas occur about 1.5 times as often in males as in females. The lesion tends to occur in younger patients (mean reported age is 27.5 years). Although either the maxilla or 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.

Radiographically, the ameloblastic fibrosarcoma shows an ill-defined destructive radiolucent lesion that suggests a malignant process (Figure 15-99).

Histopathologic Features

Ameloblastic fibrosarcomas contain an epithelial component similar to that seen in the ameloblastie fibroma, although it is frequently less prominent than that present in the typical ameloblastic fibroma. 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

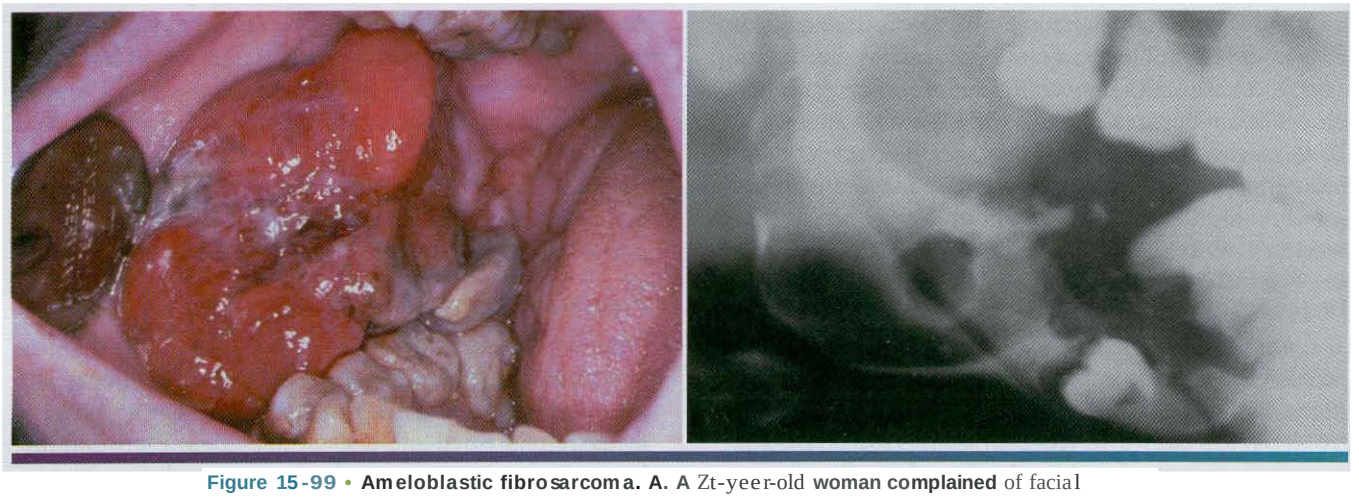

Figure 15-99 • **Ameloblastic fibrosarcoma. A.** A Zt-yeer-old woman complained of facial asymmetry and recent increase in size of a mandibular mass that had been present for some years. **B.** Radiograph of the same patient. Note the lytic destruction of the posterior mandible. (Courtesy of Dr. Sam McKenna.)

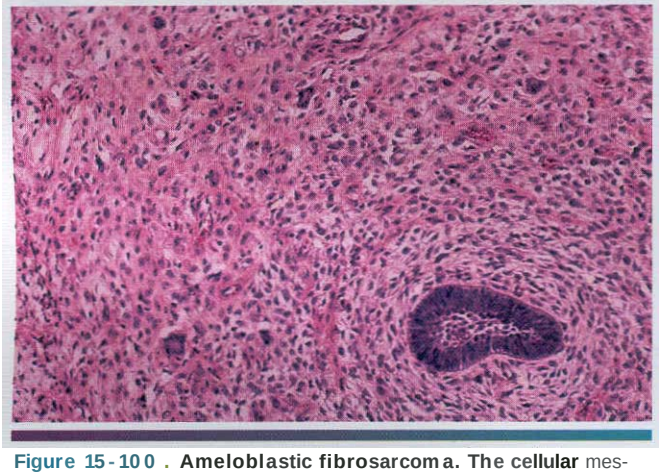

Figure 15-100 . **Ameloblastic fibrosarcoma. The cellular** mesenchymal tissue shows hyperchromatism and atypical cells. A small island of ameloblastic epithelium is present.

cells (Figure 15-100L 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. dysplastie dentin or small amounts of enamel may be formed. Sueh lesions have been called amcloblastic dentinosarcomas or amcloblastic flbro-odontosarcomas by some. This additional subclassification, however, appears unnecessary.

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 adjaeent bone and soft tissues.

The long-term prognosis is difficult 10 ascertain because of the few reported cases with adequate follow-up. Most deaths have resulted from uncontrolled local disease, and metastatic tumor has been documented in only one of 49 evaluable cases.

ODONTOAMELOBLASTOMA

The odontoameloblastoma is an extremely rare odontogenic tumor that contains an ameloblastomatous component and odontoma-like elements. This tumor was formerly called "ameloblastic odontoma" and was confused with the more common (though still relatively rare) lesion currently designated as ameloblastic libro-odontoma. Because the clinical behavior of these two tumors is quite different. they should be distinguished from one another.

Clinical and Radiographic Features

Because of the rarity of odontoameloblastomas. little reliable information is available. The lesion appears to occur more often in the mandible of younger patients. 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 odontoarneloblastoma 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 rudimen-

tary 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 puip 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. these lesions may show features of both compound and complex odontoma.

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 em 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.

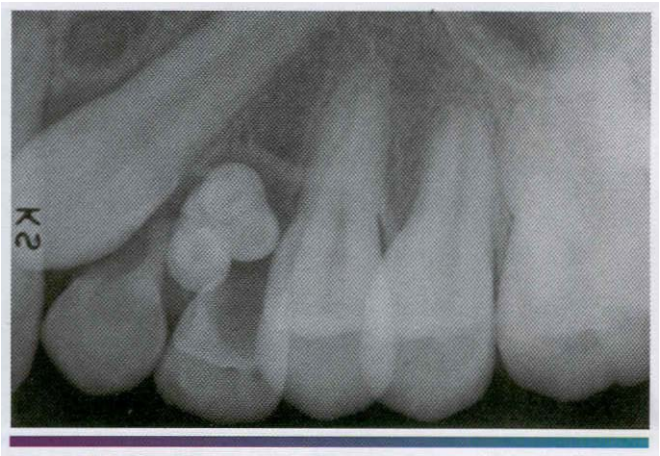

Figure 15-101 • **Compound odontoma.** A small cluster of toothlike structures is preventing the eruption of the maxillary canine. (Courtesy of Dr. Robert J. Powers.)

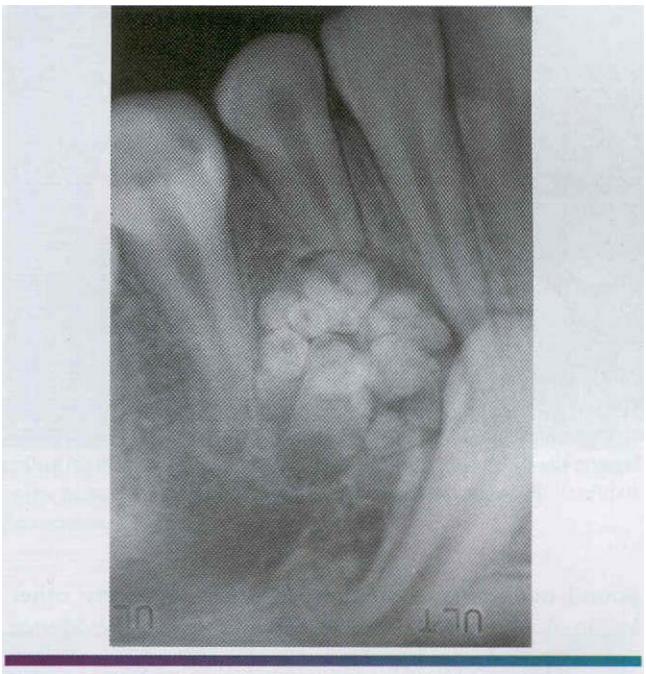

Figure 15-102 • **Compound odontoma.** Multiple toothlets preventing the eruption of the mandibular cuspid. (Courtesy of Dr. Brent Bernard.)

Radiographically. the compound odontoma appears as a collection of toothlike structures of varying size and shape surrounded by a narrow radiolucent zone (Figures 15-101 and 15-102). The complex odontoma appears as a calcified 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 (Figure 15-103). 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 com-

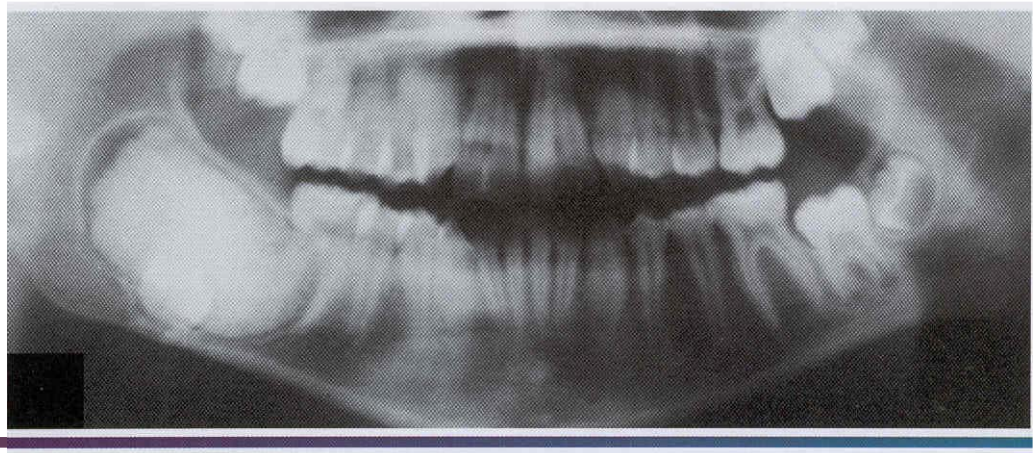

Figure 15-103 • Complex odontoma. A large radiopaque mass is overlying the crown of the mandibular right second molar, which has been displaced to the inferior border of the mandible.

Figure 15-104. Compound odontoma. Surgical specimen consisting of more than 20 malformed toothlike structures.

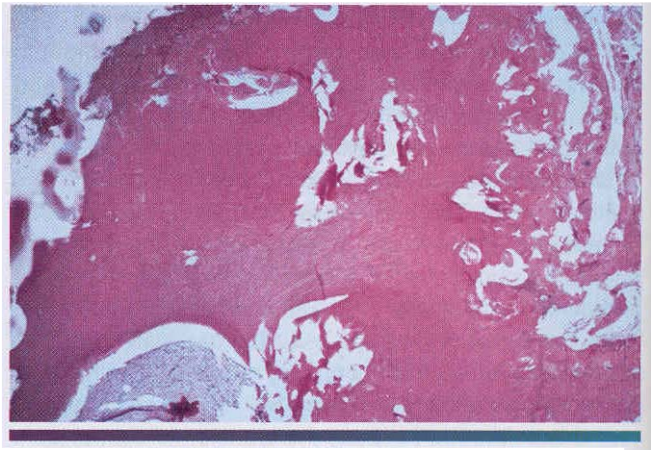

Figure 15-105. Complex odontoma. This decalcified section shows a disorganized mass of dentin intermixed with small pools of enamel matrix.

pound 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 (Figure 15-104). 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 (Figure 15-105). Small islands of eosinophilic-staining epithelial ghost cells are presenl 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 50 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 2.2 to I female predilection has been noted. About 45% of reported cases have occurred in the maxilla; most maxillary lesions are located anterior to the first molar tooth (Figure 15-106). 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.

Radiographically, smaller odontogenic fibromas tend to be well-defined, unilocular, radiolucent lesions often associated with the periradicular area of erupted teeth (Figure IS-lOII. Larger lesions tend to be multilocular **radiolucencies. Many lesions have a sclerotic** 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.

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 recently been questioned. The so-called simple odontogenic fibroma is composed of stellate fibroblasts, often arranged in a whorled pattern with fine collagen fibrils and considerable ground substance (Figure 15-108). Small foci of odontogenic epithelial rests may or may not be present. Occasional foci of dystrophic calcification may be present. Some investiga-

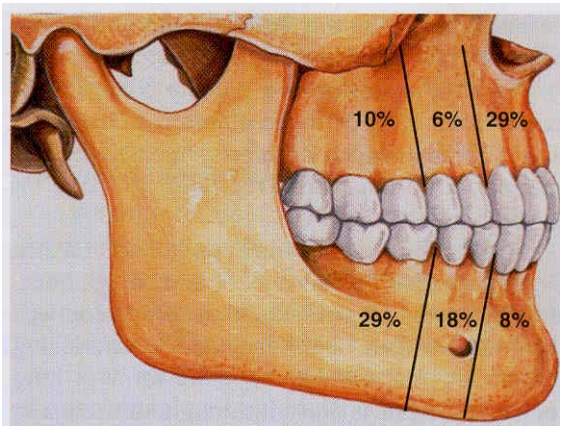

Figure 15-106 . Odontogenic fibroma. Relative distribution of odontogenic fibroma in the *jaws*.

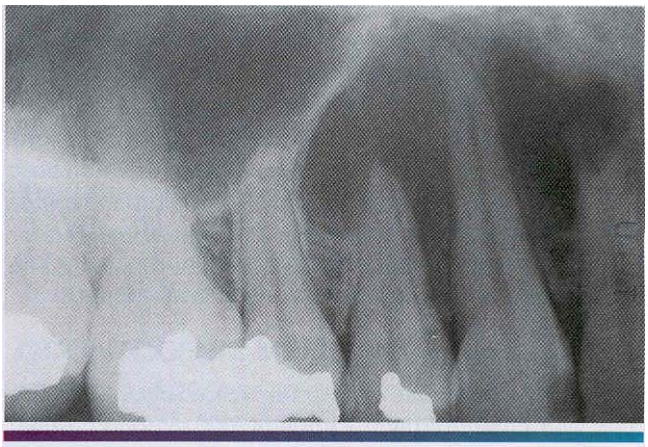

Figure 15-107 • Odontogenic fibroma. Apical radiolucent lesion in the incisor and premolar area. (Courtesy of Dr. Robert Provencher, Jr)

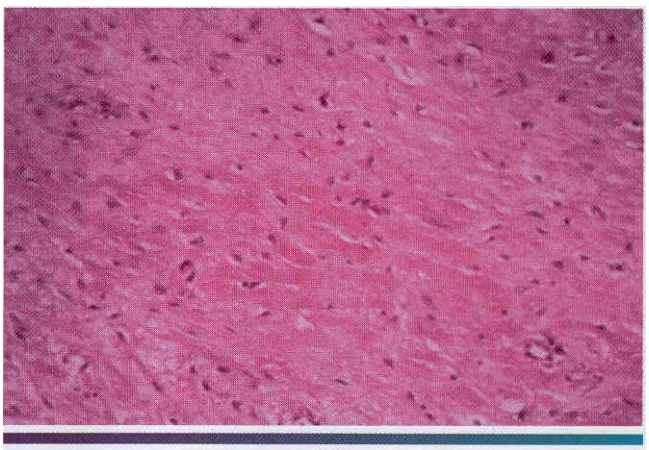

Figure 15-108 • Odontogenic fibroma (simple type). Scattered fibroblasts within a collagenous background. No epithelial rests were found on multiple sections from this tumor.

tors have suggested that this lesion actually belongs with the spectrum of odontogenic myxoma, and should be designated as a myxofibroma, A more collagenized odontogenic fibroma needs to be differentiated from a desmoplastic fibroma, which is a more aggressive lesion, **The desmoplastic fibroma. however, does not have an** epithelial component.

The central odontogenic fibroma, **WHO** (World Health Organization) type, 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 (Figure 15-109). The fibrous component may vary from myxoid to densely hyalinized. Calcifications composed of cementum-like **material or dentinoid are present in some cases.**

Twelve examples of central odontogenic fibroma associated with a giant cell granuloma-like component have been reported over the past decade. 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 or whether this is a distinct biphasic lesion remains to be clarified.

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 (Intraosscous) odontogenic fibroma. In the past, clinically and histopathologically similar lesions have been designated by some 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 reported series of this lesion have been published in the past decade, bringing the total number of cases in the literature to over 150.

Clinical and Radiographic Features

The peripheral odontogenic fibroma appears as a firm, **slow-growing, and usually sessile gingival mass covered** by normal-appearing mucosa (Figure 15-110). 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 em in diameter and they infrequently cause displacement of the teeth. Peripheral odontogenic fibromas have been recorded in patients over a wide age range, with most identified from the second to the seventh decades of life.

Radiographic studies demonstrate a soft tissue mass, **which in some cases has shown areas of calcification.** The lesion, however, does not involve the underlying bone.

Histopathologic Features

The peripheral odontogenic fibroma shows similar histopathologic features to the central odontogenic fibroma

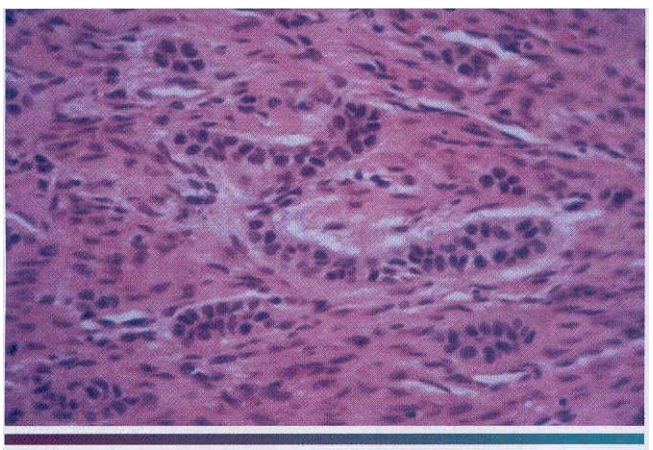

Figure 15-109 • Odontogenic fibroma (World Health Organization [WHO] type). A cellular fibroblastic lesion containing narrow cords of odontogenic epithelium.

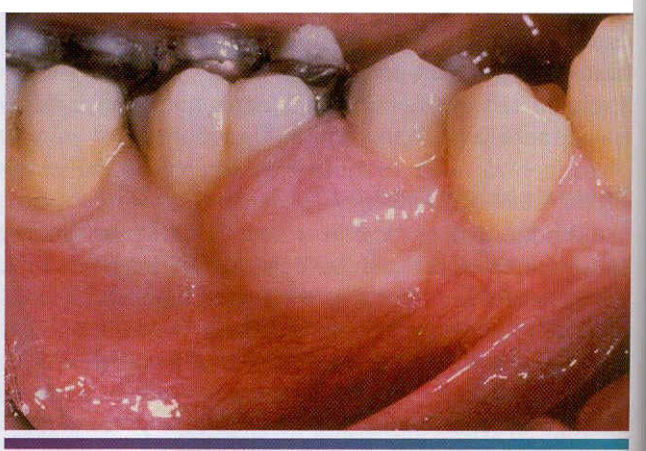

Figure 15-110. Peripheral odontogenic fibroma. This sessile gingival mass cannot be clinically distinguished from the common peripheral ossifying fibroma. (Courtesy of Dr. Jerry Stovall.]

(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. 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 excellent. Recurrence of this lesion has been documented, however, so the patient and clinician should be aware of this possibility.

GRANULAR CEII ODONTOGENIC TUMOR (GRANULAR CEII 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 20 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 over half being older than 40 years of age. 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.

Radiographically, the lesion appears as a well-demarcated radiolucency, which may be unilocular or multilocular and occasionally shows small calcifications (Figure 15-111).

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 465) or the granular cells seen in the granular cell variant of the ameloblastoma (see page 615). Narrow cords or small islands of odontogenic epithelium are scattered among the granular cells (Figure 15-112). 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.

Treatment and Prognosis

The granular cell odontogenic fibroma appears to be completely benign and responds well to curettage. No recurrences have 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 (pre-

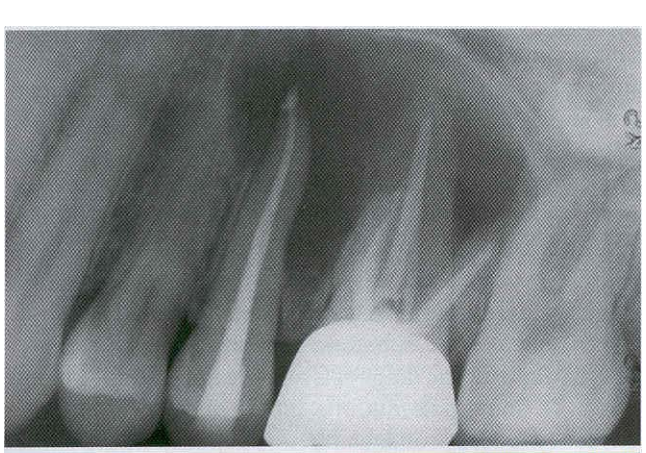

Figure 15-111 • Granular cell odontogenic tumor. Radiolucent lesion involving the apical area of endodontically treated maxillary teeth. (Courtesy of Dr. Steve Ferry.)

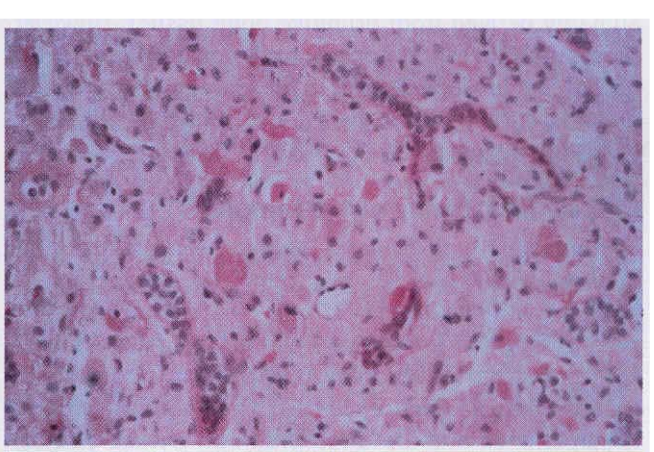

Figure 15-112 • Granular cell odontogenic tumor. Sheet of large granular mesenchymal cells with small nests of odontogenic epithelium.

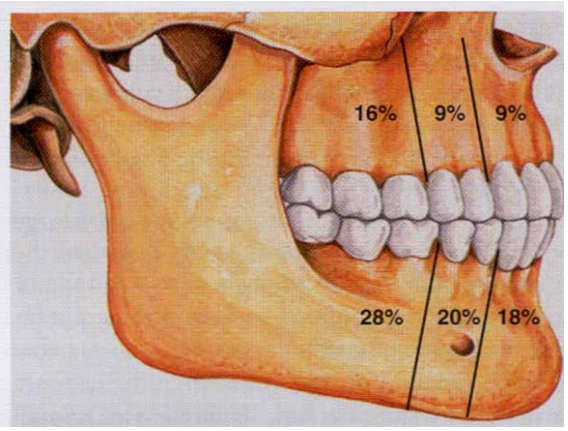

Figure 15-113 • Odontogenic myxoma. Relative distribution of odontogenic myxoma in the jaws.

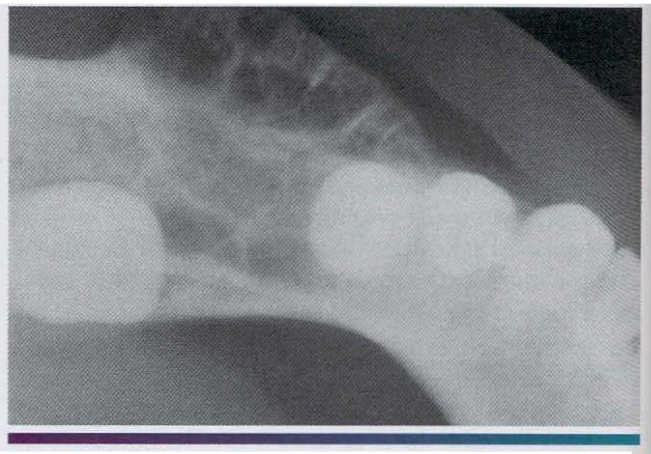

Figure 15-115 • Odontogenic myxoma. Occlusal view of a large myxoma showing buccal expansion and "soap bubble" radiolucency similar to that seen in an ameloblastoma. (Courtesy of Dr. Mike Rohrer.)

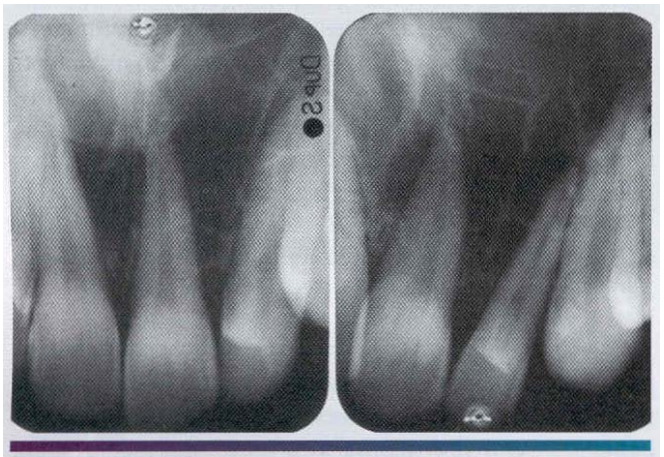

Figure 15-114 . Odontogenic myxoma. Radiolucent lesion of anterior maxilla showing fine residual bone trabeculae arranged at right angles to one another [tstepladder" pattern}.

sumably derived from primitive bone tissue). However. most authorities in orthopedic pathologic practice do not accept that myxomas occur in the extragnathic skeleton. and ali 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 over 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 maxilia (Figure 15-113). 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. The margins of the radiolucency are often irregular or scalloped. The radiolucent defect may contain thin, wispy trabeculae of residual bone. which are often arranged at right angles to one another (Figure 15-114). Large myxomas of the mandible may show a "soap bubble" radiolucent pattern, which is indistinguishable from that seen in ameloblastomas (Figure IS-It S).

Histopathologic Features

At the time of surgery or gross examination of the specimen, the gelatinous. loose structure of the myxoma is obvious. 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 (Figure 15-116). Histochemical 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 vlmentln. 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 forthe 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

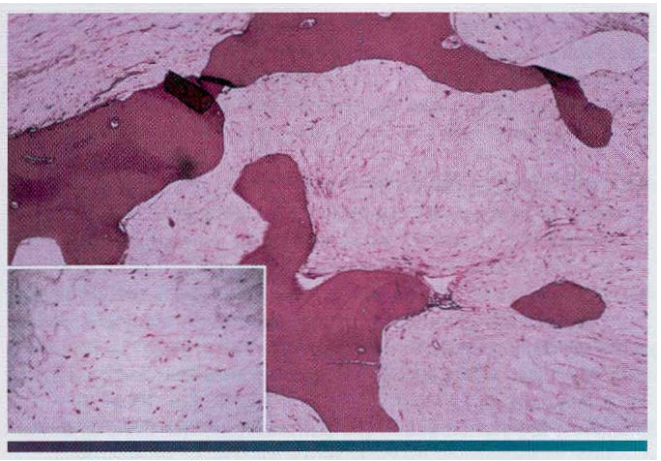

Figure 15-116 • Odontogenic myxoma. A loose, myxomatous tumor can be seen filling the marrow spaces between the bony trabeculae. The inset shows stellate-shaped cells and fine collagen fibrils.

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.

A myxoma may be microscopically confused with other myxold jaw neoplasms, such as the rare chondrornyxoid fibroma (see page 571) or the myxold neurofibroma (see page 457). Chondromyxoid fibroma should have areas of cartilaginous differentiation, whereas myxoid neurofibromas tend to have scattered lesional cells that arc positive for antibodies directed against S-IOO 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, will prevent overdiagnosis of these lesions as myxomas.

Treatment and Prognosis

Small myxomas arc 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 aggresstvely in most instances. Recurrence rates from various studies average approximately 25%. In spite of iocal recurrences, the overall prognosis is good, and metastases do not occur.

In rare cases, the myxoma microscopically shows marked cellularity and cellular atypism. These lesions have been designated by some as myxosarcomas. They appear to have a more aggressive local course than do the usual myxomas. 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 cernentoblastornas of the jaws are identical to those of a bone tumor, osteoblastorna, seen both in the jaws and extragnathic skeleton. Cementoblastomas are discussed in Chapter 14 (see page 570).

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CHAPTER 16

Dermatologic Diseases

CHAPTER OUTLINE

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. such as skin, hair. nails, teeth, or sweat glands, may be seen. The various types of this disorder may be inherited in anyone of several genetic patterns. including autosomal dominant, autosomal recessive. and X-linked. Even though by some accounts over 150 different subtypes of ectodermal dysplasia can be defined, these disorders are considered to be relatively rare. with an estimated frequency of I case occurring in every 10.000 to 100,000 births. For a few of these conditions, the specific genetic mutations and their chromosomal locations have been identified.

Clinical Features

Perhaps the best known of the ectodermal dysplasia syndromes Is hvpohidrotic ectodermal dysplasia. In most instances, this disorder seems to show an X-linked inheritance pattern; 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 individuais typically dispiay heat intolerance because of a reduced number of 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. 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 blonde hair, including a reduced density of eyebrow and eyelash hair (Figure 16-1). The periocular skin may show a fine wrinkling with hyperpigmentation (Figure 16-2), and midface hypoplasia is frequently observed, often resulting in protuberant lips. Because the salivary glands are ectodermally derived, 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 (Figure 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.

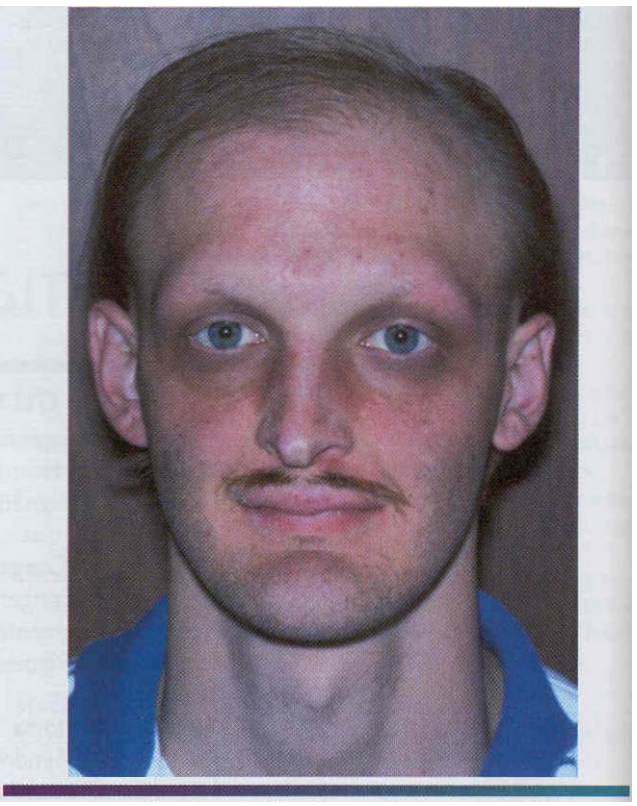


Figure 16-1 • Ectodermal dysplasia. The sparse hair, periocular hyperpigmentation, and mild midfacial hypoplasia are characteristic features evident in this affected patient.

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 pattern 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, ovcrdcntures, or fixed appliances, depending on the number and location of the remaining teeth. With careful

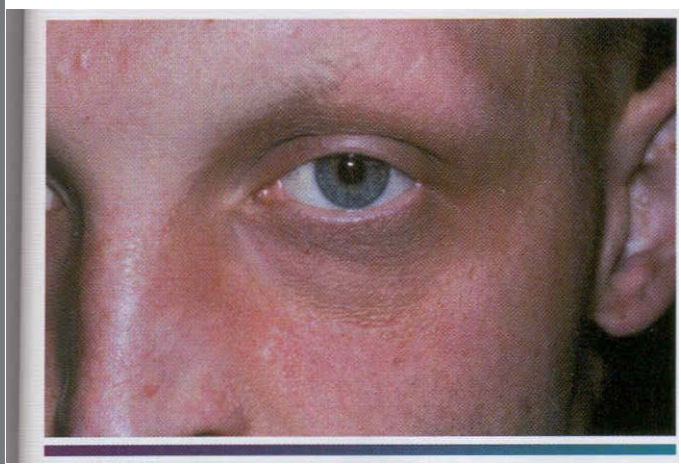


figure 16-2 • Ectodermal dysplasia. Closer view of the same patient depicted in Figure 16-1. Fine periocular wrinkling, as well as sparse eyelash and eyebrow hair can be observed.

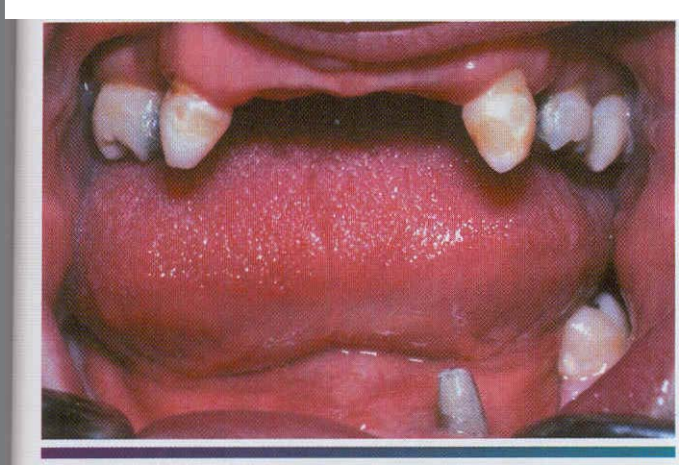


figure 16-3 • Ectodermal dysplasia. Oligodontia and conical crown forms are typical oral manifestations. (Courtesy of Dr. Charles Hook and Dr. Bob Gellin.)

site selection, endosseous dental implants may be considered for facilitating prosthetic management of patients older than 5 years of age.

WHITE SPONGE NEVUS (CANNON'S 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 3D-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

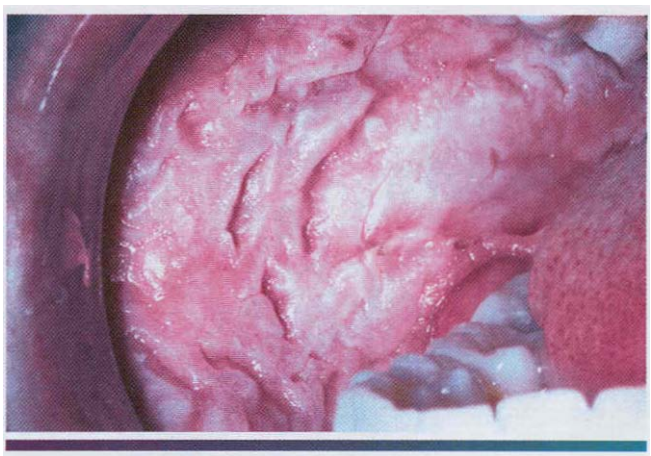


Figure 16-4 • White sponge nevus. Diffuse thickened white plaques of the buccal mucosa.

have been shown to be responsible for the clinical manifestations of white sponge nevus.

Clinical Features

The lesions of white sponge nevus usually appear at birth or in early childhood, but sometimes the condition develops during adolescence. Symmetric, thickened, white, corrugated or velvety, diffuse plaques affect the buccal mucosa bilaterally in most instances (Figure 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 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 (Figures 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

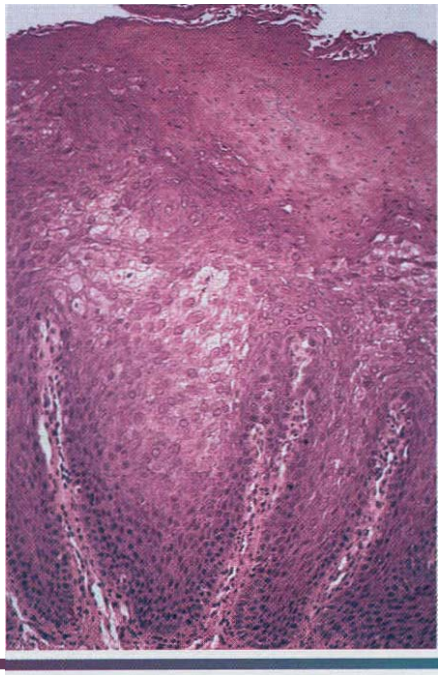


Figure 16-5 • White sponge nevus. This medium-power photomicrograph shows prominent parakeratosis, marked thickening (acanthosis), and vacuolation of the spinous cell layer.

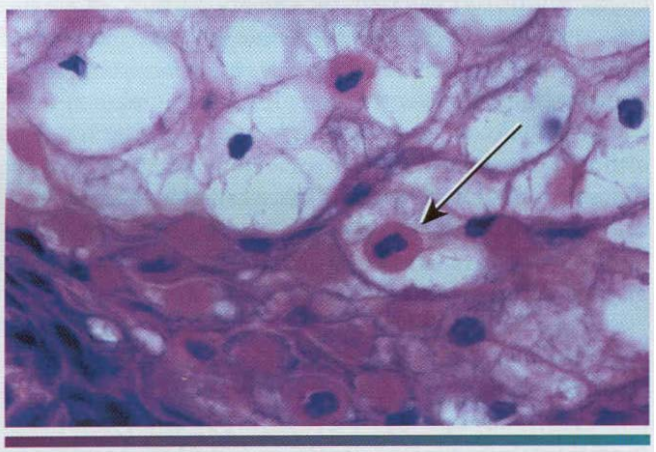


Figure 16-6 • White sponge nevus. This high-power photomicrograph shows vacuolation of the cytoplasm of the cells of the spinous layer, with no evidence of epithelial atypia. Perinuclear condensation of keratin tonofilaments can also be observed in some cells *(arrow)*.

eosinophilic perinuclear condensation of the epithelial cell cytoplasm to a greater extent than does the histopathologic section (Figure 16-7).

Treatment and Prognosis

Because this is a benign condition, no treatment is necessary. The prognosis is good.

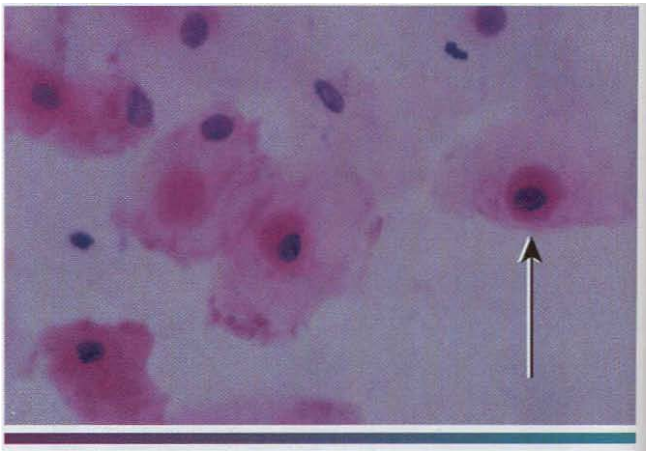


Figure 16-7. White sponge nevus. This high-power photomicrograph of a Papanicolaou-stained cytologic preparation shows the pathognomonic perinuclear condensation of keratin tonofilaments *(arrow)*.

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 (Figure 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 appear as thick, opaque, gelatinous plaques affecting the bulbar conjunctiva adjacent to the cornea (Figure 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

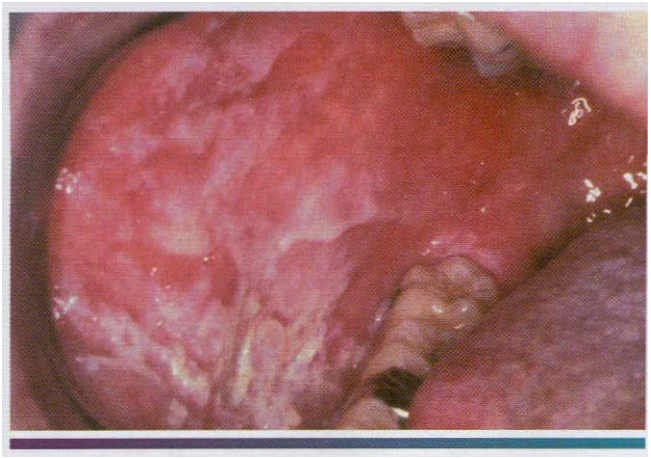


Figure 16-8 • Hereditary benign intraepithelial dyskeratosis (HBID). Oral lesions appear as corrugated white plaques of the buccal mucosa. (Courtesy of Dr. John McDonald.)

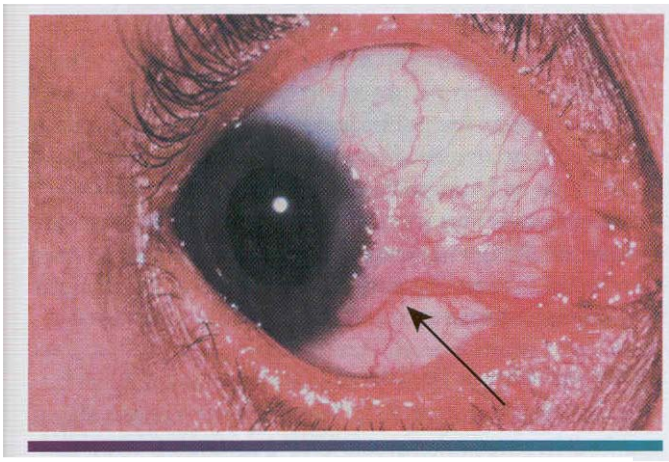


Figure 16-9 • Hereditary benign intraepithelial dyskeratosis (HBID). Ocular lesions appear as gelatinous plaques *(arrow)* of the bulbar conjunctivae. (Courtesy of Dr. Carl Witkop.)

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 Darter's disease. is scattered throughout the upper spinous layer of the surface oral epithelium (Figure 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.

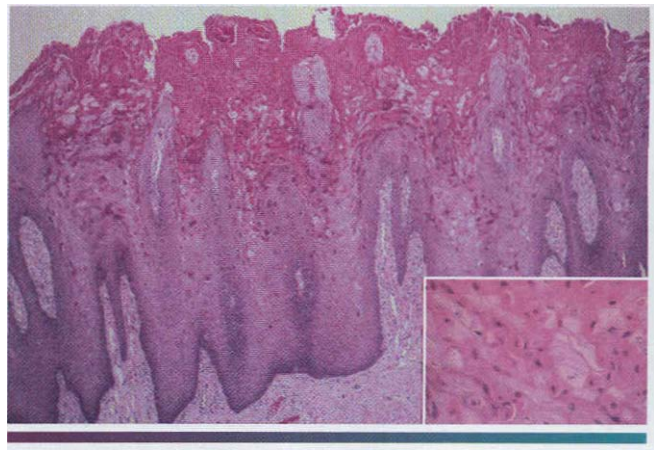


Figure 16-10 • Hereditary benign intraepithelial dyskeratosis (HBID). Medium-power photomicrograph exhibiting hyperparakeratosis. acanthosis. and dyskeratosis. Inset shows dyskeratotic cells at higher magnification.

Treatment and Prognosis

Because HBJD is a benign condition. no treatment is generally required or indicated for the oral lesions. If superimposed candidiasis *develops*. 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 OADASSOHN-LEWANDOWSKY TYPE; JACKSON-LAWLER TYPE)

Pachyonychia congenita is a group of rare genodermatoses that are usually inherited as an *autosomal* dominant trait. The nails are dramatically affected in most patients, but oral lesions are seen only in patients affected by the [adassohn-Lewandowsky form of the disease. Fewer than 200 cases have been reported. Specific mutations in the keratin 16 gene have been detected for the Jadassohn-lewandowsky type of pachyonychia congenita, whereas mutations of the keratin 17 gene are associated with the Jackson-Lawler form.

Clinical Features

Virtually all patients with pachyonychia congentta 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. Ultimately, nail loss may occur (Figure 16-11).

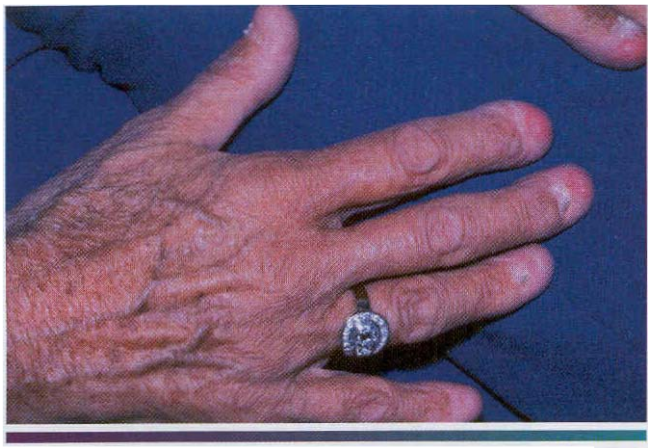


figure 16-11 • **Pachyonychia congenita. loss of fingernails.** (Courtesy of Dr. John Lenox.)

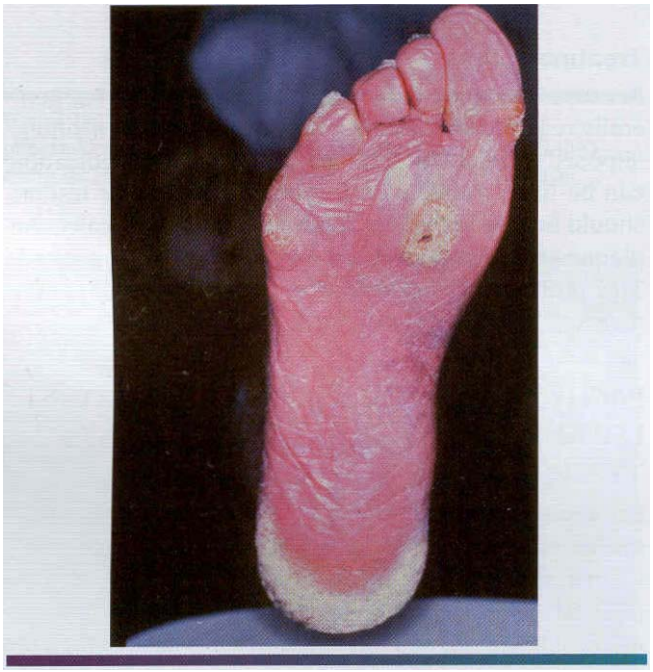


Figure 16-12 • **Pachyonychia congenita. The soles of the feet of affected patients typically show marked calluslike thickenings.** (Courtesy of Dr. Iou Young.)

Other skin changes that may occur include marked hyperkeratosis of the palmar and plantar surfaces, producing thick, callouslike lesions (Figure 16-12). Hyperhidrosis of the palms and soles is also commonly present. The rest of the skin shows punctate papules. representing an abnormal aceumulation of keratin in the hair follicles. One disabling feature of the syndrome is the formation of painful blisters on the soles of the feet after a few minutes of walking during warm weather.

The oral lesions seen in the ladassohn-Lcwandowsky form consist of thickened white plaques that involve the

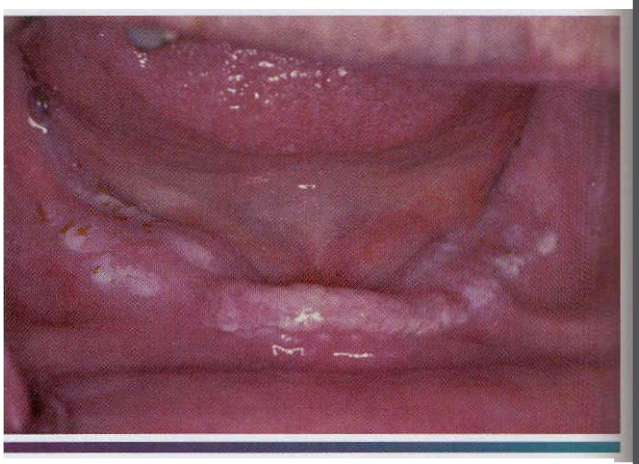


Figure 16-13 . **Pachyonychia congenita. Although tongue lesions are more common in patients with pachyonychia congenita. other oral mucosal sites exposed to minor trauma. such as the alveolar mucosa. may develop thickened white** patches. (Courtesy of Dr. John lenox.)

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 (Figure 16-13), Neonatal teeth have been reported in patients affected by the Jackson-Lawler form, but these individuals do not have oral white lesions. Hoarseness and dyspnea have been described in some patients as a result of laryngeal **mucosal involvement.**

Histopathologic Features

Microscopic examination of lesional oral mucosa shows marked hyperparakeratosts 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. Patients **should receive genetic counseling; however, mutations** in the keratin 16 gene have been identified using molecular techniques to evaluate material obtained from chorionic villus sampling, allowing prenatal diagnosis.

DYSKERATOSIS CONGENITA (COLE-ENGMAN SYNDROME; ZINSSER-COLE-ENGMAN SYNDROME)

Dyskeratosis congcnita is a rare genodermatosis thats usually inherited as an X-linked recessive tralt. resulting in a striking male predilection. Autosomal dominant and autosomal recessive forms, although less common, have been reported. Mutations in the DKC1 gene have been

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. 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 thefirst 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 (Figure 16-) 4).

Intraorally, the tongue and buccal mucosa develop buiiae; these are followed by erosions and. eventually. leukoplakic lesions (Figure 16-15). The leukoplakic lesions are considered to be premalignant. and approximately one third of them become malignant in a 10- to so-yeer 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 70% of these patients (see page 504). Mild-to-moderate mental retardation may also be present. Generally. the autosomal recessive **and X-linked recessive forms show a more severe pat-*tern* of disease expression.**

Histopathologic Features

Biopsy specimens of the early oral mucosal lesions show hyperorthckeratosis 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. Selected patients may be considered for allo**geneic bone marrow 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. but identification of the DKC1 gene should **allow for accurate confirmation of carriers of the gene** and for prenatal diagnosis.

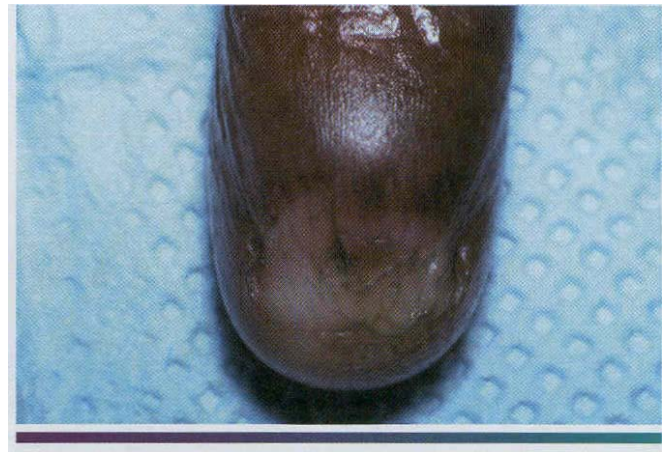


Figure 16-14 • Dyskeratosis congenita. Dysplastic nail changes.

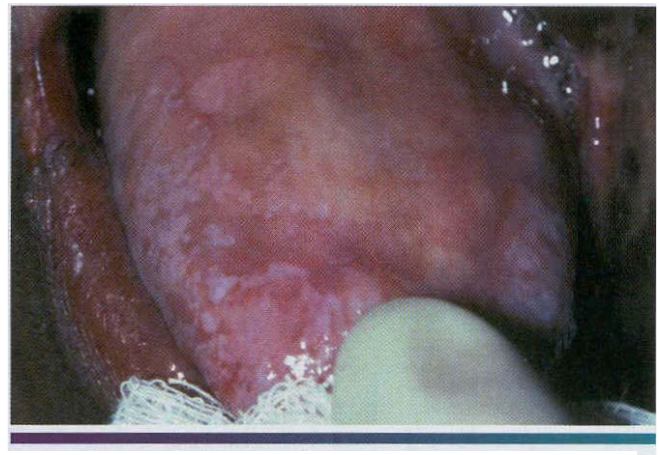


Figure 16-15 • Dyskeratosis congenita. Atrophy and hyperkeratosis of the dorsal tongue mucosa are visible.

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. The con**dition 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 light-induced damage. mutations in the epithelial cells occur, leading to the development of skin cancer at a rate 1000 to 4000 times what would normally be expected in people under 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.

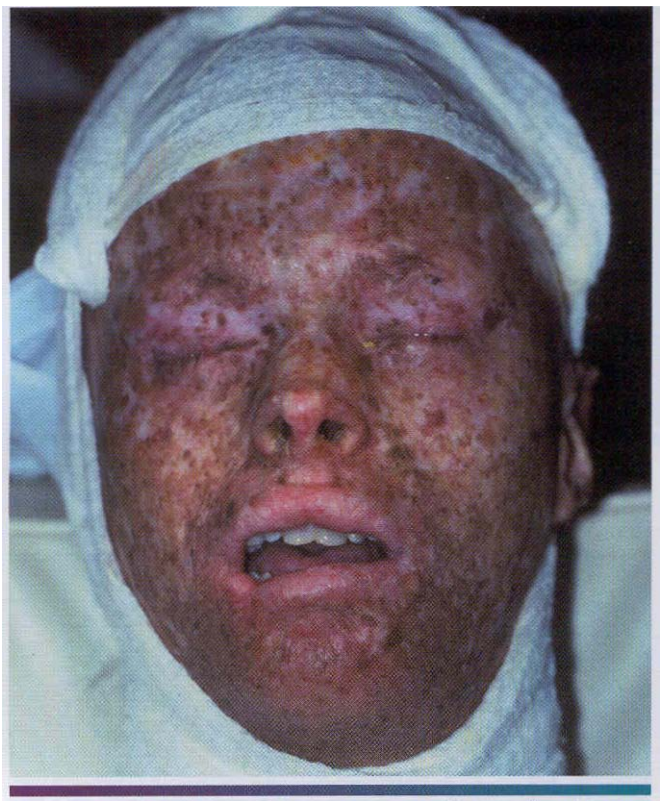


Figure 16-16 • Xeroderma pigmentosum. The atrophic changes and pigmentation disturbances shown are characteristic of xeroderma pigmentosum.

freckled pigmentation, and patchy depigmentation, soon follow (Figure 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 manifestations include subnormal intelligence in 80% of affected individuals.

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.

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. 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.

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, as well as oral structures. There is a marked female predilection, with a 37:1 female-to-male ratio reported. The condition is thought to be inherited as an X-linked dominant trait, with the single unpaired gene on the X chromosome being lethal for most males. Recent studies suggest that affected patients show chromosomal instability, which may lead to a small increased risk of childhood malignancy.

Clinical Features

The clinical manifestations of incontinentia pigmenti usually begin in the first few weeks of infancy. There are four stages.

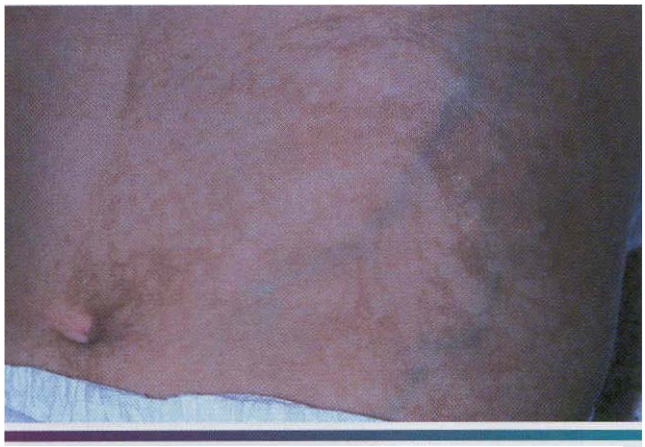


Figure 16-17 • Incontinentia pigmenti. Swirling pattern of pigmentation on the abdomen of an infant.

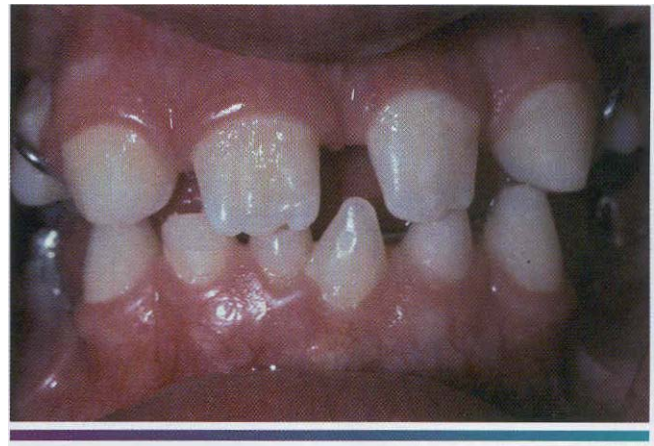


Figure 16-18 e Incorrtinent la pigmenti. Hypodontia and conical teeth.

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 (Figure 16-17).
4. *Atrophy and depigmentation stage*. Atrophy and depigmentation of the skin ultimately occur.

Central nervous system abnormalities occur in 10% to 30% of affected patients. The most common problems are mental retardation, seizure disorders, and motor difficulties. Ocular problems (e.g., strabismus, cataracts, retinal vascular abnormalities, optic nerve atrophy) may also be identified in approximately 30% of these patients.

The oral manifestations of incontinentia pigmenti, noted in 60% to 80% of the cases, include oligodontia (hypodontia), delayed eruption, and hypoplasia of the teeth (Figure 16-18). 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 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 central nervous system problems are severe.

DARIER'S DISEASE (KERATOSIS FOLLICULARIS; DYSKERATOSIS FOLLICULARIS; DARIER-WHITE DISEASE)

Darter's **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 that encodes an intracellular calcium pump has been identified as the cause for abnormal desmosomal organization in the affected epithelial cells. Estimates of the prevalence of Darter's disease in northern European populations range from 1 in 36,000 to 1 in 100,000,

Clinical Features

Patients with Darter's disease have numerous erythematous, often pruritic, papules on the skin of the trunk and the scalp that develop during the second decade of life (Figure 16-19). 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 ultraviolet light

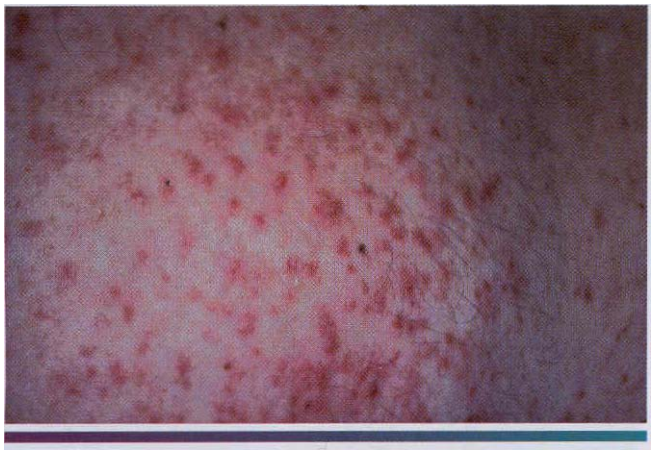


Figure 16-19 • Darter's disease. Erythematous cutaneous papules on the chest.

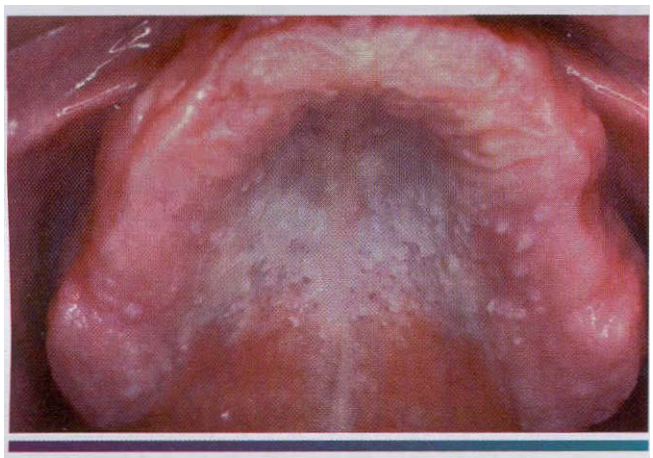


Figure 16-20 • Oarier's disease. The oral mucosa may show multiple white papules. (Courtesy of Dr. George Blozis.)

or because increased heat results in sweating, which induces more epithelial clefting. The paims and soies often exhibit pits and keratoses. The nails show iongitudlnal llnes, ridges, or painful splits.

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 (Figure 16-20). 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, 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.**

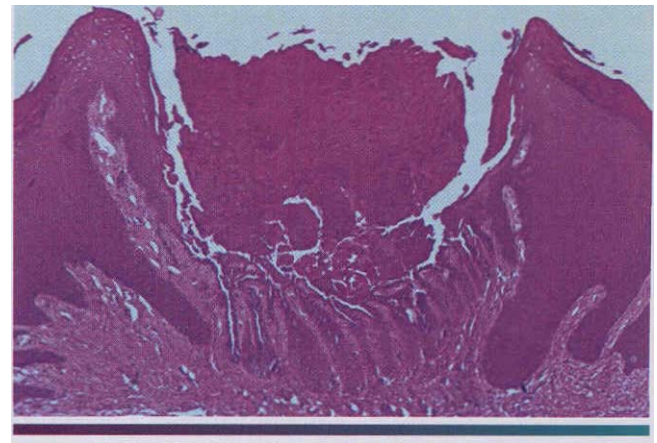


Figure 16-21 • Darier's disease. Low-power photomicrograph showing a thick keratin plug. intraepithelial c1efting, and elongated rete ridges.

Histopathologic Features

Microscopic examination of the cutaneous or mucosal lesions shows a dyskeratotic process characterized *by* a central keratin plug that overlies epithelium exhibiting a suprabastlar cleft (Figure 16-21). This intraeplthellal clefting phenomenon, also known as acantholysis, is not **unique to** Darter's **disease and may be seen in conditions** such as pemphigus vulgaris (see page 664). 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 rands*** (round bodies) or grains (because they resemble cereal grains).

Treatment and Prognosis

Treatment of Darter's 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 *may* be the only treatment required. For more severely affected patients, systemic retinoids are often beneficial, but the side effects of such medications have to be carefully monitored by the physician. Although the condition is not premalignant or otherwise life threatening, genetic counseling is appropriate.

WARTY DYSKERATOMA (ISOLATED DARIER'S DISEASE; ISOLATED DYSKERATOSIS FOLLICULARIS; FOCAL ACANTHOLYTIC DYSKERATOSIS)

The warty dyskeratoma is a distinctly uncommon solitary lesion ***that*** **can occur on skin or oral mucosa. It** is histopathologically identical to Darier's disease. For this reason, the lesion has been termed isolated Darter's disease. The lesion is not otherwise related to Darier's disease, **however, and its cause remains unknown.**

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. 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 follicularts. Both conditions display dyskeratosis and a suprabasilar cleft. 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-Ieghers syndrome is a relatively rare but well-recognized condition, having a prevalence of approximately I in t20,000 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 35% of cases represent new mutations. Mutation of a gene known as LKBI, which encodes for a serine/threonine kinase, has been found to be responsible for Peutz-Iegh ers syndrome.

Clinical Features

The skin lesions of Peutz-lcghers syndrome usually develop early in childhood and involve the perio rificial areas (e.g., mouth, nose, anus, genital region). The skin of the extremities is affected in about 50% of patients (Figure 16-22). 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 (vtelescoping" 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** 2% to 3% of affected patients, although the polyps themselves do not appear to be premalignant. Other tumors affecting the pancreas, male and female genital tract, breast, and ovary may also develop, and the increased frequency overall is estimated to be approximately 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 and are seen in more than 90% of these patients (Figure 16-23). The number of lesions and the extent of involvement can vary markedly from patient to patient.

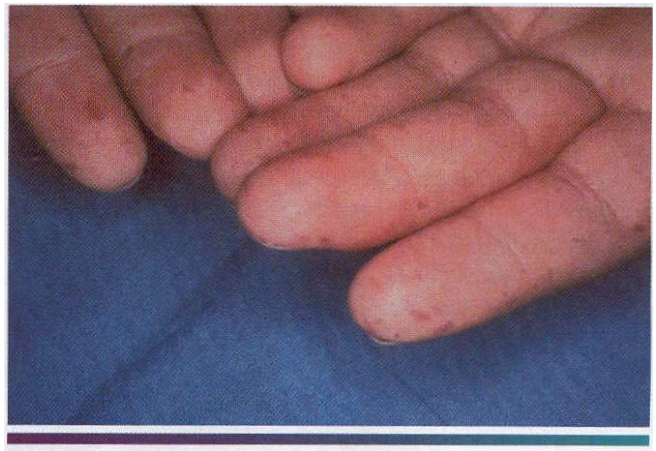


Figure 16-22 • Peutz-Jeghers syndrome. Cutaneous lesions appear as brown, macular, freckle-like **areas, often concentrated around the mouth or on the hands. (Courtesy of Dr. Ahmed** Uthman.)

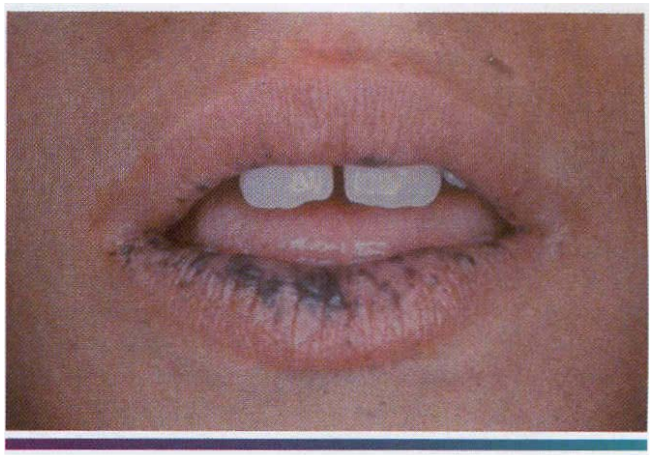


Figure 16-23 • Peutz-Jeghers syndrome. Oral manifestations include multiple, dark, freckle-like lesions of the lips. (Courtesy of Dr. Ahmed Uthman.)

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 567).

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 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 has a prevalence of 2** to 19 per 100,000 population. Mutation of either one of two different genes at two separate loci is responsible for the condition. HHT I is caused by a mutation of the endoglin gene on chromosome 9, whereas ALK-I (activin receptor-like kinase-I) mutation 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 HHT I tend to have more pulmonary involvement, whereas those with HHT2 generally have milder disease of later onset. 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 (Figures 16-24 and 16-25).

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, liver, or brain. The brain lesions seem to predispose these patients to the **development of brain abscesses. In at least one instance,** periodontal vascular malformations were felt to be the

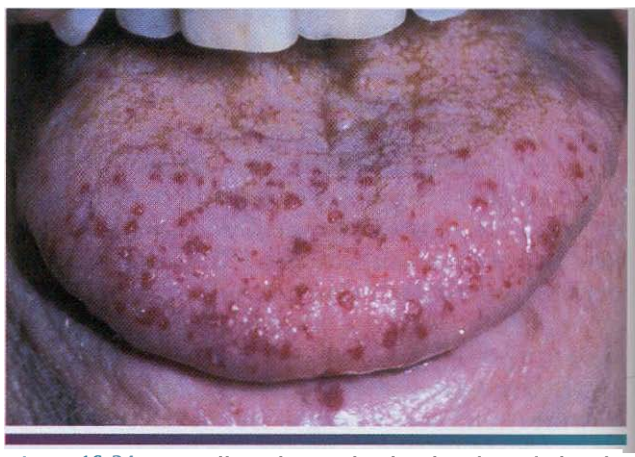


Figure 16-24 . Hereditary hemorrhagic telangiectasia (HHT). The tongue of this patient shows multiple red papules, which *represent superficial collections of dilated capillary spaces.*

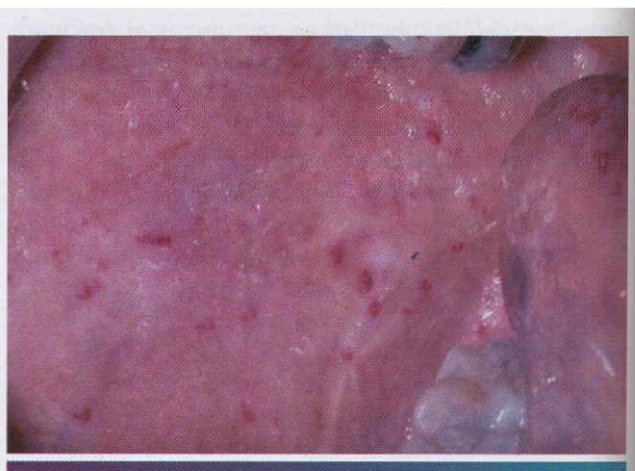


Figure 16-25 • Hereditary hemorrhagic telangiectasia (HHT). Red macules similar to the tongue lesions are observed on the buccal mucosa.

cause of septic pulmonary emboli that resolved only after several teeth with periodontal abscesses were extracted.

In some instances. CREST syndrome (sec page 695) 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 wou ld 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 (Figure 16-26).

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. More severely affected patients. particularly those troubled by repeated episodes of epistaxis. may require a surgical procedure *at* the nasal septum (septal dermoplastyl. The involved nasal mucosa is removed and replaced by a skin graft. Laser ablation of the telangiectatic lesions has also been used wi th varying degrees of success.

Combined progesterone and estrogen therapy may benefit some patients. but because *at* the potentially serious side effects. this should be limited to the most severely affected individuals. Iron replacement therapy is indicated *tor* the iron-deficient patient. and occasionally blood tran sfusions may be necessary to compensate for blood loss.

From a dental standpoint. some authors recommend the usc of prophylactic antibiotics before dental procedures that might cause bacteremia in pa tlcn ts with HHT and evidence of a pulmonary arteriovenous malformation. For patients with a history of HHT. such antibiotics are advocated until a pulmona ry arteriovenous malformation is ruled out because of the I% prevalence of brain abscesses in affected individuals. It is believed that antibiotic coverage. similar to that for endocarditis prophylaxis. may prevent this serious complication.

The prognosis is generally good. although a I% to 2% mortality rate is reported from complications related to blood loss. For patients with brain abscesses. the mortality rate is 10%. even wi th early diagnosis and appropriate therapy.

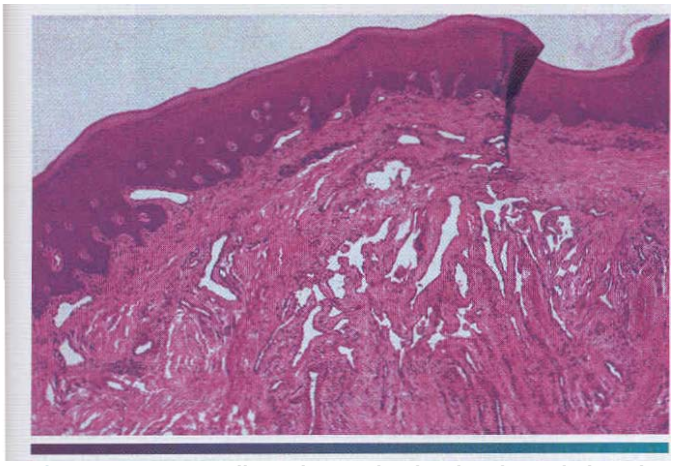


Figure 16-26 • Hereditary hemorrhagic telangiectasia (HHT). This low-power photomicrograph shows multiple dilated vascular spaces located immediately subjacent to the epithelium.

EHLERS-DANLOS SYNDROMES

The Ehlers-Danlos syndrome s, a group of inherited connective tissue disorders. are relatively heterogeneous. At least ten types have been descr ibed over the years, but recent clinical and molecular evidence suggests that six categories of this disease may be more appropriate. The pati ent exhibits problems that arc 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 bio chemical steps that are controlled by several genes, the potential exists for anyone 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-Da nlos syndrome (Table 16-1l. This discussion will concentrate on the most common and significant form s *at* this grou p of conditions.

Typ ical clinical findings include hypermobility of the joi nts, easy bruisability. and marked elasticity of the skin. Some patients 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 cla ssical 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 identified in others, suggesting genetic heterogeneity. Hyperelasticity of the skin (Figure 16-27) and cutaneous fragility can be observed. An unusual healing response that often occurs with relatively minor injury to the skin is termed papyraceou s scarring because it resembles cru mpled cigare tte paper (Figure 16-28).

Table 16-1 *Elhers-Danlos (ED) 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, arterial and uterine rupture	AD. AR	Collagen type III mutations
Kyphoscoliosis	Ocular 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 III defect; possible defect in fibronectin

AD, Autosomal dominant; *AR*, autosomal recessive; *XLR*, X-Hnked recessive.

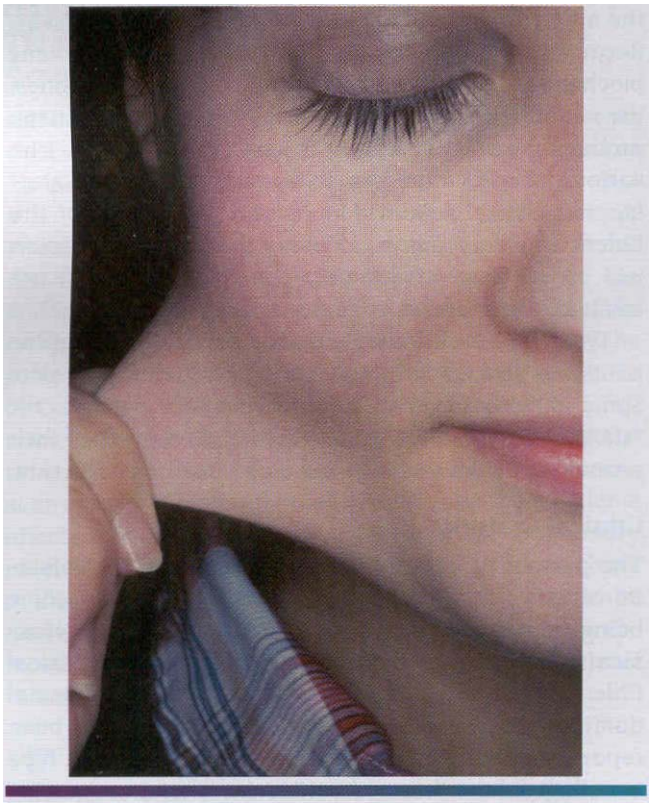


Figure 16-27 • Ehlers-Danlos syndrome. The hyperelasticity of the skin is evident in this patient affected by the mild form of classical Ehlers-Danlos syndrome.

Patients with the hypermobility type of Ehlers-Danlos syndrome exhibit remarkable joint hypermobility but no evidence of scarring.

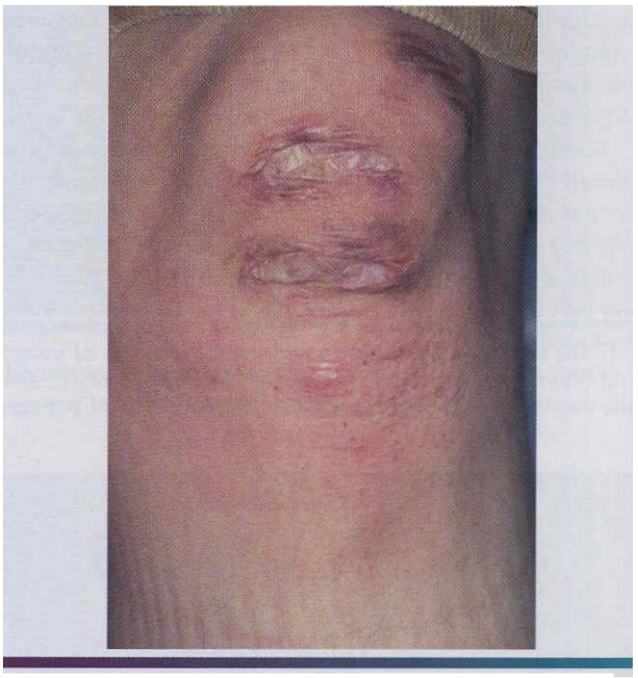


Figure 16-28 • Ehlers-Danlos syndrome. Scarring that resembles crumpled cigarette paper (papyraceous scarring) is associated with minimal trauma in patients with Ehlers-Danlos syndromes. These lesions involve the skin of the knee.

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 lit collagen have been identified In this disorder. This form is inherited in an autosomal dominant pattern, and the 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 (originally reported as type VIII) was described as having dental manifestations as a hallmark feature. with patients showing marked periodontal disease activity at a relatively early age. More recent studies suggest that these patients have overlapping features with either the classical or vascular forms of the disease.

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 can be achieved by less than 10% of normal people. 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) has also been reported.

. Most patients with Ehlers-Danlos syndrome have normal teeth. A variety of dental abnormalities have been described, however, ineluding malformed, stunted tooth roots, large pulp stones, and hypoplastic enamel. These findings, however, have not been consistently correlated with any particular type of the 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.

TUBEROUS SCLEROSIS (EPILOIA; BOURNEVILLE-PRINGLE SYNDROME)

Tuberous sclerosis is an uncommon syndrome that is classically characterized by mental retardation. 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 recentiy described genes: TSC I (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. and milder forms may be difficult to diagnose.

The prevalence is between I in 10.000 and I in 23.000 in the general population, although in some long-term care facilities tuberous sclerosis accounts *tor* as high as I% of the mentally retarded 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 (Figure 16-29). Similar lesions, called ungual or periungual fibromas. are seen around or under the margins of the nails (Figure 16-30).

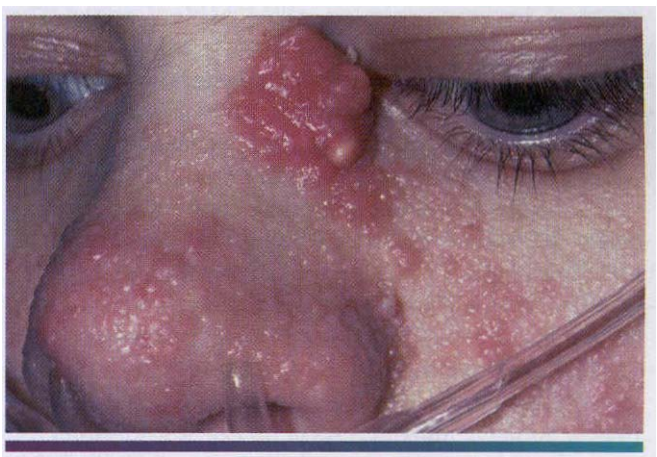


Figure 16-29 • **Tuberous sclerosis. Patients typically have multiple papular facial lesions that microscopically are angiofibromas.**

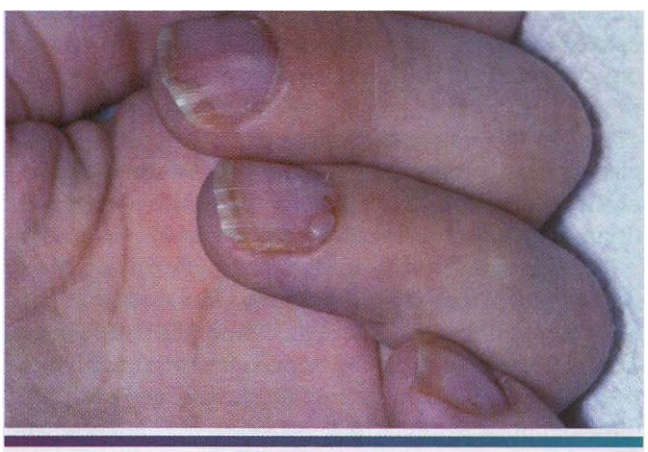


Figure 16-30 • **Tuberous sclerosis. Examination of the fingers often shows periungual fibromas.**

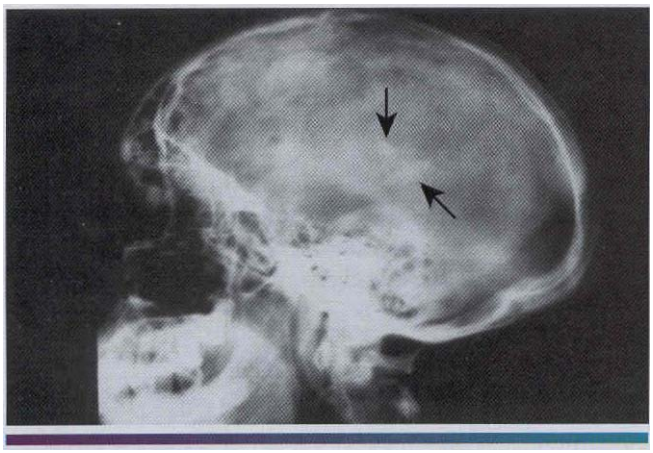


figure 16-31 • Tuberous sclerosis. Patchy calcifications *(arrows)* associated with intracranial hamartoma formation are seen on this lateral skull radiograph. (Courtesy of Dr. Reg Munden.)

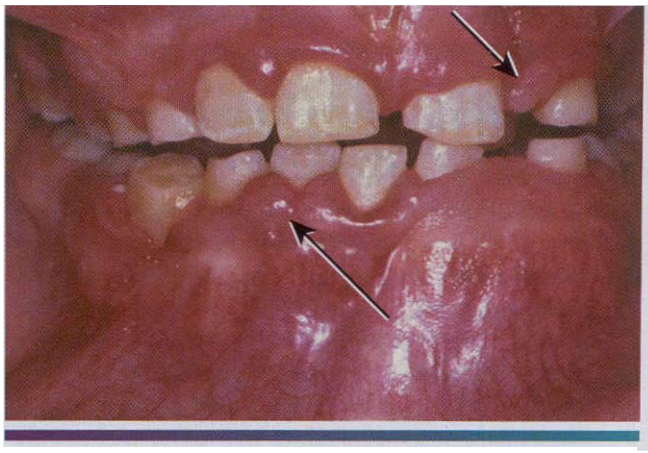


Figure 16-32 • Tuberous sclerosis. Patients often exhibit gingival hyperplasia, which may be secondary to phenytoin medications used to control seizures in some cases. Fibrous papules of the gingiva *(arrows)* may also be present.

Two other characteristic skin lesions are connective tissue hamartomas called shagreen patches and ovoid areas of hypopigmentation called ashleaf spots. 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** ultraviolet (Wood's lamp) illumination.

eNS manifestations include seizure disorders in nearly 90% of affected patients and mental retardation in 33% to 60%. 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 (Figure 16-31). The tuberous hamartomas can best be visualized using T2-weighted magnetic resonance imaging (MRI).

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 50% of affected patients. Problems with myocardial function often develop as a result of this **process.**

Another hamartomatous type of growth related to this **disorder is the angiomyoliporna. This is a benign neo**plasm composed of vascular smooth muscle and adipose tissue and occurs primarily in the kidney.

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 II % to 56% of patients. The fibrous papules are seen predominantly on the anterior gingival mucosa (Figure 16-32). although the lips. buccal mucosa. palate, and tongue may be involved. Diffuse fibrous gingival enlargement is reported in affected patients 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 (Figure 16-33).

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 maculcs (three or more)
- Shagreen patch
- CNS hamartomas
- Cardiac rhabdomyoma
- 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.**

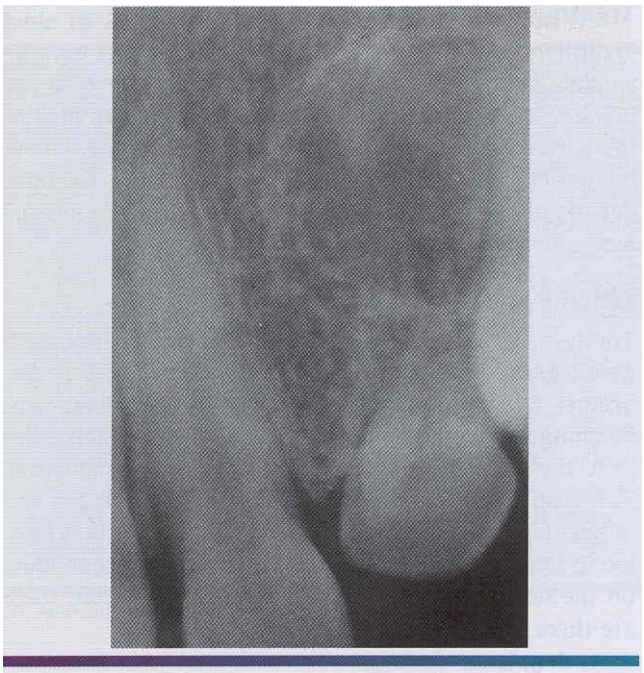


Figure 16-33 • Tuberous sclerosis. Periapical radiograph exhibiting a well-defined radiolucency apical to the maxillary left lateral incisor. Biopsy revealed an intraosseous fibrous proliferation.

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. Mentally retarded patients may have problems with oral hygiene procedures, and poor oral hygiene contributes to phenytoin-induced gingival hyperplasia. Patients affected by this condition 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.

MULTIPLE HAMARTOMA SYNDROME (COWDEN 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 PTEN (*phosphatase and tensin homolog deleted on chromosome* 10) gene has been implicated in its pathogenesis. Over 170 affected patients have been described in the literature.

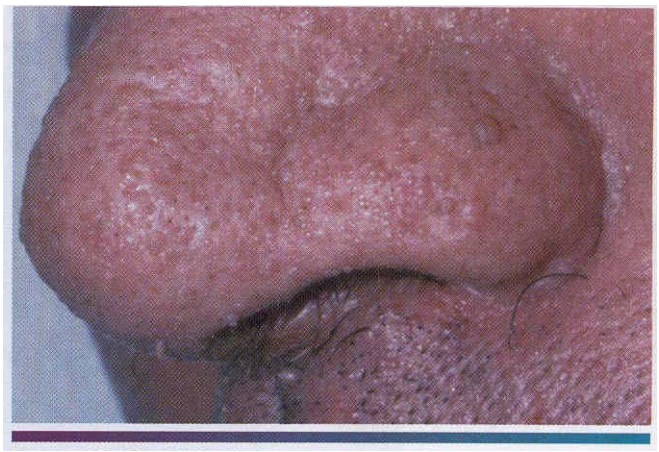


Figure 16-34 • Multiple hamartoma syndrome. These tiny cutaneous facial papules represent hair follicle hamartomas (trichilemmomas).

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 (Figure 16-34). Microscopically, most of these papules represent hair follicle **hamartomas called trichilemmomas. Other commonly noted skin lesions are acral keratosis,** a wart-appearing growth that develops on the dorsal surface of the hand, and palmoplantar keratosis, a prominent calluslike lesion on the palms or sales. Cutaneous **hemangiomas, 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 follicular adenocarcinoma may develop. In women, fibroeystic disease of the breast is frequently observed. Unfortunately, breast cancer occurs with a relatively high frequency (20% to 36%) 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 (Figures 16-35 and 16-36). 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.

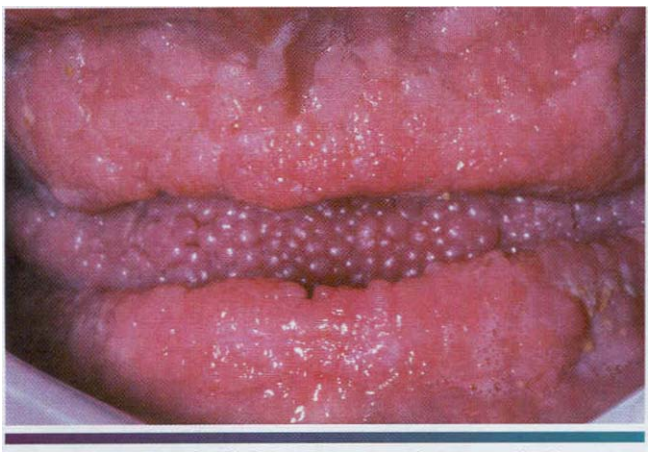


Figure 16-35 • Multiple hamartoma syndrome. Multiple, irregular fibroepithelial papules involve the tongue (center) and alveolar ridge mucosa.

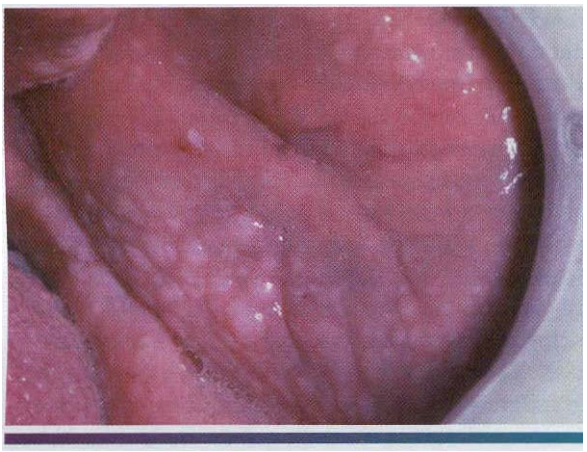


Figure 16-36 • Multiple hamartoma syndrome. Multiple papules on the left buccal mucosa.

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.

Diagnosis

The diagnosis is based on the finding of two of the following three signs:

1. Multiple facial trichilemmomas
2. Multiple oral papules
3. Acral keratoses

A positive family history is also helpful in confirming the diagnosis.

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. 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, epidemiologic, and molecular genetic abnormalities of these conditions have led to the identification of 21 different forms. Depending on the defective mechanism of cellular cohesion, there are three broad categories:

1. Simplex
2. Junctional
3. Dystrophic

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 for laminin-5, type XVII collagen, and $\alpha 6\beta 4$ integrin have been documented for the junctional types. Most of the dystrophic types appear to be caused by mutations in the genes responsible for type VII collagen production, with nearly 200 distinctly different mutations identified to date.

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, our discussion centers on these. Dental abnormalities, such as anodontia, enamel hypoplasia, pitting of the enamel, neonatal teeth, and severe dental caries, have been variably associated with several of the different types of epidermolysis bullosa, although recent studies have indicated that the prevalence of dental abnormalities is increased only with the junctional type. A disorder termed epidermolysis buJlosa acquisita is mentioned because of the similarity of its name; however, this appears to be an unrelated condition, having an autoimmune (rather than a genetic) origin (see page 672).

Table 16-2 *Examples of Epidermolysis Bul/osa (EB)*

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 ES, Pasini type	AD	Generalized blistering. white papules	Defect in type VII collagen
Dominant. dystrophic ES, 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

AD, Autosomal dominant; *AR,* autosomal recessive.

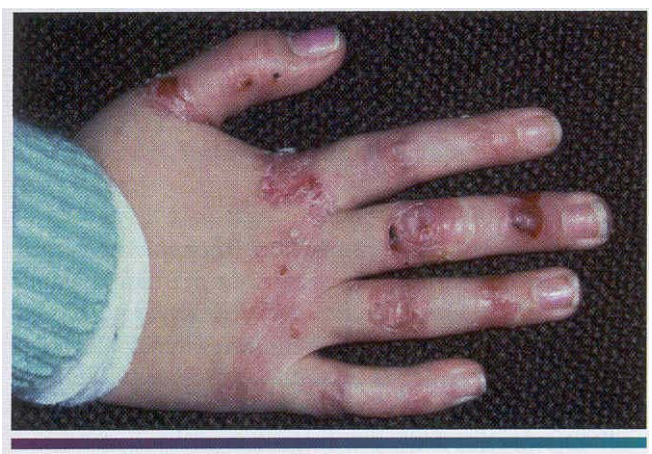


Figure 16-37 . Epidermolysis bullosa. A young girl, affected by the dominant dystrophic form of epidermolysis bullose, shows the characteristic hemorrhagic bullae, scarring, and erosion associated with minimal trauma to the hands.

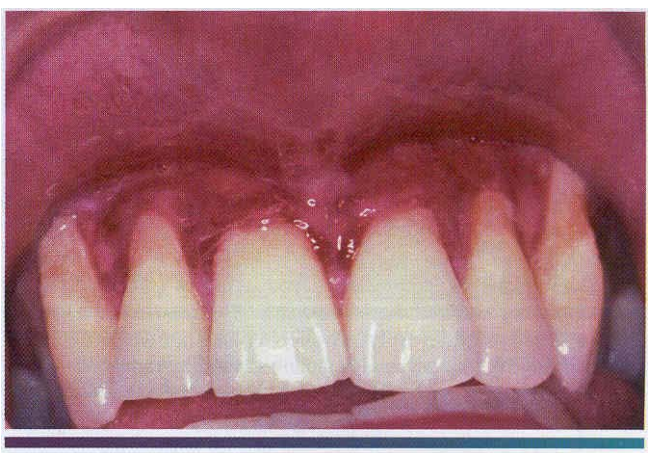


Figure 16-38 • Epidermolysis bullosa. A teenaged boy, affected by dominant dystrophic epidermolysis bullose. shows a reduced depth of the labial vestibule caused by repeated mucosal tearing and healing with scarring.

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 (Figure 16-37). 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 (Figure 16-38).

*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 to survive into the second decade, hand function is often greatly diminished because of the repeated episodes of cutaneous breakdown and

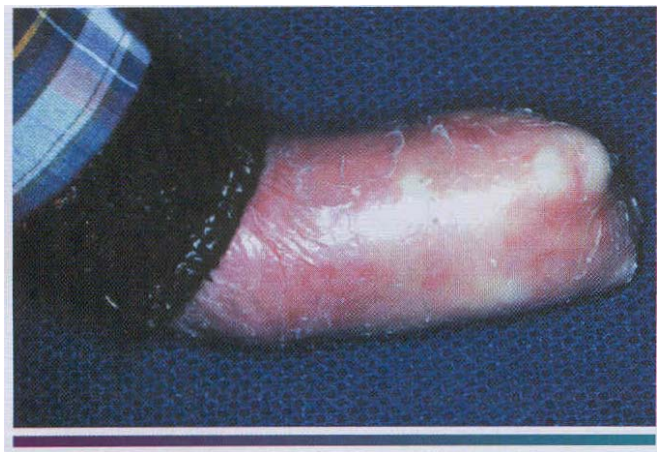


Figure 16-39 • Epidermolysis bullosa. A ts-yeer-old man. affected by recessive dystrophic epidermolysis bullose. shows the typical mittenlike deformity of the hand caused by scarring of the tissue after damage associated with normal activity.

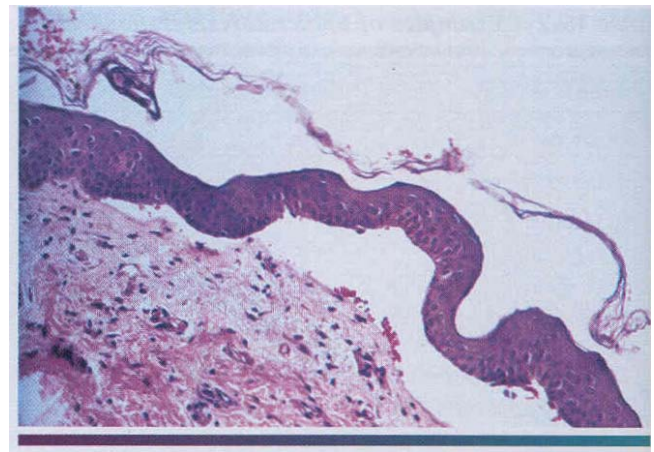


Figure 16-41 • Epidermolysis bullosa. Complete separation of the epithelium from the connective tissue is seen in this photomicrograph of a tissue section obtained from a patient affected by a junctional form of epidermolysis bullosa.

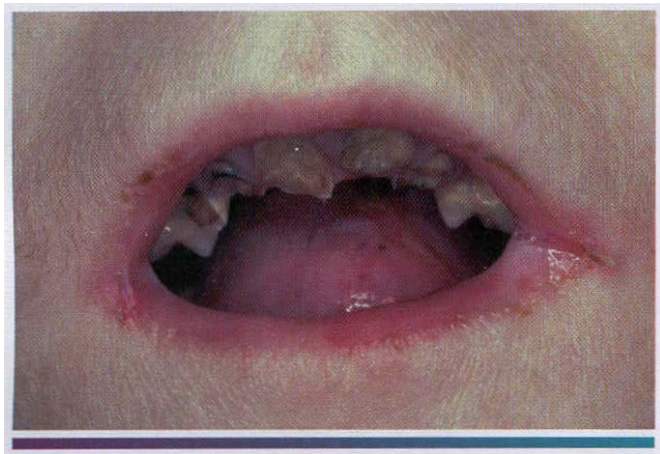


Figure 16-40 • Epidermolysis bullosa. Same patient as depicted in Figure 16-39. Microstomia has been caused by repeated trauma and healing with scarring. Note the severe dental caries activity associated with a soft cariogenic diet.

healing with scarring, resulting in fusion of the fingers into a mittenlike deformity (Figure 16-39),

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 (Figure 16-40) 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. lunctional and dystrophic forms show subepithelial clefting (Figure 16-41). Electron microscopic examination, which is still considered the diagnostic "gold standard," 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. Immunohistochemical evaluation of perilesional tissue may help to identify specific defects to classlfy and subtype the condition further.

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 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 non-**cariogenic 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.

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 families is indicated. and prenatal diagnosis is available.

Immune-Mediated Diseases and Their Evaluation

Several conditions discussed in this chapter are caused by the 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 (I) direct immunofluores**cence and (2) indirect immunofluorescence studies.** Fol-1DIVing 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.** Antibodies directed against human immunoglobulins are created by inoculating human immunoglobulins into a goat. The antibodies raised ill response to the human **immunoglobulins are harvested from the animal and**

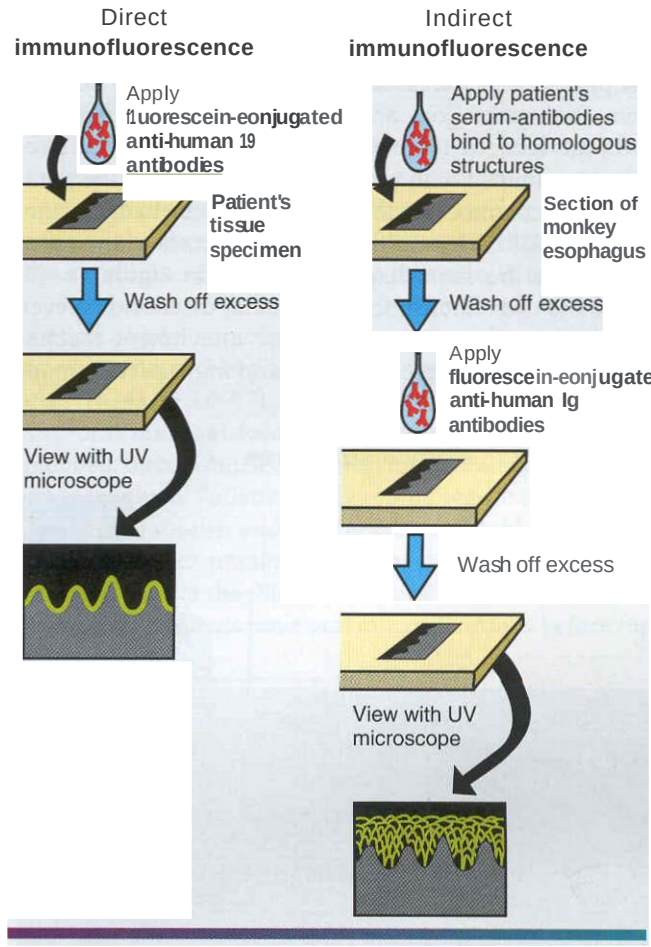


Figure 16-42 • Immunofluorescence techniques. Comparison of the techniques for direct and indirect immunofluorescence. The left side depicts the direct immunofluorescent findings in cicatricial pemphigoid, a disease that has autoantibodies directed toward the basement *lone*. The right side shows the indirect immunofluorescent findings for pemphigus vulgaris. a disease that has autoantibodies directed toward the intercellular areas between the spinous cells of the epithelium.

tagged with fluorescein. a dye that glows when viewed with ultraviolet light. As illustrated on the left side of **Figure 16-42, 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 micro**scope having an ultraviolet 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 Figure **16-42, a frozen section of tissue that is similar to human** oral mucosa (such as 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, 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 ultraviolet 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 Figure 16-43. 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 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

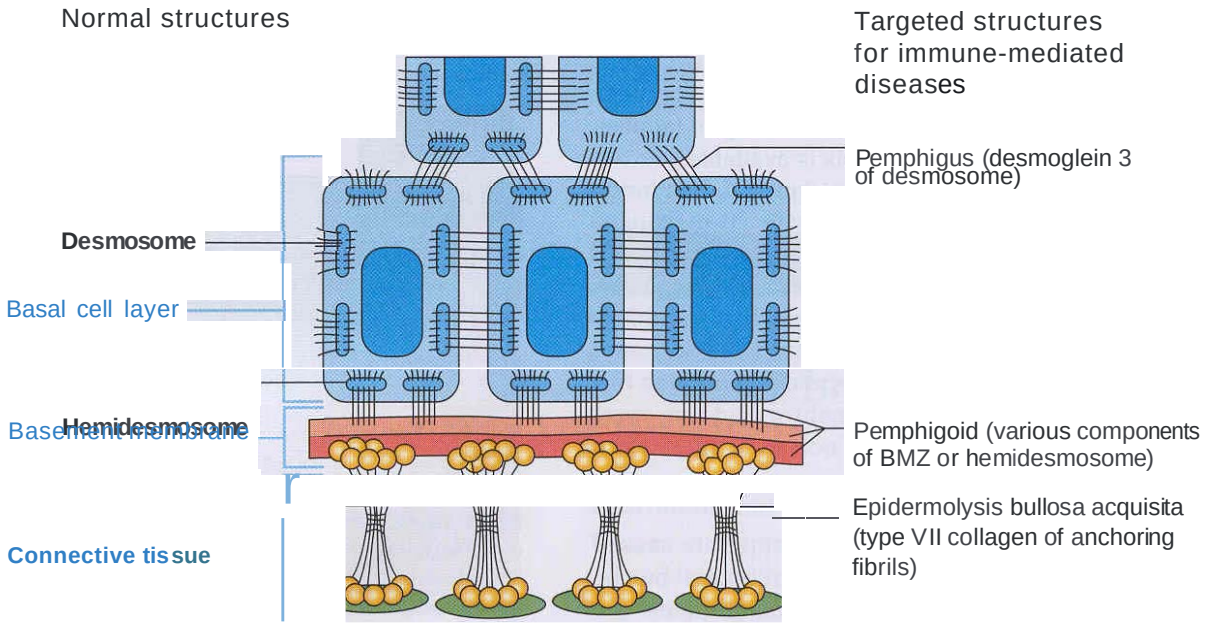


Figure 16-43 • Epithelial attachment apparatus. Schematic diagram demonstrating targeted structures in several immune-mediated diseases.

Table 16-3 ***Chronic vesiculoulcerative Diseases***

CONDITION	MEAN AGE	SEX PREDILECTION	CLINICAL FEATURES	HISTOPATHOLOGIC FEATURES
Pemphigus vulgaris	Fourth to sixth decade	Equal	Vesicles, erosions, and ulcerations on any oral mucosal or skin surface	Intraepithelial clefting
Paraneoplastic pemphigus	Sixth to seventh decade	Equal	Vesicles, erosions, and ulcerations on any mucosal or skin surface	Subepithelial and Intraepithelial clefting
Cicatricial pemphigoid	Sixth to seventh decade	Female	Primarily mucosal lesions	Subepithelial clefting
Bullous pemphigoid	Seventh to eighth decade	Equal	Primarily skin lesions	Subepithelial clefting
Erythema multiforme	Third to fourth decade	Male	Skin and mucosa involved; target lesions on skin	Subepithelial edema and perivascular inflammation
Lichen planus	Fifth to sixth decade	Female	Oral and/or skin lesions; may or may not be erosive	Hyperkeratosis, saw-teethed rete ridges, bandlike infiltrate of lymphocytes

Only the first two of these affect the oral mucosa. and the discussion is limited to pemphigus vulgaris. Pemphigus vegetans is not only rare, but 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 surfaceglycoproteins, desmoglein 3 and desmoglein I. 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 a result of this immunologic attack on the desrnosornes, a split develops within the epithelium, causing a blister to form.

Occasionally, a pemphigus-like oral and cutaneous eruption may occur in patients taking certain medications. such as penicillamine, or in patients suffering from malignancy. especially lymphoreticular malignancies (so-called paraneoplastic pemphigus) (see page 667). Similarly, a variety of other conditions may produce chronic veslculoulcerative 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.

DIRECT IMMUNOFLUORESCENCE	INDIRECT IMMUNOFLUORESCENCE
Positive intercellular	Positive
Positive. intercellular, and basement membrane zone	Positive (rat bladder)
Positive, basement membrane zone	Negative
Positive, basement membrane zone	Positive
Nondiagnostic	Negative
Fibrinogen. basement membrane zone	Negative

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 Jews.

Patients usually complain of oral soreness. and examination shows superficial. ragged erosions and ulcerations distributed haphazardly on the oral mucosa (Figures 16-44 to 16-47). 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 intraoraJly, and such lesions can seldom be identified by the examining clinician. probably because of early rupture of the thin. friable roof of the blisters. Over 50% of the patients have oral mucosal lesions before the

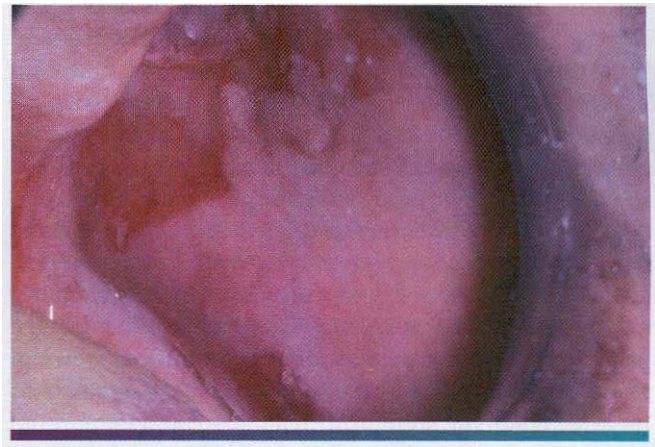


Figure 16-44 • Pemphigus vulgaris. Multiple erosions of the left buccal mucosa.

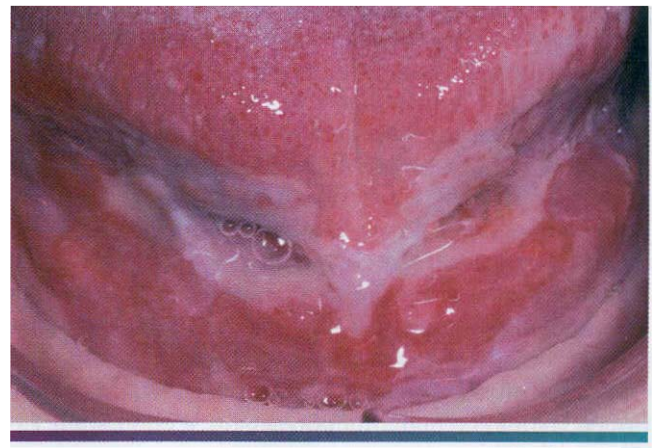


Figure 16-45 • Pemphigus vulgaris. Large. irregularly shaped ulcerations involving the floor of the mouth and ventral tongue.

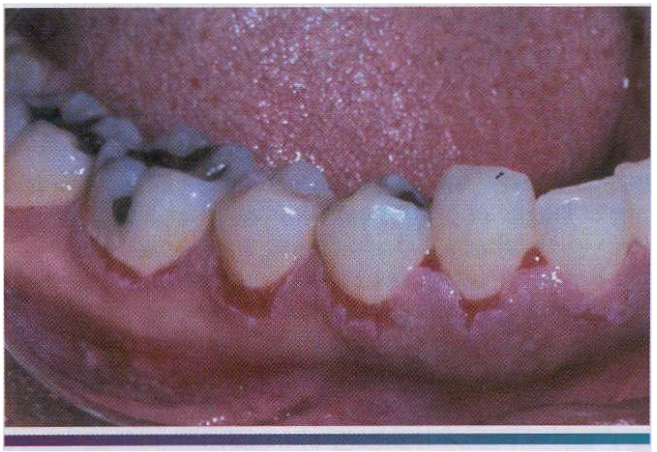


Figure 16-46 . Pemphigus vulgaris. Multiple erosions affecting the marginal gingiva.

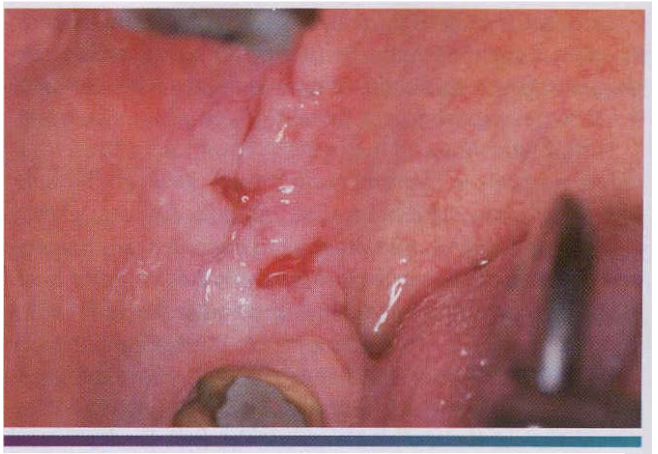


Figure 16-47 • Pemphigus vulgaris. The patient. with a known diagnosis of pemphigus vulgaris. had been treated with immunosuppressive therapy. The oral erosions shown here were the only persistent manifestation of her disease.

onset of cutaneous lesions. sometimes by as much as I year or more. Eventually. however, nearly all patients have intraoral involvement. The skin lesions appear as flaccid vesicles and bullae (Figure 16-48) 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 clcatriclal pemphigoid, the ocular lesions of pemphigus do not tend to produce scarring and symblepharon formation (see page 670).

Without proper treatment, the oral and cutaneous lesions tend *to* persist and progressively involve more surface are" . A characteristic feature of pemphigus vulgaris is that a bull" can be induced on normal-appearing skin if firm lateral pressure is exerted. This is called a positive Nikolsky sign.

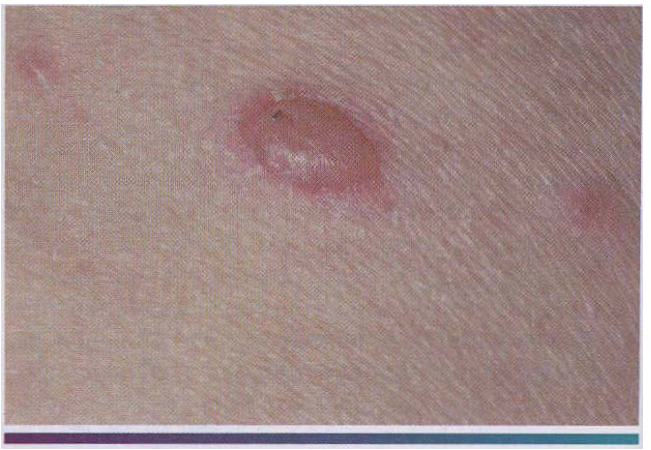


Figure 16-48 • Pemphigus vulgaris. This flaccid cutaneous bulla is characteristic of skin involvement.

Histopathologic Features

Biopsy specimens of penlesiona! tissue show characteristic intracplthclial separation, which occurs just above the basal cell layer of the epithelium (Figure 16-49). Sometimes the entire superflcia! 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 acantholysts, and the loose cells tend to assume a rounded shape (Figure 16-50). This feature of pemphigus vulgaris can be used in making " 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, antibodlcs (usually IgG or IgM) and complement components (usually C3) can be demonstrated in the intercellular spaces between the epithelial cells (Figure 16-51) 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.

It is cntical that perlleslonal 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. the results arc often inconclusive because of either a lack of an intact interface between the epithelium and connective tissue or a great deal of nonspecific inflammation.

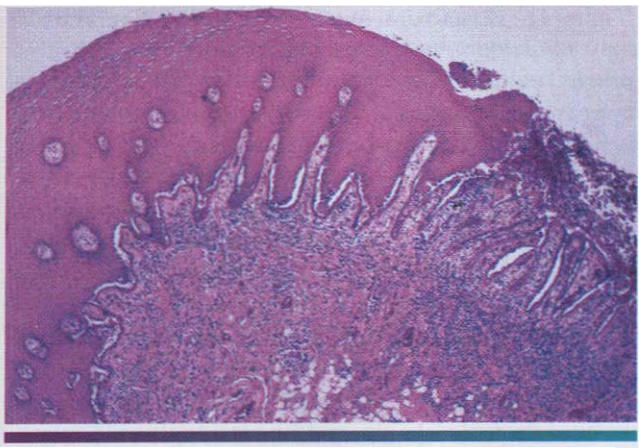


Figure 16-49 • Pemphigus vulgaris. Low-power photomicrograph of perilesional mucosa affected by pemphigus vulgaris. An intraepithelial cleft is located just above the basal cell layer.

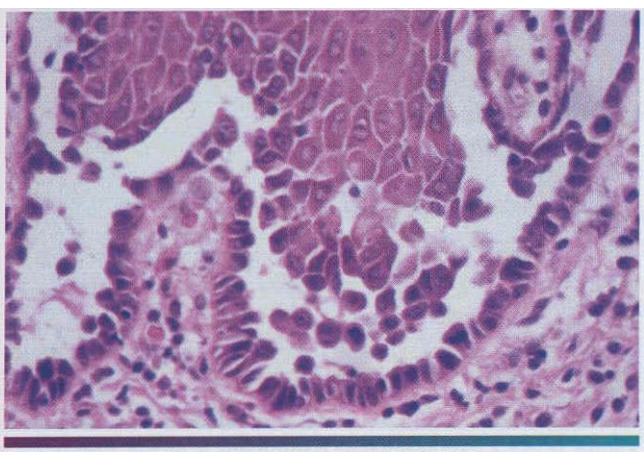


Figure 16-50 . Pemphigus vulgaris. High-power photomicrograph showing rounded. acantholytic epithelial cells sitting within the intraepithelial cleft.

Treatment and Prognosis

Adiagnosis 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. treatment consists primarily of systemic corticosteroids (usually prednisone), often in combination with other immunosuppressive drugs (so-called "steroid-sparing" agents), such as azathioprine. Although some clinicians have used 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:

- Diabetes mellitus
- Adrenal suppression

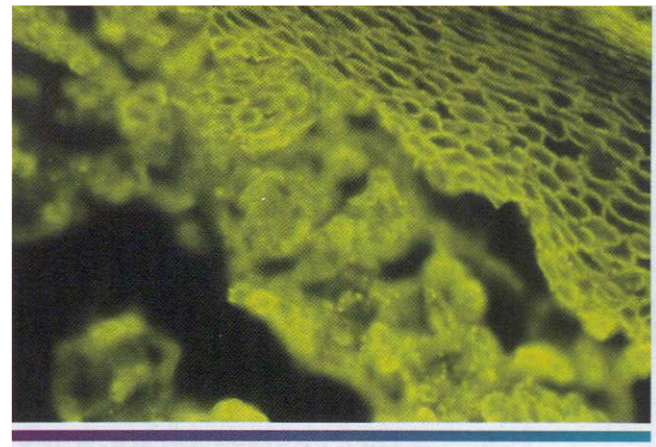


Figure 16-51 • Pemphigus vulgaris. Photomicrograph depicting the direct immunofluorescence pattern of pemphigus vulgaris. Immunoreactants are deposited in the intercellular areas between the surface epithelial cells.

- 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. then attempt to maintain the patient on as low a dose of corticosteroids as is necessary to control the condition. Often the success of therapy can be monitored by measuring the titers of circulating autoantibodies using indirect immunofluorescence, because disease activity often correlates with the abnormal antibody levels. Pemphigus rarely undergoes complete resolution, although remissions and exacerbations are common.

Before the development of corticosteroid therapy, as many as 60% to 80% 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 pemphigus is a recently described. rare vesiculobullous disorder that affects patients who have a neoplasm, usually lymphoma or chronic lymphocytic leukemia. It is thought that cross-reactivity develops between antibodies produced in response to the tumor and antigens associated with the desmosomal complex and the basement membrane zone of the epithelium. A variety of different antibodies that attack these epithelial adherence structures are produced, resulting in an

array of clinical features, histopathologic findings, and immunopathologic findings that may be perplexing if the **clinician is unfamiliar with this disease process.**

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 or thymoma. In some cases, paraneoplastic pemphigus develops before a malignancy is identified, thus signaling the presence of a tumor. The neoplastic disease mayor 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 (Figure 16-52) 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 (Figure 16-53). The oral mucosa shows multiple areas of erythema and diffuse, irregular ulceration (Figure 16-54), affecting virtually any oral mucosal surface. If the lesions remain untreated, they persist and worsen.

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** (Figure 16-55). The vaginal mucosa and mucosa of the respiratory tract may be involved.

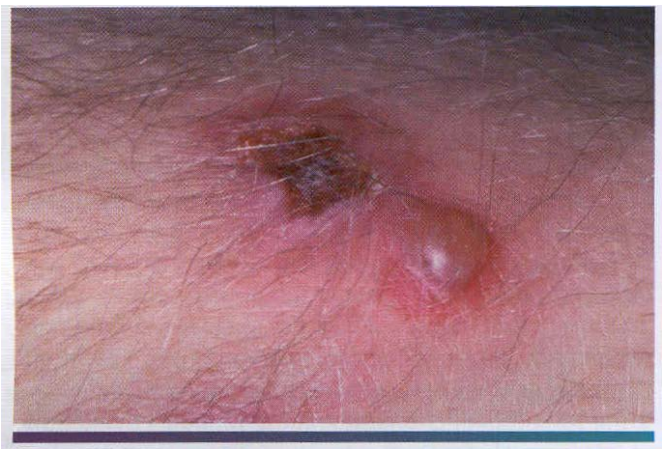


Figure 16-52 • Paraneoplastic pemphigus. The bulla and crusted ulcerations on this patient's arm are representative of the polymorphous cutaneous lesions.

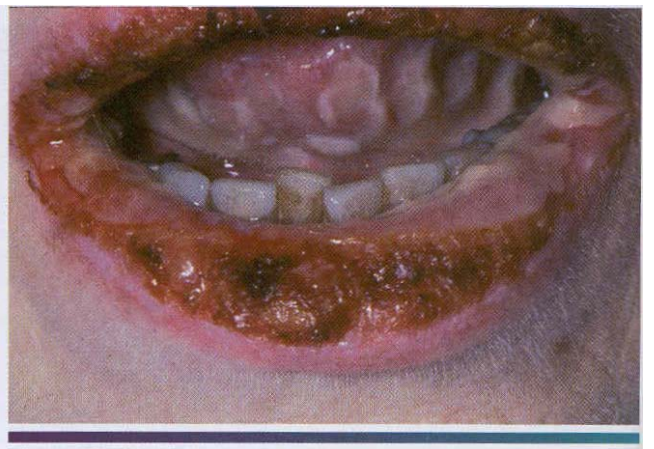


Figure 16-53 • Paraneoplastic pemphigus. Crusted, hemorrhagic lip lesions may be mistaken for erythema multiforme or herpes simplex infection.

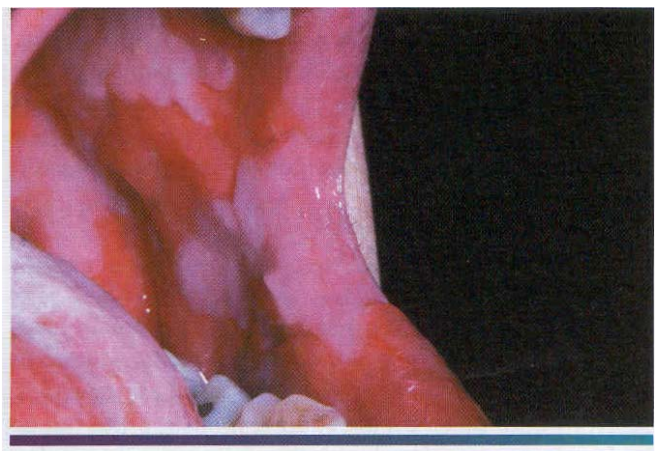


Figure 16-54 • Paraneoplastic pemphigus. These diffuse oral ulcerations are quite painful.

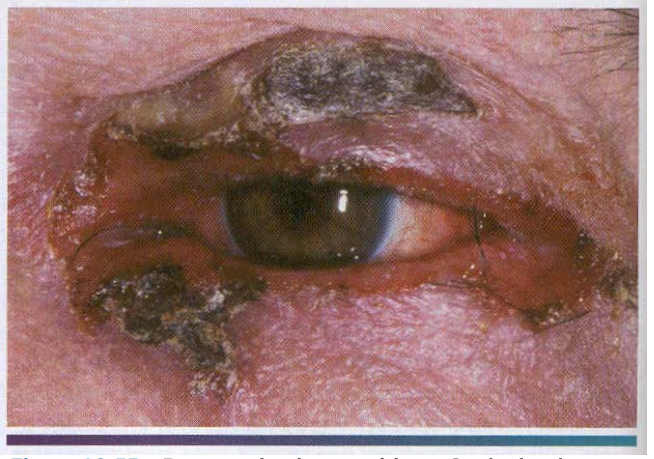


Figure 16-55 • Paraneoplastic pemphigus. Ocular involvement.

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 cleft ing (like pemphigoid) or intraepithelial cleft ing (like pemphigus) (Figure 16-56),

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. Indirect immunofluorescence should be conducted using a transitional type of epithelium (such as rat urinary bladder mucosa) as the substrate. This shows a fairly specific pattern of antibody localization to the intercellular areas of the epithelium. Immunoprecipitation studies remain the gold standard for the diagnosis of paraneoplastic pemphigus. however. because the various antibodies that characterize this condition can be identified with a considerable degree of specificity. Antibodies directed against desmoplakin I and II. major bullous pemphigoid antigen. envoplakin. and pertplakin, in addition to desmoglein i and 3. are typically detected.

Treatment and Prognosis

Paraneoplastic pemphigus is often a very serious condition with a high morbidity and mortality rate. 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 essentially consists of systemic prednisone. typically combined with another immunosuppressive agent. such as azathioprine. methotrexate. or cyclophosphamide. 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. 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.

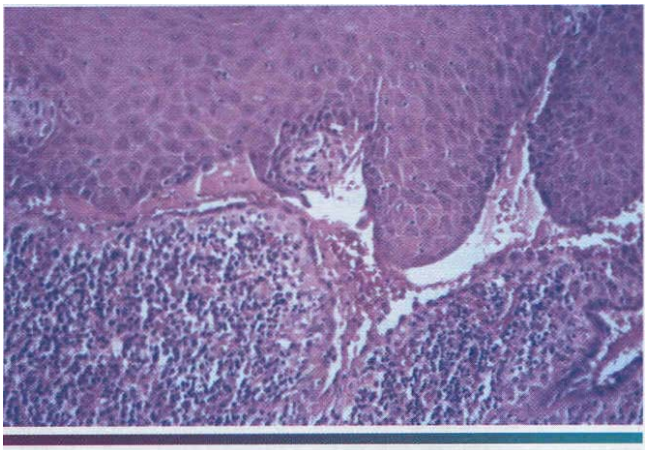


Figure 16-56 • Paraneoplastic pemphigus. This medium-power photomicrograph shows both intraepithelial and subepithelial cleftlng,

CICATRICIAL PEMPHIGOID (BENIGN MUCOUS MEMBRANE PEMPHIGOID; MUCOUS MEMBRANE PEMPHIGOID)

Evidence has accumulated to suggest that cicatricial 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 anyone of a variety of basement membrane components. all of which produce similar clinical manifestations. The precise incidence 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.

The term cicatricial 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

Cicatricial 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 (Figure 16-57) may be involved.

The oral lesions of pemphigoid begin as either vesicles or bullae that may occasionally be identified clinically (Figure 16-58). In contrast. patients with pemphigus rarely display such blisters. The most likely explanation for this difference is that the pemphigoid blister forms in

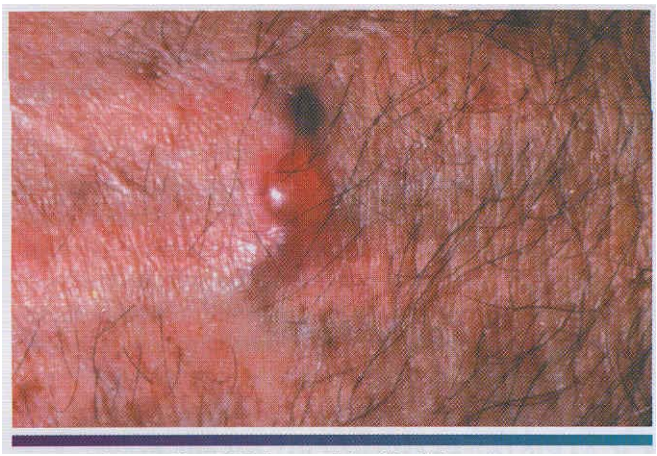


Figure 16-57 . Cicatricial pemphigoid. Although cutaneous lesions are not common, tense bullae such as these may develop on the skin of 20% of affected patients. (Courtesy of Dr. Charles Camisa.)

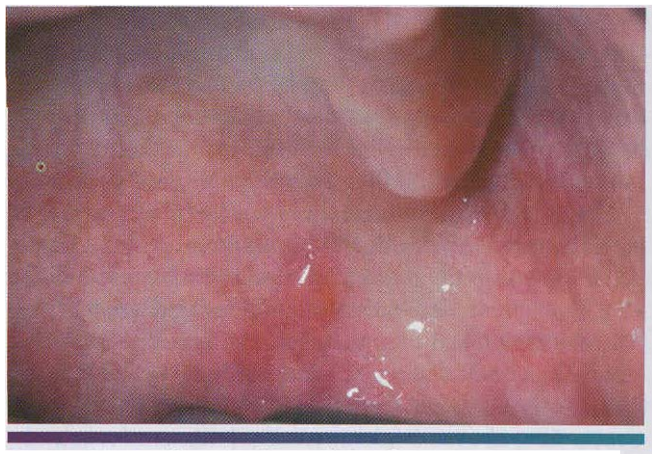


Figure 16-58 . Cicatricial pemphigoid. One or more intraoral vesicles, as seen on the soft palate, may be detected in patients with cicatricial pemphigoid. Usually, ulcerations of the oral mucosa are also present.

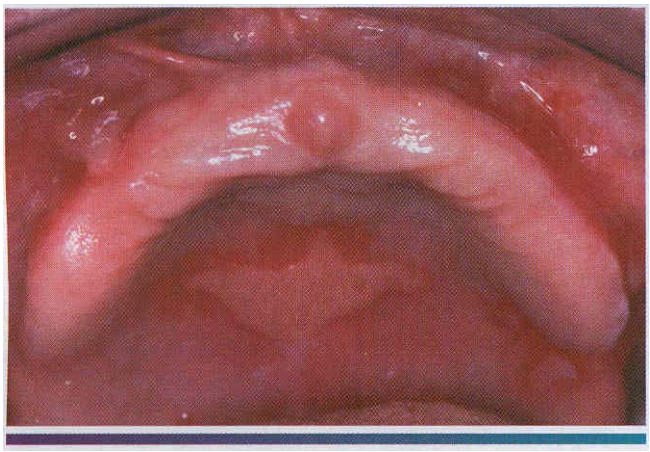


Figure 16-59 • Cicatricial pemphigoid. Large, irregular oral ulcerations characterize the lesions after the initial bullae rupture.

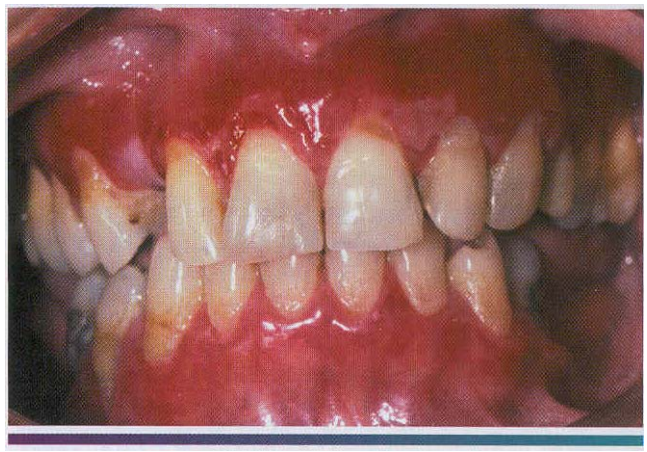


Figure 16-60 • Cicatricial pemphigoid. Often the gingival tissues are the only affected site, resulting in a clinical pattern known as desquamative gingivitis. Such a pattern may also be seen with lichen planus and pemphigus vulgaris.

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 (Figure 16-59). 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 (Figure 16-60). Gingival involvement **produces a clinical reaction pattern termed desquamative** gingivitis (see page 144). 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 cicatricial 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 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) conjunctiva. Adhesions called symblepharons result (Figure 16-61). Without treatment the inflammatory changes **become marc severe, although conjunctival vesicle for-** mation is rarely seen (Figure 16-62). Scarring can ultimately cause the eyelids to turn inward (entropion). This causes the eyelashes to rub against the cornea and globe (trichiasis) (Figure 16-63). The scarring closes off the openings of the lacrimal glands as well, and with the loss

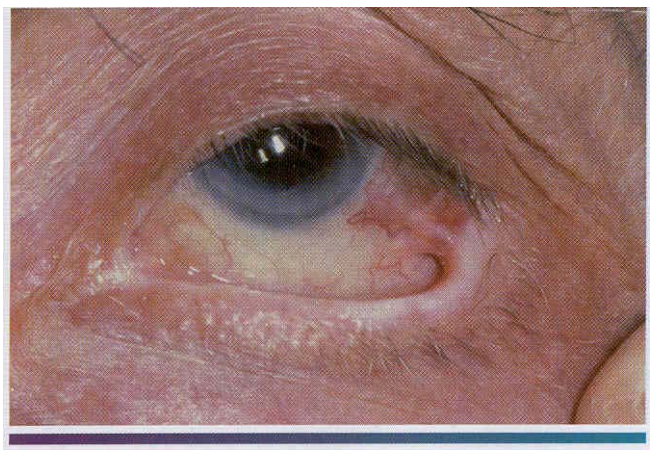


Figure 16-61 • Cicatricial pemphigoid. Although the earliest ocular changes are difficult to identify, patients with ocular involvement may show adhesions (symbJepharons) between the bulbar and palpebral conjunctivae before severe ocular damage occurs.

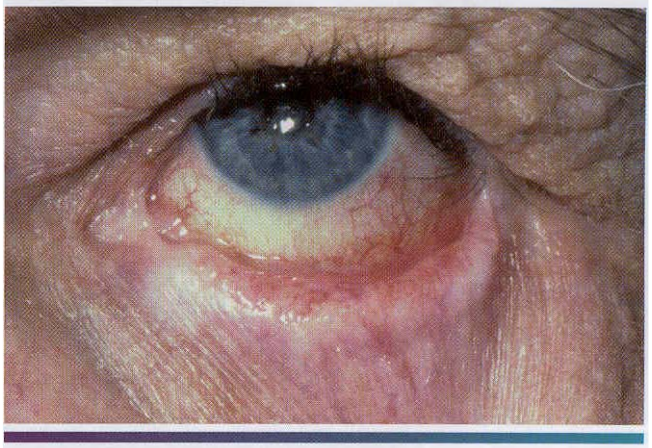


Figure 16-62 • Cicatricial pemphigoid. The disease has caused the upper eyelid of this patient to turn inward (entropion), resulting in the eyelashes rubbing against the eye itself (trichiasis). Also note the obliteration of the lower fornix of the eye.

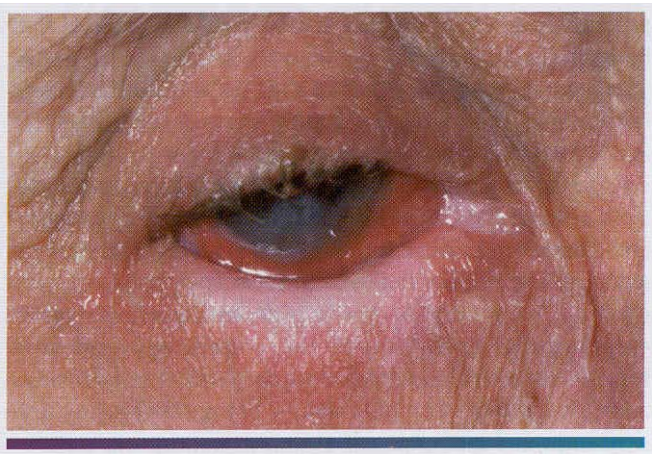


Figure 16-63 • Cicatricial pemphigoid. A patient with ocular involvement shows severe conjunctival inflammation. The lower eyelashes were removed by an ophthalmologist because of trichiasis associated with entropion.

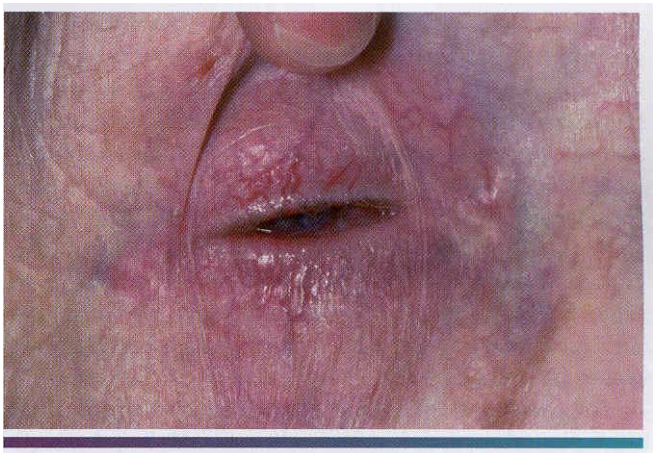


Figure 16-64 • Cicatricial pemphigoid. In this patient, the ocular involvement has resulted in nearly complete scarring between the conjunctival mucosa and the eyelids themselves, producing blindness.

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 eyeiids themselves (Figure 16-64l.

Other mucosal sites may also be involved and cause considerable difficulty for the patient. In femaie patients, **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 difficuity breathing should undergo examination with laryngoscopy.

Histopathologic Features

Biopsy of penlesional mucosa shows a split between the surface epithelium and the underlying connective tissue (Figure i6-65). A mild chronic inflammatory cell infil**trate 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 (Figure 16-66). 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 immuno**reactants may playa role in the pathogenesis of the subepitheiial *vesicle* formation by weakening the attachment of the basement membrane through a *variety*

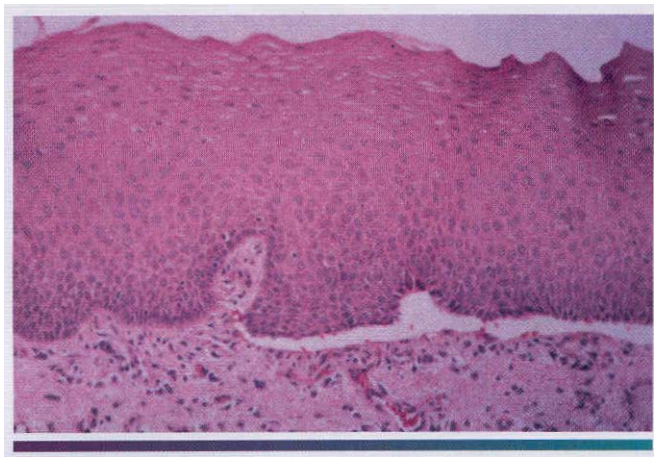


Figure 16-65 • Cicatricial pemphigoid. Medium-power photomicrograph of perilesional tissue shows characteristic subepithelial cleft ing.

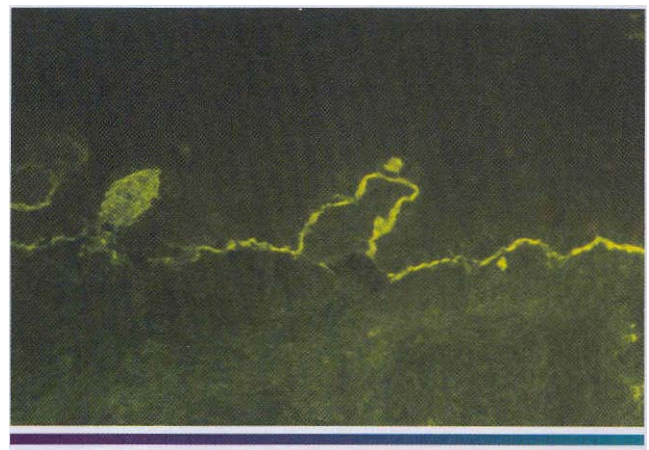


Figure 16-66 • Cicatricial pemphigoid. Direct immunofluorescence studies show a deposition of immunoreactants at the basement membrane zone of the epithelium. (Courtesy of Dr. Ronald Grimwood.)

of mechanisms, including complement activation with recruitment of inflammatory cells, particularly neutrophils.

Indirect immunofluorescence is positive in only 5% of these patients, indicating a relatively consistent lack of circulating autoantibodies. One type of cicatricial pemphigoid that has been characterized recently produces low levels of circulating autoantibodies to epiligrin (laminin-5), a component of the basement membrane. Antiepiligrin cicatricial pemphigoid seems to have more widespread involvement, affecting oral, nasal, ocular, and laryngeal mucosa, compared with other forms of cicatricial pemphigoid.

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 loose 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 disease, angina bullosa hemorrhagica, and epidermolysis bullosa acquisita.

Linear IgA disease. Linear IgA disease, as the name indicates, is characterized by the linear deposition of only IgA along the basement membrane zone; thus, this disease can be distinguished from cicatricial pemphigoid on an immunopathologic 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. 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 roie 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.

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 cleft ing, 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 of the bulla. This finding is in contrast to that of most forms of cicatricial pemphigoid, in which the autoantibodies are usually localized to the roof of the induced blister.

Treatment and Prognosis

Once the diagnosis of cicatricial 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 expe-

riencing ocular complaints. 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 oniy 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 corticosteroids plus other immunosuppressive agents (particularly cyclophosphamide) may be used if the patient has no medical contraindications. This type of aggressive treatment is absolutely indicated in the presence of advancing ocular disease. Attempts at surgical correction of the symblepharons must be done when the disease is under control or quiescent; otherwise, the manipulation often induces an acute flare of the ocular lesions.

One alternative systemic therapy that may produce fewer serious side effects is the use of dapsone, a sulfa drug derivative. 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 gm of each drug have been reported (in open-label trials) to be effective in controlling cicatricial pemphigoid. Double-blind, placebo-controlled studies on larger groups of patients should be done to confirm this form of therapy, however.

BULLOUS PEMPHIGOID

Bullous pemphigoid is the most common of the autoimmune blistering conditions. occurring at an estimated rate of 10 cases per million population per year. The disease is characterized by the production of autoantibodies directed against components of the basement membrane.

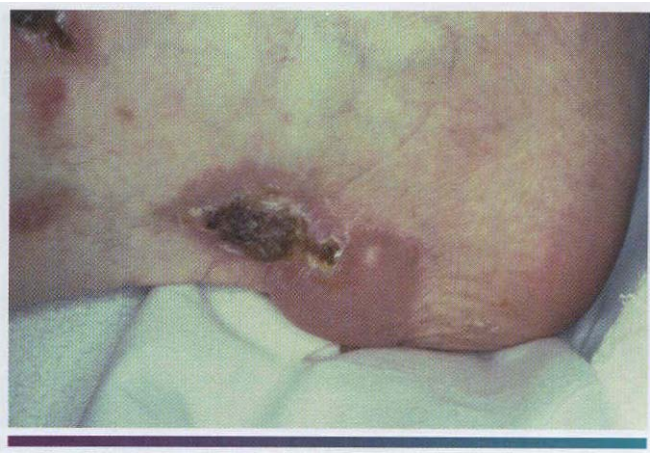


Figure 16-67 • Bullous pemphigoid. Cutaneous vesiculobullous lesions of the heel. The bullae eventually rupture, leaving hemorrhagic crusted areas.

In many respects, bullous pemphigoid resembles cicatricial 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 limited, whereas the course in patients with cicatricial pemphigoid is usually protracted and progressive.

Clinical Features

Bullous pemphigoid typically develops in older people: most patients are between 60 and 80 years of age. No sex or racial predilection is seen. Pruritus may be an early symptom. This is followed by the development of multiple, tense bullae on either normal or erythematous skin (Figure 16-67). These lesions eventually rupture after several days. causing a superficial crust to form. Eventually, healing takes place without scarring.

Oral mucosal involvement is uncommon, although the reported prevalence in several series of cases has ranged from 8% to 39%. Referral bias may explain the discrepancy in prevalence rates. 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 (Figure 16-68).

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.

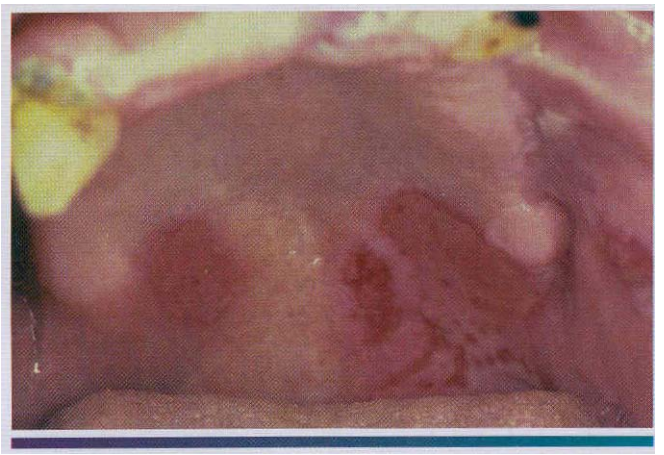


Figure 16-68 • Bullous pemphigoid. These oral lesions appear as large, shallow ulcerations involving the soft palate.

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 may 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, 40% to 70% 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.

Treatment and Prognosis

Management of the patient with 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, another immunosuppressive agent, such as azathioprine, 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 many patients experiencing spontaneous remission after 2 to 3 years. Problems may develop with immunosuppressive therapy in this elderly population, however, and mortality rates of up to 20% have been reported in some series.

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 either a preceding infection, such as herpes simplex or *Mycoplosma pnrumoniae*, or exposure to anyone 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 vcsiculobullous diseases.

Clinical Features

Erythema multiforme usually has an acute onset and may dispiay a wide spectrum of clinical disease. On the mild end of the spectrum, ulcerations develop, affecting the oral mucosa primarily. In its most severe form, diffuse sloughing and ulceration of the entire skin and mucosal surfaces may be seen (toxic epidermal necrolysis or Lyell's disease).

Patients are usually young adults in their 20s or 30s. Men are affected more frequently than women.

Prodromal symptoms include fever, malaise, headache, cough, and sore throat, occurring approximately I week before onset. Although the disease is self-limiting, usually lasting 2 to 6 weeks, about 20% of patients experience recurrent episodes, usually in the spring and autumn.

Erythematous skin lesions develop in about 50% of cases. A variety of appearances (*multiforme* = many forms) may be present. Typically, early lesions appear on the extremities and are flat, round, and dusky-red in hue. These become slightly elevated and may evolve into bullae with necrotic centers. Sometimes particular skin lesions develop that are highly characteristic for the disease. These lesions appear as concentric circular erythematous rings resembling a target or bull's-eye (target lesions) (Figure 16-69).

The oral lesions begin as erythematous patches that undergo epithelial necrosis and evolve into large, shallow

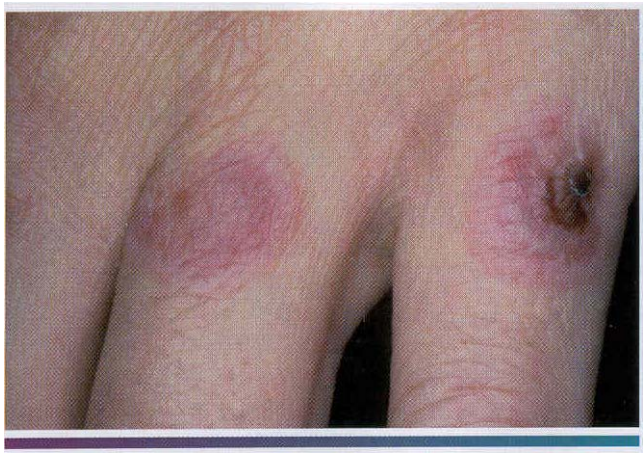


Figure 16-69 • Erythema multiforme. The concentric erythematous pattern of the cutaneous lesions on the fingers resembles a target or buli's-eye.

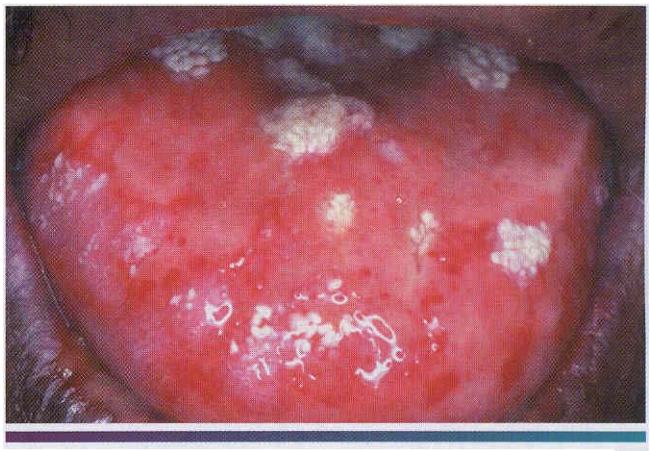


Figure 16-70 . Erythema multiforme. Diffuse ulcerations and erosions involving the dorsal surface of this patient's tongue.

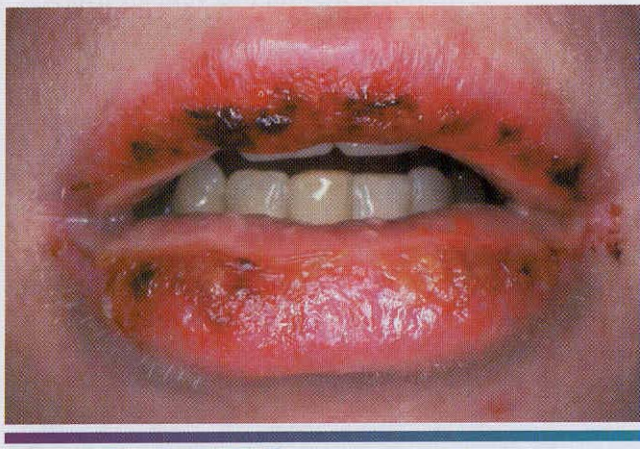


Figure 16-71 • Erythema multiforme. Ulceration of the labial mucosa, with hemorrhagic crusting of the vermilion zone of the lips.

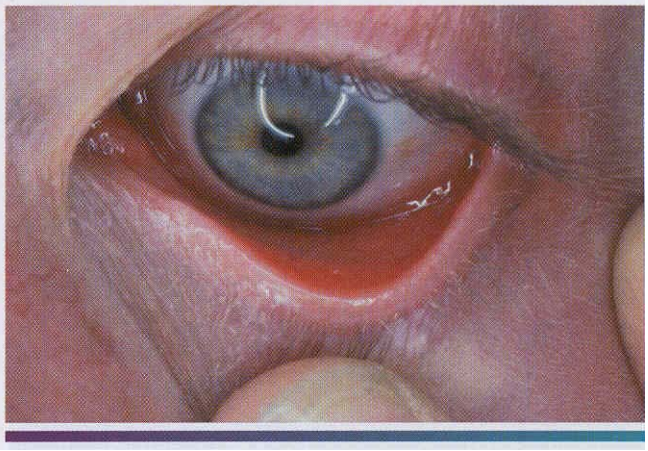


Figure 16-72 • Stevens-Johnson syndrome. With erythema multiforme major (Stevens-Johnson syndrome), other mucosal surfaces may show involvement, such as the severe conjunctivitis depicted in this photograph.

erosions and ulcerations with irregular borders (Figure 16-70). Hemorrhagic crusting of the vermilion zone of the lips is common (Figure 16-71). 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 more severe form of the disease, known as erythema multiforme major or Stevens-Johnson syndrome, is usually triggered by a drug rather than infection. For such a diagnosis to be made, either the ocular (Figure 16-72) or genital (Figure 16-73) mucosae should be affected in conjunction with

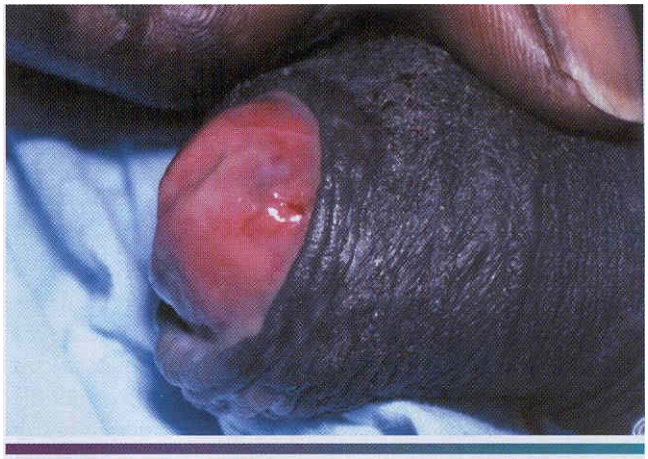


Figure 16-73 • Stevens-Johnson syndrome. Genital ulcerations, demonstrated in this patient by the involvement of the glans penis, may also be a component.

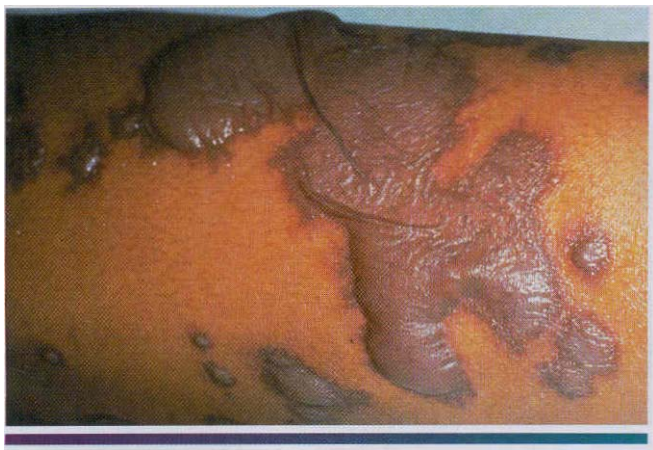


Figure 16-74 . Toxic epidermal necrolysis. This severe form of erythema multiforme exhibits diffuse bullous skin lesions. (Courtesy of Dr. Peter tersen.)

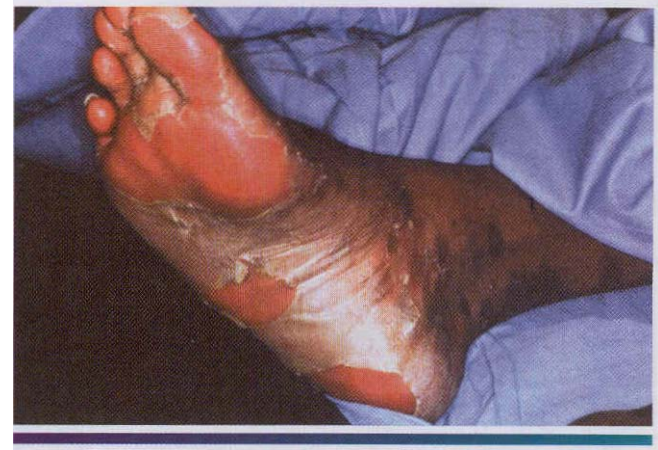


figure 16-75 • Toxic epidermal necrolysis. The desquamation of the skin of the foot is characteristic of the diffuse sloughing cutaneous lesions. (Courtesy of Dr. Peter larsen.)

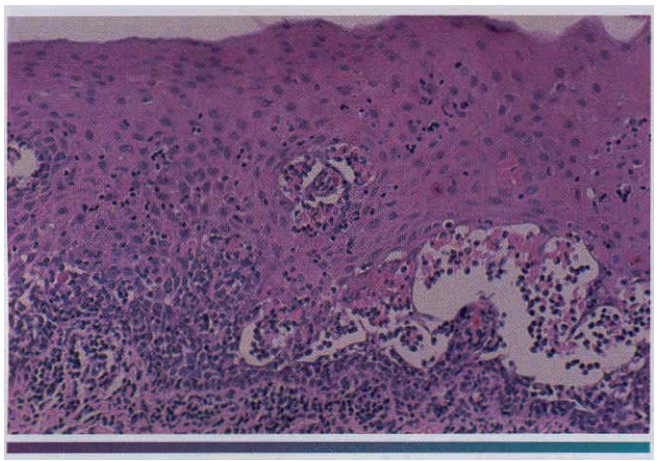


Figure 16-76 • Erythema multiforme. This medium power photomicrograph shows inflammation and intraepithelial vesicle formation in the basilar portion of the epithelium. Numerous necrotic eosinophilic keratlnocytes are present in the blister area.

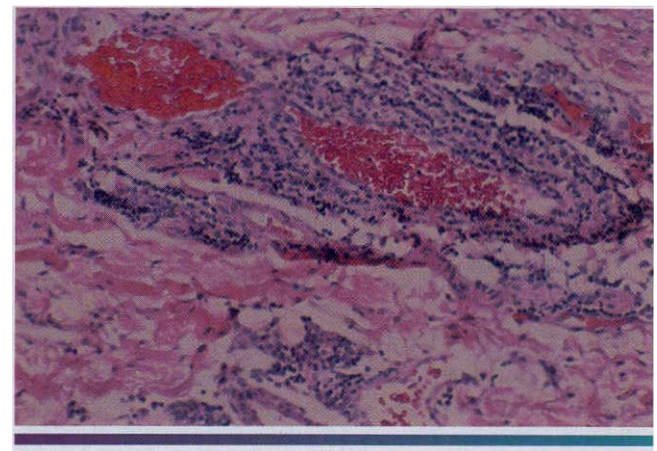


figure 16-77 • Erythema multiforme. This medium power photomicrograph shows the perivascular inflammatory infiltrate, typically seen in erythema muitiforme.

the oral and skin lesions. With severe ocular involvement. scarring (symblepharon formation) may occur. similar to that in cicatriciai pemphigoid (see page 670).

***Toxic** epiderma! necroly sis*. Many dermato logists consider toxic epidermal nccrolysis to represent the most *severe* form of erythema multiforme. It is almost always triggered by drug exposure. Recent studies *have* shown that the damage to the epithelium is due to increased apoptosis of the epithelial cells. Diffuse sloughing of a significant proportion of the skin and mucosal surfaces makes it appear as if the patient had been badly scalded (Figures 16-74 and 16-75). In contrast to erythema multiforme major. toxic epidermal necrolysis tends to occur in older people. A female predilection is observed. If the patient survives. the cutaneous process resolves in 2 to 4 weeks: however. oral lesions may take longer to heal. and significant residual ocular damage is evident in half the patients. These more severe presentations of erythema multiforme are rare. Erythema multiforme major occurs at an *average* rate of five cases per million population per year, and toxic epidermal necrolysis occurs at a rate of about one case per million per year.

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 (Figure 16-76), A mixed inflammatory infiltrate is present. consisting of lymphocytes. neutrophils, and often eosinophils. Sometimes these cells are arranged in a perivascular orientation (Figure 16-77). Because the immunopathologic features are also nonspecific. the diagnosis is often based on the clinical presentation and the exclusion of other vesiculobullous disorders.

Treatment and Prognosis

Management of erythema multiforme, particularly the minor and major forms, includes the use of systemic corticosteroids, especially in the early stages of the disease. Sometimes oral lesions in patients with the minor form of the condition may be managed effectively with topical corticosteroid syrups or elixirs. If a causative drug is identified or suspected, it should be discontinued immediately.

If the patient is dehydrated as a result of an inability to eat because of oral pain, intravenous rehydration may be necessary along with topical anesthetic agents to decrease discomfort.

If recurrent episodes of erythema multiforme are a problem, an initiating factor, such as recurrent herpesvirus infection or drug exposure, should be sought. If disease is triggered by herpes simplex, continuous oral acyclovir therapy can prevent recurrences.

Generally, erythema multiforme is not life threatening except in its most severe forms. The mortality rate in patients with toxic epidermal necrolysis historically has been approximately 34%; the rate in those with Stevens-Johnson syndrome is 2% to 10%. Corticosteroids should probably be avoided in the management of toxic epidermal necrolysis because some investigators *have* found that such drugs may be detrimental. Recently, intravenous administration of pooled human immunoglobulins has been shown to produce remarkable resolution of toxic epidermal necrolysis, presumably because of blockade of Fas ligand, which induces epithelial cell apoptosis. 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.

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. Females are affected more frequently than males by a 2:1 ratio. Patients may occasionally 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, thus raising the possibility that it represents a type of hypersensitivity to an environmental factor. In addition, the lesions of erythema migrans in one female patient reportedly waxed and waned predictably with oral contraceptive therapy, suggesting that hormonal factors may be relevant.

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 (Figures 16-78 and 16-79), 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, yellowish-white, serpentine or scalloped border (Figure 16-80). The patient who is aware of the process is

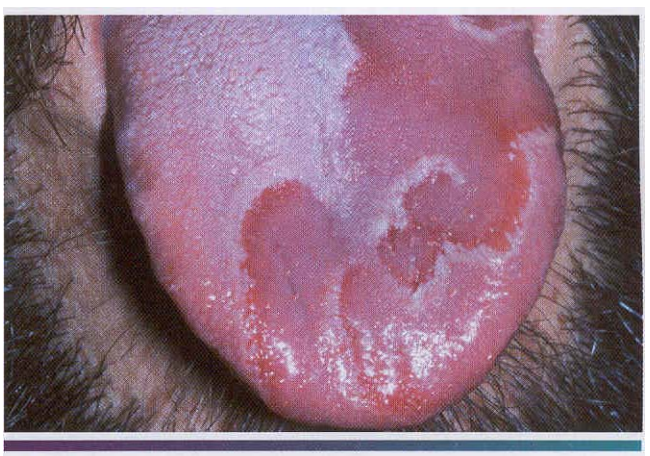


Figure 16-78 • Erythema migrans. The erythematous, well-demarcated areas of papillary atrophy are characteristic of erythema migrans affecting the tongue (benign migratory glossitis). Note the asymmetric distribution and the tendency to involve the lateral aspects of the tongue.

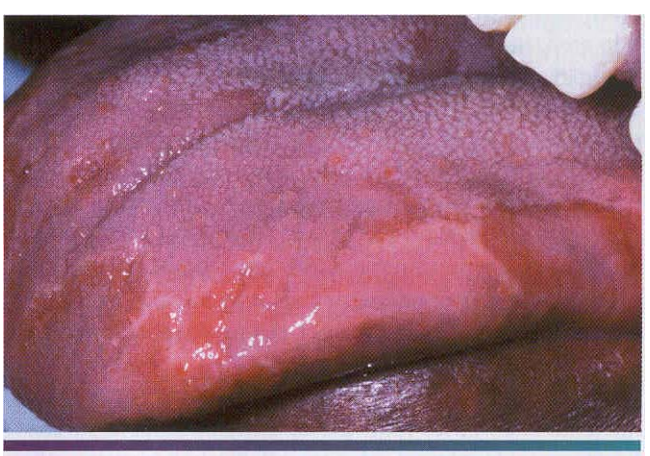


Figure 16-79 • Erythema migrans. lingual mucosa of a different patient than the one in Figure 16-78. The lateral distribution of the lesions is shown.

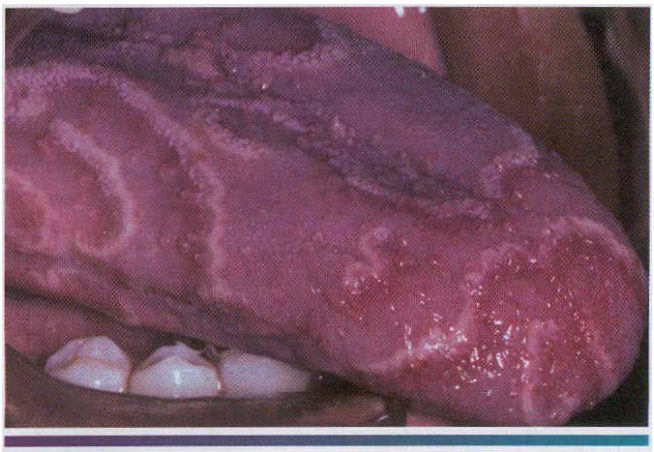


Figure 16-80- Erythema migrans. Striking involvement of the dorsal and lateral surfaces of the tongue.

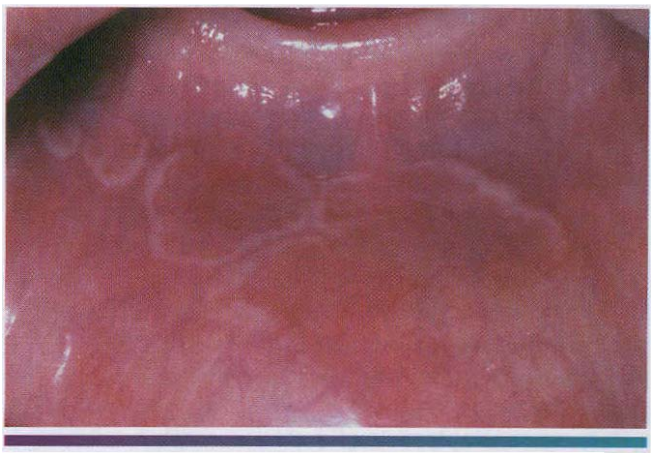


Figure 16-81- Erythema migrans. lesions of the lower labial mucosa.

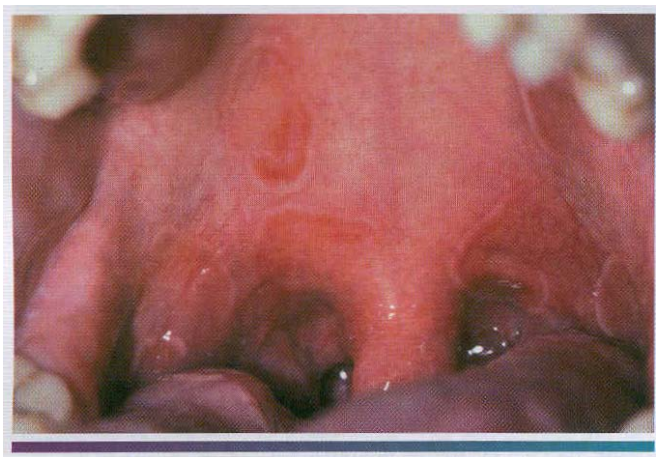


Figure 16-82- Erythema migrans. These palatal lesions show well-demarcated erythematous areas surrounded by a white border. similar to the process involving the tongue.

often able to describe the lesions as appearing quickly in one area, healing within a few days or weeks, 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. Often patients with fissured tongue (see page 12) are affected with erythema migrans as well. Some patients may have only a soiitary 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 (Figures 16-81 and 16-82). These lesions typically produce no symptoms, and they can be identified by a yellowish-white serpentine or scalloped border that surrounds an erythematous zone. **These features should prevent confusion with** such conditions as candidiasis or eryth roplakia.

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 (Figure 16-83). In addition, collections of ncutrophils (Munro abscesses) are observed within the epithelium (Figure 16-84): 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. In one case-control** study of psoriatic patients, erythema rnlgrans 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 psoriatics and patients 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 psorlancs are [ust more susceptible to erythema migrans is open to debate.

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. Infrc-

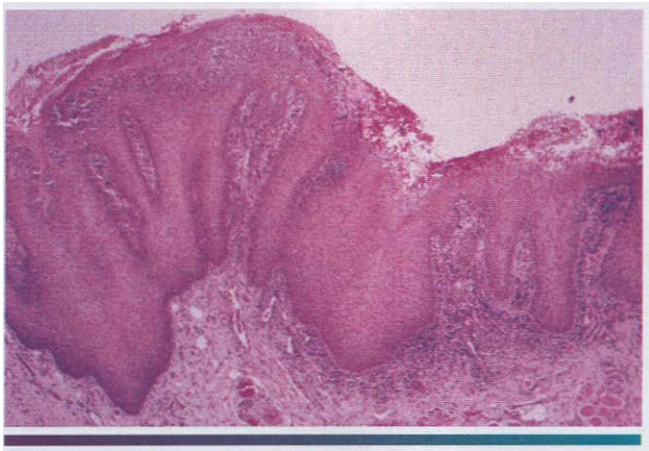


Figure 16-83 - Erythema migrans. This low-power photomicrograph shows the elongation of the rete ridges with parakeratosis and neutrophilic infiltration. Such features are also common in psoriasis, which explains why this is known as a *psoriasiform mucositis*.

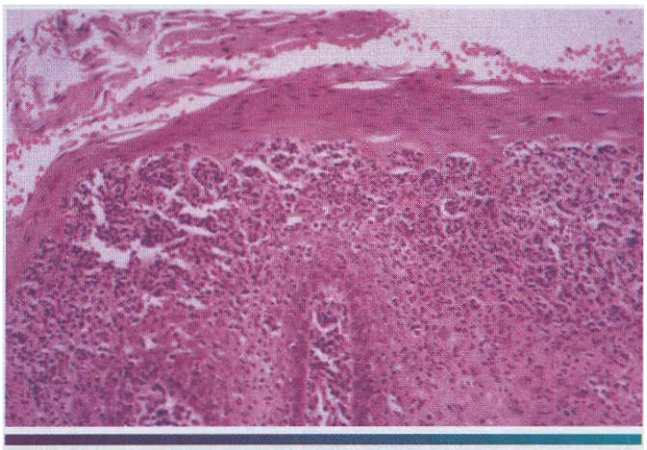


Figure 16-84 - Erythema migrans. This medium-power photomicrograph shows collections of neutrophils in the superficial spinous layer of the epithelium.

quently, 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. One uncontrolled study has recently suggested that zinc supplementation may be effective for symptomatic erythema migrans.

REITER'S SYNDROME

Reiter's syndrome is an uncommon disease that most likely represents an immunologically mediated condition. Current evidence suggests that the disorder may be triggered by anyone of several infectious agents in a genetically susceptible person. 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.

It is interesting that Reiter's syndrome has been reported with some frequency in patients infected with the human immunodeficiency virus (HIV).

Clinical Features

Reiter's syndrome is particularly prevalent in young adult **men. According to most series, there is a male-to-female** ratio of 9:1. The majority (60% to 90%) of these patients are positive for HLA-B27, a haplotype present in only 4% to 8% of the population. The syndrome usually develops 1 to 4 weeks after an episode of dysentery or venereal disease.

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 usu**ally appears concurrently with the urethritis, and after several days, arthritis ensues. The arthritis usually affects the joints of the lower extremities. Skin lesions often take the form of a characteristic lesion of the glans penis (**balanitis** clrclnata), **These lesions develop in about one** third of patients with Reiter's syndrome, 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 Reiter's syndrome, probably because geographic tongue bears a superficial resemblance to the **lesions of balanitis circinata.**

The American Rheumatism Association has defined Reiter's syndrome based on the clinical findings of a peripheral arthritis that lasts longer than 1 month in con**junction with urethritis, cervicitis, or both.**

Histopathologic Features

The histopathologic findings of the cutaneous lesions in patients with Reiter's syndrome 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 Reiter's syndrome experience spontaneous resolution of their disease, but many others have

chronic symptoms that may wax and wane. Treatment may not be necessary for the milder cases. For symptomatic patients, particularly those with urethritis, a course of doxycycline or minocycline may be helpful. Nonsteroidal antiinflammatory agents are initially used *tor* managing arthritis, and sulfasalazine may be helpful in resolving cases that do not respond. Immunosuppressive agents. such as azathioprine 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 to% to 25% 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 pianus suggests a flat. fungal condition, current evidence indicates that this is an immunologically mediated mucocutaneous disorder.

A variety of medications may induce lesions that appear clinically identical 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 300). Similarly, foreign material that becomes inadvertently embedded in the gingiva may elicit a host response that is termed lichenoid foreign-body gingivitis (see page t43). Reports of hepatitis C infection associated with oral lichen planus occasionally appear 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. Genetic influences presumably may influence 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. One study attempted to use psychologic questionnaires 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.

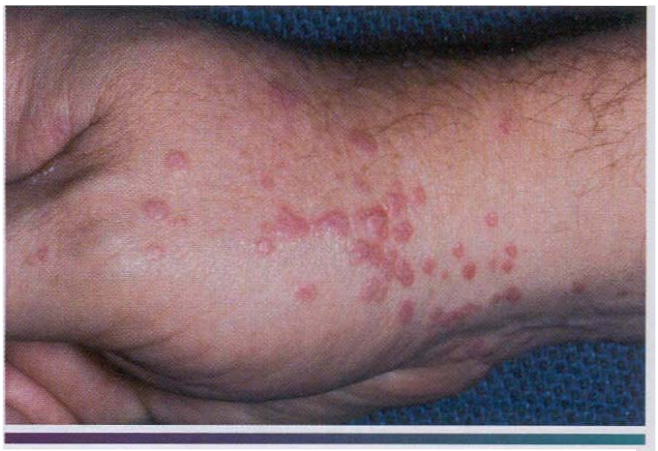


Figure 16-85 • lichen **planus. The cutaneous lesions on the wrist appear as purple, polygonal papules. Careful examination shows a network of fine white lines (Wickham's striae) on the surface of the papules.**

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 (Figure J6-85). 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's striae). Other sites of extraoral involvement include the glans penis. the vulvar mucosa, and the nails (Figure 16-86).

Essentially there are two forms of oral lesions: (1) reticular and (2) erosive.

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). The reticular form usually causes no symptoms and involves the posterior buccal mucosa bilaterally (Figures 16-87 and 16-88). Other oral mucosal surfaces may also be involved concurrently, such as the lateral and dorsal tongue, the gingivae, the palate, and vermilion border (Figure 16-89).

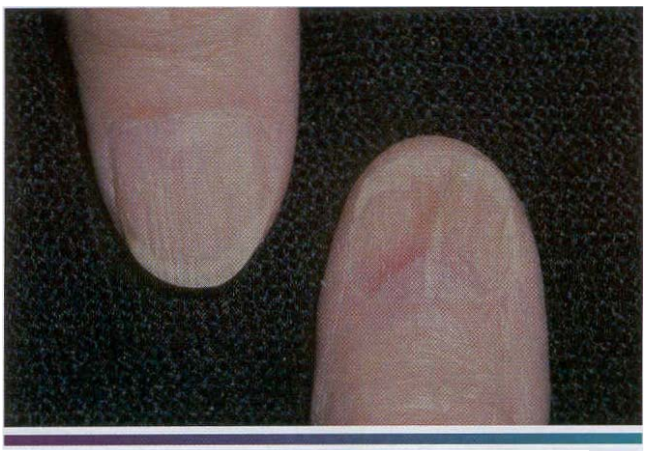


Figure 16-86 • Lichen planus. Dysplastic appearance of the fingernails.

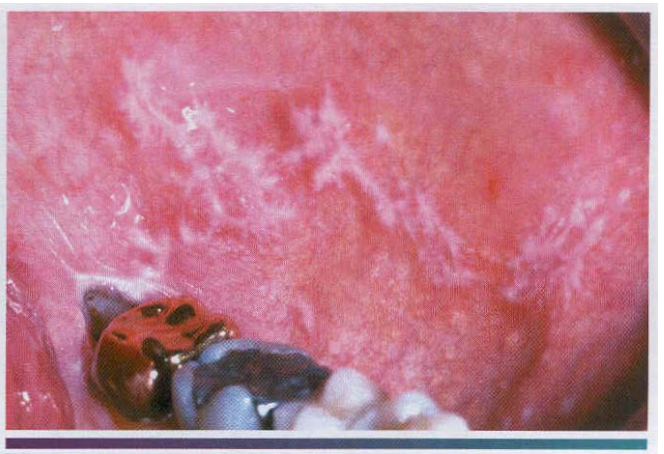


Figure 16-87 • lichen planus. The interlacing white lines are typical of reticular lichen planus involving the posterior buccal mucosa, the most common site of oral involvement.

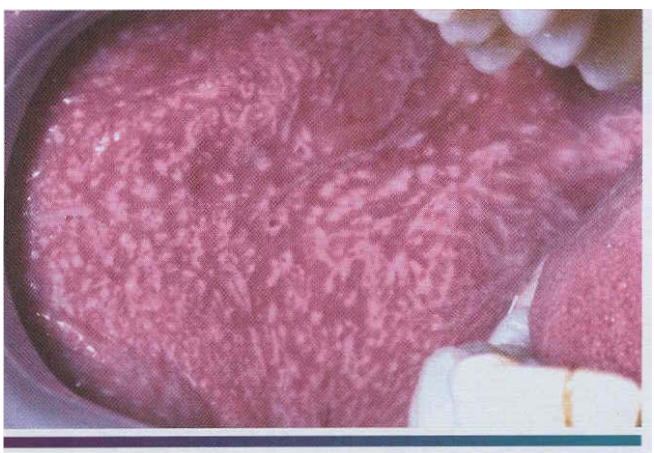


figure 16-88 • lichen planus. Diffuse papular and reticular lesionsof the right buccal mucosa.

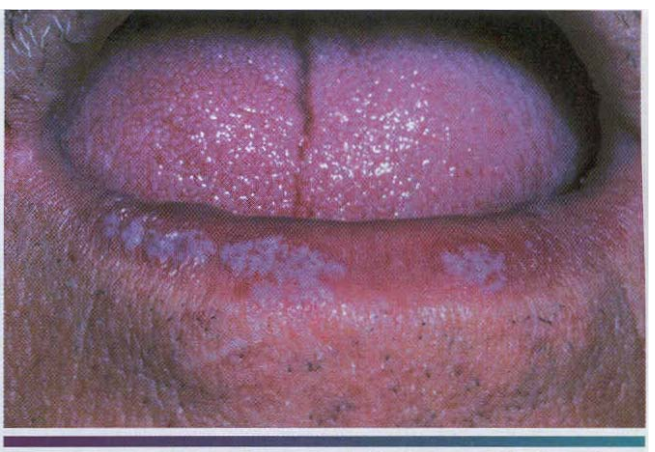


Figure 16-89 • lichen planus. Reticular lesions of the lower lip vermilion.

Reticular lichen planus is thus named because of its characteristic pattern of interlacing white lines (also referred to as Wickham's 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 (Figure 16-90), The reticular pattern may not be as evident in some sites, such as the dorsal **tongue. where the lesions appear more as keratotic** plaques with atrophy of the papillae (Figure J6-91),

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 (Figures 16-92 and J6-93). Sometimes the atrophy and ulceration are confined to the gingival mucosa, producing the reaction pattern called desquamative gingivitis (see page 144) (Figure 16-94). In such cases, biopsy specimens should be obtained for light **microscopic and immunofluorescent studies of** perilesional tissue, because cicatricial pemphigoid (see page 669) and pemphigus vulgaris (see page 664) may appear **in a similar fashion.**

If the erosive component is severe, epithelial separation 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

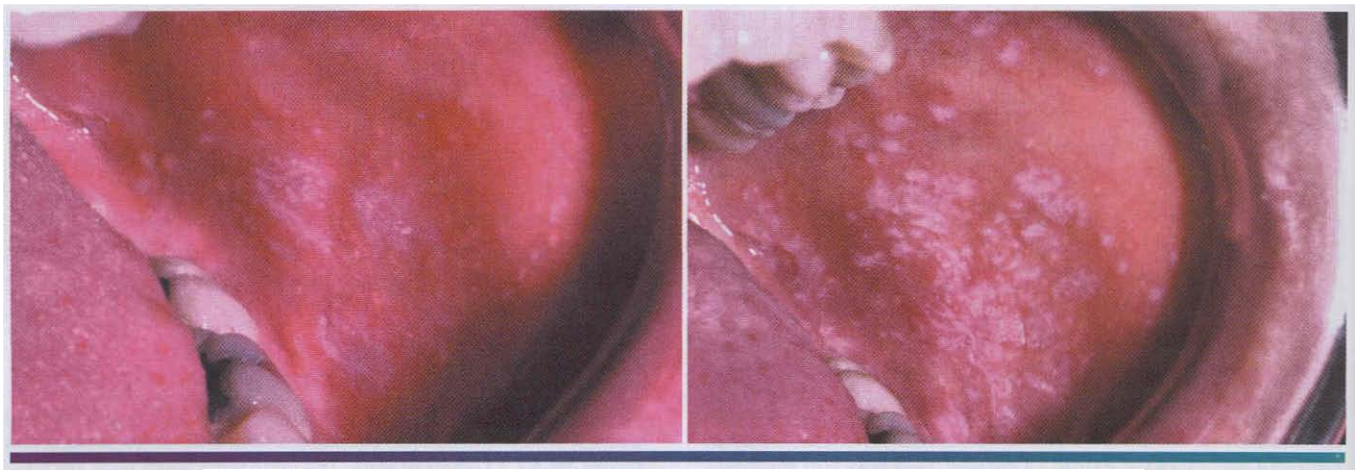


Figure 16-90 • lichen planus. A, Middle-aged woman with mild reticular lichen planus of the left buccal mucosa. B, Same patient 2 weeks later. showing exacerbation of the lesions. Such waxing and waning is characteristic of lichen planus.

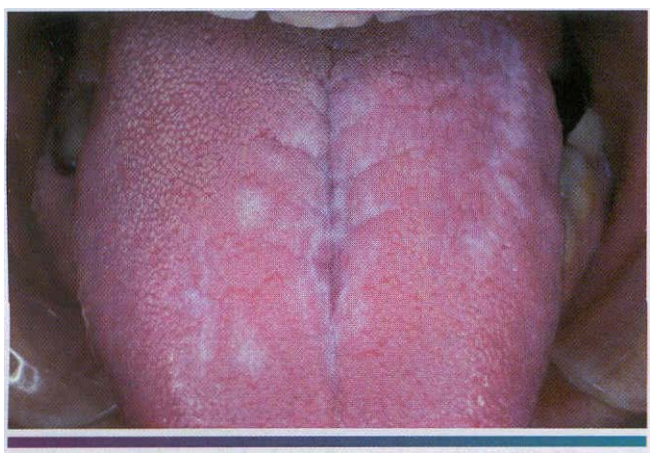


Figure 16-91 • lichen planus. With involvement of the dorsal tongue by reticular lichen planus, the characteristic interlacing striae seen in the buccal mucosal lesions are usually not present. Instead. smooth. white plaques are typically observed replacing the normal papillary surface of the tongue.

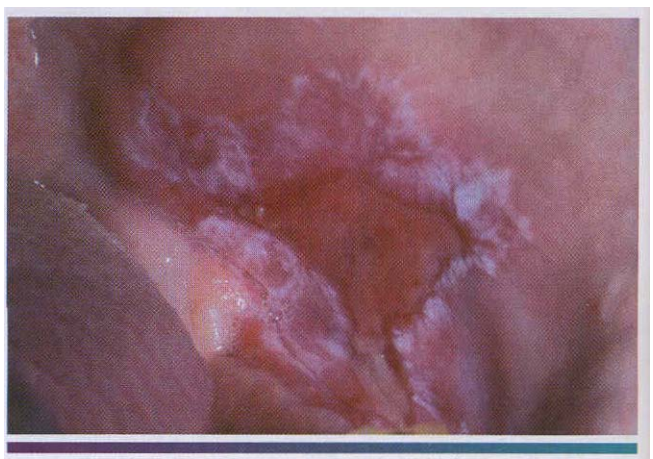


figure 16-92 • lichen planus. Ulceration ofthe buccal mucosa shows peripheral radiating keratotic striae. characteristic of oral erosive lichen planus.

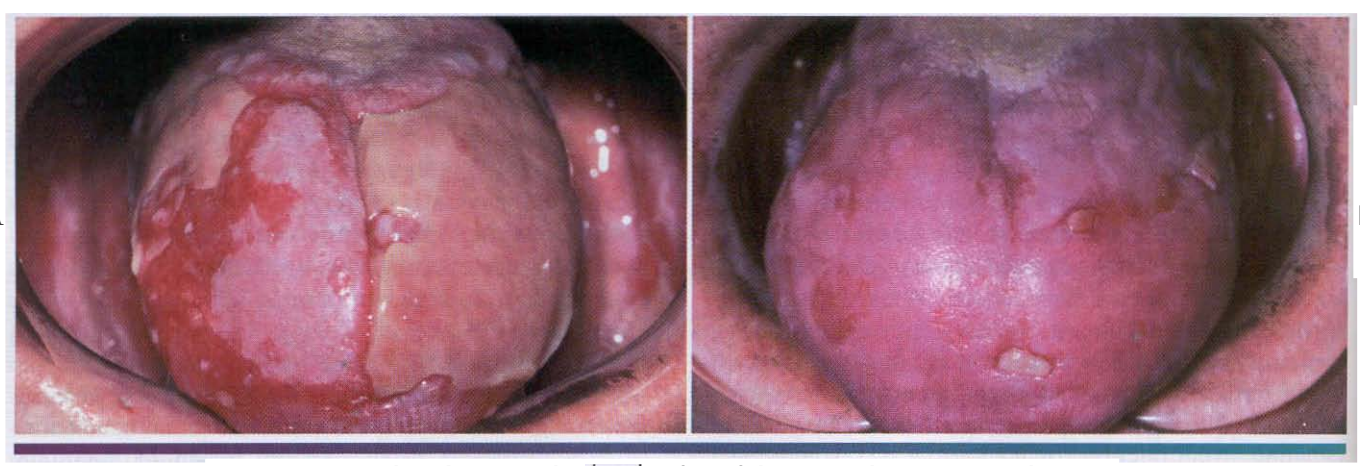


Figure 16-93 • Lichen planus. A, The dorsal surface of the tongue shows extensive ulceration caused by erosive lichen planus. Note the fine white streaks at the periphery of the ulcerations. B. Same patient after systemic corticosteroid therapy. Much of the mucosa has reepithelialized, with only focal ulcerations remaining.

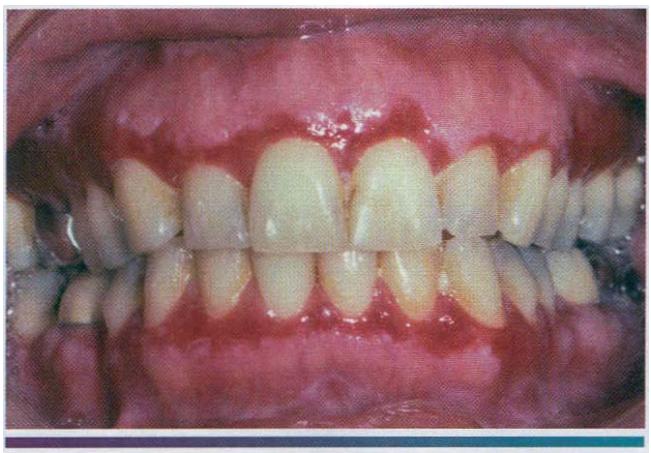


figure 16-94 • Lichen planus. Erosive lichen planus often appears as a desquamative gingivitis, producing gingival erythema and tenderness.

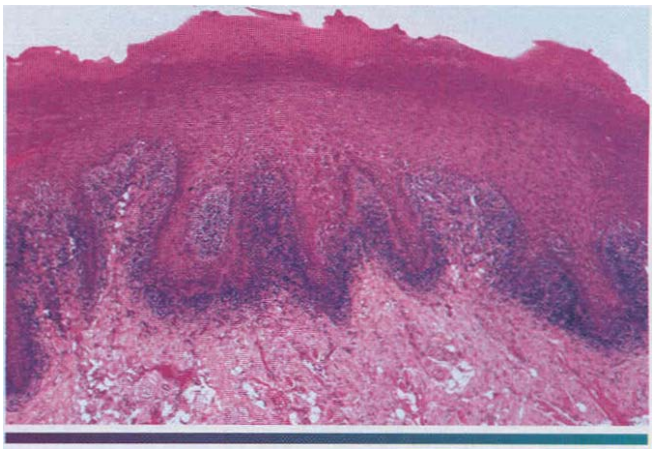
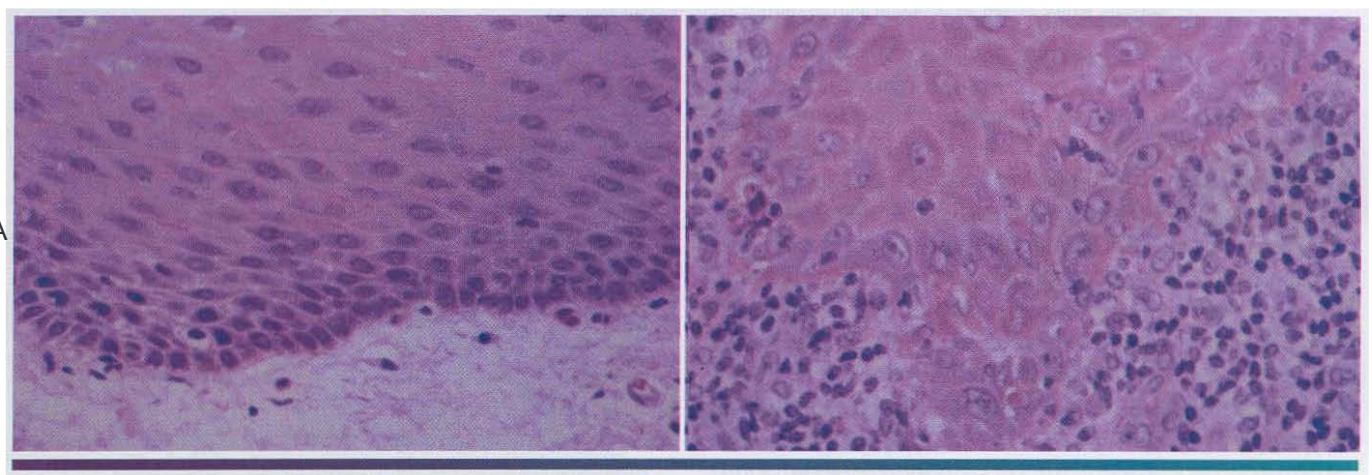


Figure 16-95 • Lichen planus. This low-power photomicrograph of an oral lesion shows hyperkeratosis. saw-toothed rete ridges, and a bandlike infiltrate of lymphocytes immediately subjacent to the epithelium.



A B

Figure 16-96 • 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.

reaction, lupus erythematosus, 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.

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 (Figure 16-95l.

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 (Figure 16-96). 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.

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 disturb the characteristic reticular pattern of the lichen pianus (Figure 16-97).

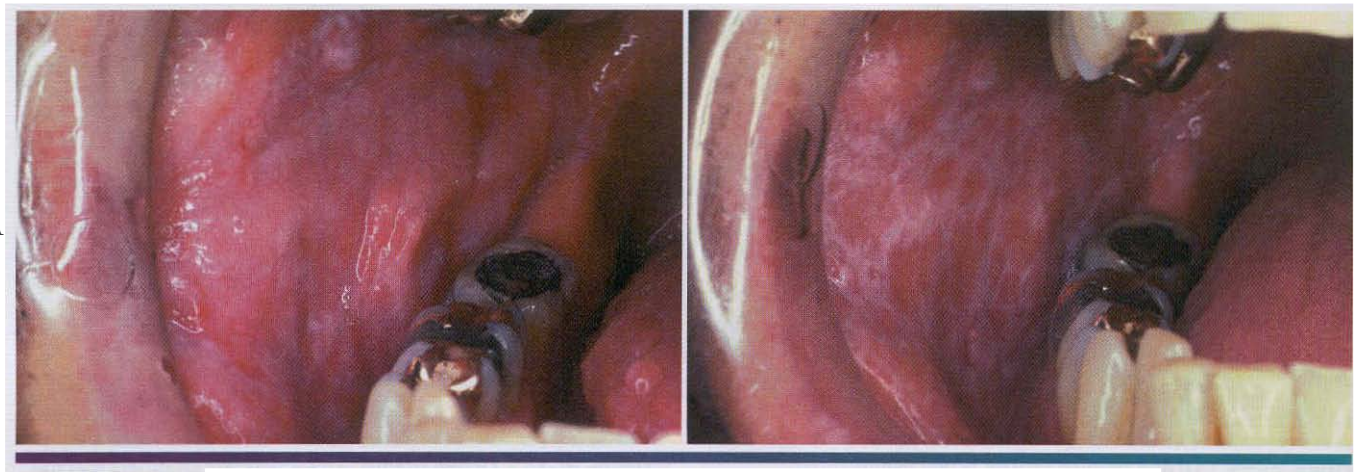


Figure 16-97 . lichen planus. A, These relatively nondescript white lesions affected the buccal mucosa of a patient who had complained of a burning sensation. Histopathologic evaluation of the lesion showed a lichenoid mucositis with superimposed candidiasis. B, Same patient 2 weeks after antifungal therapy. Once the mucosal reaction to the candidal organism was eliminated, the characteristic white striae of reticular lichen planus were identified.

Erosive lichen planus is sometimes more challenging to diagnose (based on clinical features alone) than the reticuiar form. **If** the typical radiating white striae and erythematous. atrophic mucosa arc present at the periphery of well-demarcated ulcerations on the posterior buccal mucosa, the diagnosis can sometimes be rendered without the support of histopathologic findings. *However*. a biopsy is often necessary to rule out other ***ulcerative*** **or erosive diseases, such as lupus erythematosus** or the recently described entity chronic *ulcerative* **stomatitis.**

Chronic ulcerative stomatitis usually affects adult **women. It may appear as desquamative gingivitis or as** ulcerations of the tongue or buccal mucosa. 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 contains plasma cells and lymphocytes. Its characteristic immunopathologic pattern. *however*. consists of autoantibodies directed against the nuclei of stratified squamous epithelial cells. Both direct and indirect immunofluorescence studies are positive for these antibodies, which recently *have* been shown to react with a p53-like nuclear protein. Unlike the lesions of *erosive* lichen planus. the lesions associated with chronic ulcerative **stomatitis are less responsive to topical or systemic corticosteroid therapy.** Management with hydroxychloroquine has been recommended.

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 307).

Treatment and Prognosis

Reticular lichen planus typically produces no symptoms. and no treatment is needed. Occasionally. affected patients 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.• Iluoclnonlde, betamethasone. c1obetasol gel) applied *several* times per day to the most symptomatic areas is usually sufficient to induce healing within I or 2 weeks. 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. 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 (Figure 16-98). Although the use of agents such as topical retinoids or cyclosporine has occasionally been *advocated* for recalcitrant cases of *erosive* lichen planus,

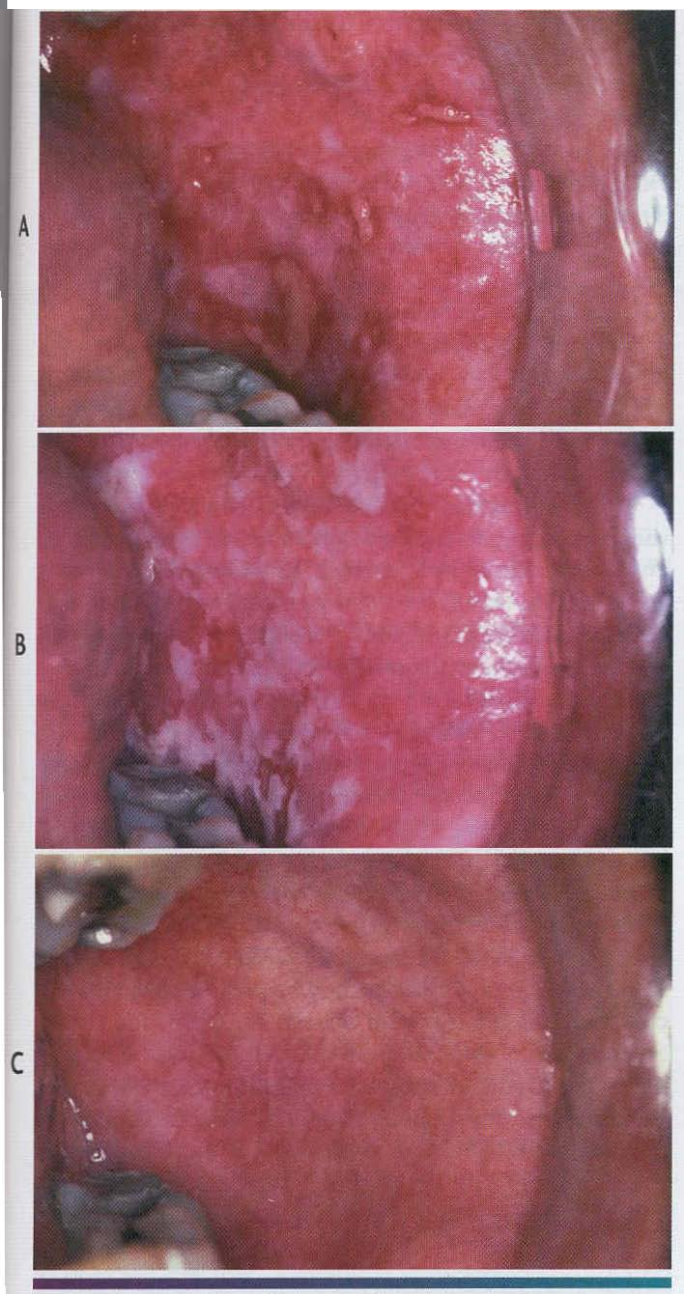


Figure 16-98 • **Lichen planus. A. This patient was diagnosed with erosive lichen planus affecting the buccal mucosa and was treated with topical corticosteroids. B.** Same patient 2 weeks later. **The creamy-white plaques of pseudomembranous candidiasis have developed as a result of the corticosteroid therapy. C,** Same patient after antifungal therapy. At this point. he was asymptomatic.

reports of their efficacy *have* been contradictory. Furthermore. their side effects can be significant. and in the case of cyclosporine. the cost of the drug may be prohibitive. Some investigators suggest that patients with oral erosive lichen planus be evaluated every 3 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 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. A recent study examined the molecular **characteristics of classic reticular lichen planus, com**paring the loss of heterozygosity at purported tumor suppressor gene loci in these lesions with that of *varying* grades of oral epithelial dysplasia. squamous cell carci**noma, 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. If the potential for malignant transformation exists. it appears to be small and generally confined to patients with the erosive form of lichen planus.

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease (GVHD) occurs mainly in **recipients of allogeneic bone marrow transplantation, a** procedure performed on approximately 4000 patients in the United States each year. Such transplants are per**formed at major medical centers to treat life-threatening** diseases of the blood or bone marrow. such as leukemia. **aplastic 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 either 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'Sbone 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 own environment. When this happens, these cells start attacking what they perceive as a foreign body. The result of this attack is known as graft-versus-host disease (GVHD), and it can be quite devastating to the patient.

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 (by definition, within 100 days after the procedure). 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 676). 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 33% to 64% of bone marrow transplant recipients, and it often mimics anyone of a variety of autoimmune conditions, such as systemic lupus erythematosus, 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 (Figures 16-99 to 16-101). 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

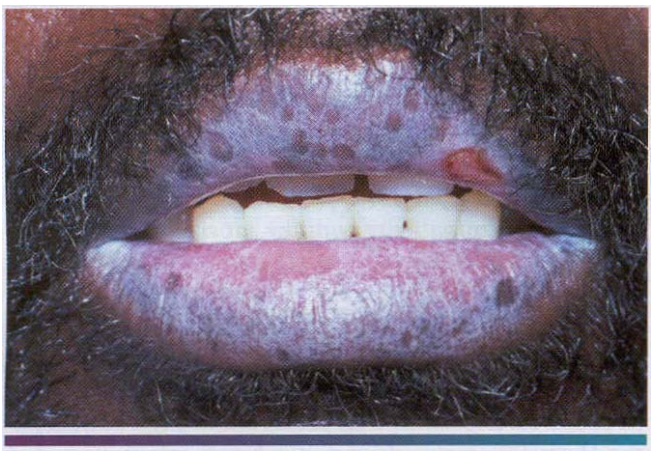


Figure 16-99 • Graft-versus-host disease (GVHD). Confluent, interlacing white linear lesions of the vermilion zone superficially resemble oral lichen planus.

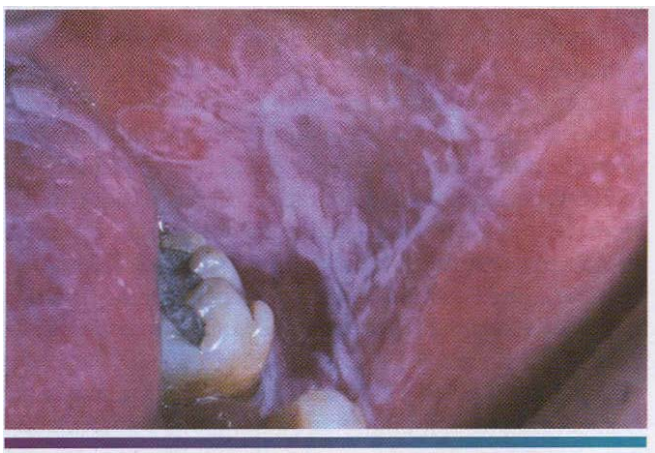


figure 16-100 • Craft-versus-host disease (GVHD). Lichenoid lesions of the left buccal mucosa.

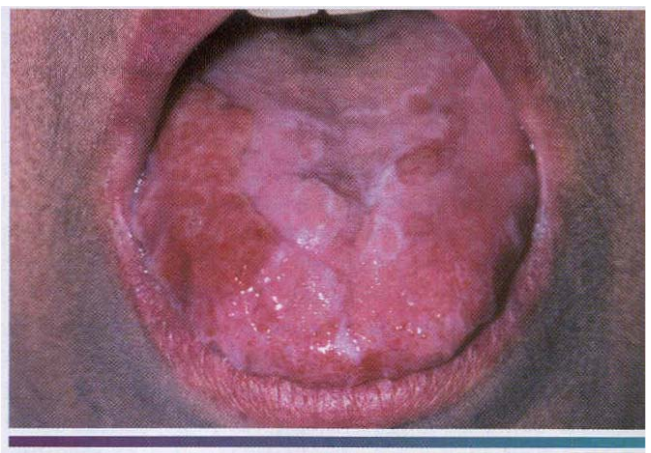


Figure 16-101 • Craft-versus-host disease (CVHD). Involvement of the tongue showing erosions and ulcerations that resemble erosive lichen planus.

GVHD. and these should be differentiated from intraoral **herpesvirus infection or bacterial infection.**

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 rnucoceles, 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. 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 inflammation in the early stages. with gradual acinar destruction and extensive 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 cyclosporine and** prednisone. The addition of the immunosuppressive drug methotrexate to this regimen has reduced the prevalence of acute *GVHD* even further. If *GVHD* develops. the doses **of these drugs may be increased or similar pharmaco**logic agents 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*. Topical anesthetic agents are prescribed to provide patient comfort while the lesions are present. although narcotic analgesics may be required in some cases. The use of Psoralen and Ultra-Violet A (PUVA) therapy 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. topical fluorides should be used daily to prevent **xerostomia-related caries.** One recent **study has** shown improvement in the salivary flow of patients who are treated with pilocarpine hydrochloride.

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 sig**nificance of this complication is reflected in the survival** of 55% of patients with relatively mild *GVHD.* compared with 15% of patients with severe *GVHD.*

PSORIASIS

Psoriasis is a common chronic skin disease affecting 1% to 2% of people in the United States. According to some estimates. approximately 4 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 our 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 cytoklncs, 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. Yet. if one twin in a set of identical twins has psoriasis. there is only a 35% chance that the other twin will have it. This suggests that **genetic factors are not entirely responsible for the condition, and that one or marc 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 often report that **the lesions improve during the summer and worsen** during the winter. an observation that may be related to lesional exposure to ultraviolet light. The lesions are often 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 (Figure 16-102). The lesions are typically asymptomatic. but occasionally an affected patient complains of itching. An unfortunate complication affecting approximately 4% of these patients is psoriatic arthritis. which may involve the temporomandibular joint.

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

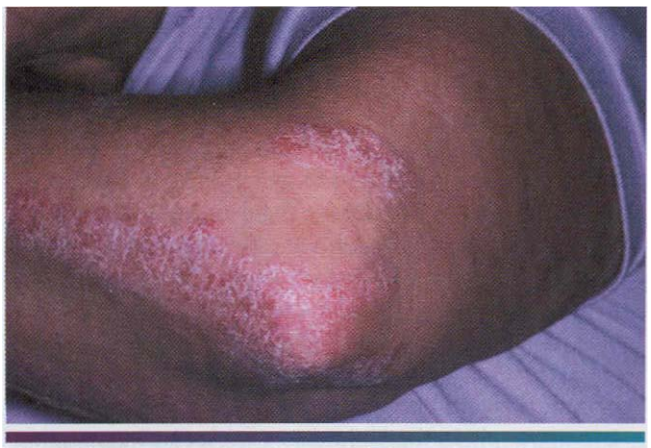


Figure 16-102 • Psoriasis. Characteristic cutaneous lesions on the skin of the elbow. Note the erythematous plaques surmounted by silvery keratotic scales.

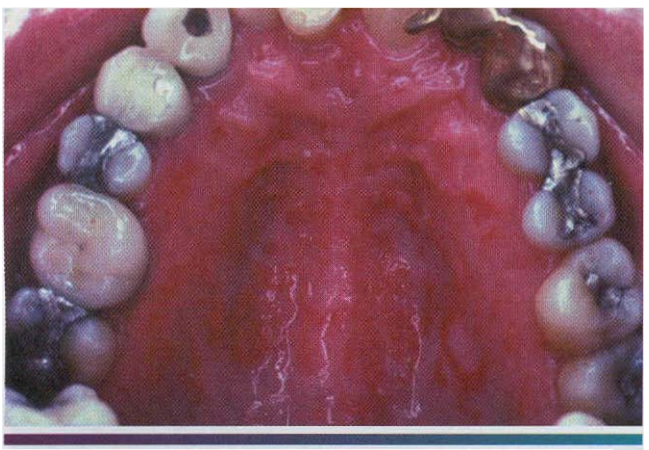


Figure 16-103 • Psoriasis. This is an example of relatively rare involvement of the oral mucosa by psoriasis. The erythematous linear patches tended to flare with the patient's cutaneous lesions. (Courtesy of Dr. George Blozis.}

plaques to ulcerations. it is difficult to determine the true nature of intraoral psoriasis (Figure 16-103). 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 677) 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.

Histopathologic Features

Microscopically, psoriasis has a characteristic pattern. The surface epithelium shows marked parakeratin production. and the epithelial rete ridges are elongated (Figure 16-104). 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.

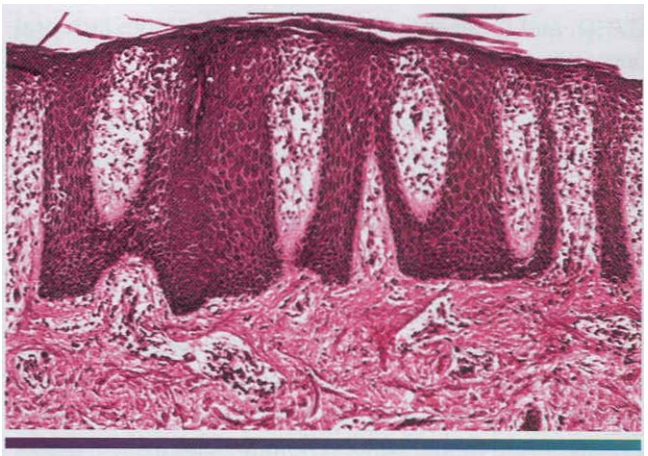


Figure 16-104 • Psoriasis. low-power photomicrograph showing elongation of the rete ridges, hyperkeratosis, and inflammation of the papillary dermis.

With respect to oral lesions. good correlation with skin disease activity should be seen in addition to the characteristic histopathology. because other intraoral lesions. such as erythema migrans and oral mucosal cinnamon reaction (see page 305), 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. Newer topical drugs that have proven effective include calcipotriene, a vitamin D_3 analog, and tazarotene, a retinoid (vitamin A) compound. Exposure to ultraviolet radiation may also be helpful for mild to moderate disease.

For severe cases. PUVA (Psoralen and UltraViolet A) therapy or ultraviolet B therapy may be needed. Methotrexate or cyclosporine may also be used as systemic treatments for severe disease, however these drugs have significant side effects.

Although the mortality rate is not increased in patients with psoriasis. the condition often persists for years despite therapy. Some studies have shown a modest increase in the risk for cutaneous squamous cell carcinoma in psoriasis patients. possibly related to their PUVA or methotrexate therapy.

IUPUS 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 (SLEl is a serious multisystem disease with a variety of cutaneous and oral manifestations. There is an increase in the activity of the humoral limb (6 lymphocytes) of the immune system in conjunction with abnormal function of the T lymphocytes. Although genetic factors probably playa role in the pathogenesis of SIE, the precise cause is unknown. Undoubtedly, an interplay between genetic and environmental factors occurs, for if SLEdevelops in one monozygotic (identical) twin, the other twin has a 32% chance of having SLE as well. In contrast, if one dizygotic (fraternal) twin has SLE, the othertwin has only a 6% chance of being affected.

Chronic cutaneous lupus erythematosus (CCLEl may represent a different, but related, process. It primarily affects the skin and oral mucosa, and the prognosis is good.

Subacute cutaneous lupus erythematosus 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 (Figure 16-[05). 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.

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 (Lihman-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 a 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 (Figure 16-106). 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).

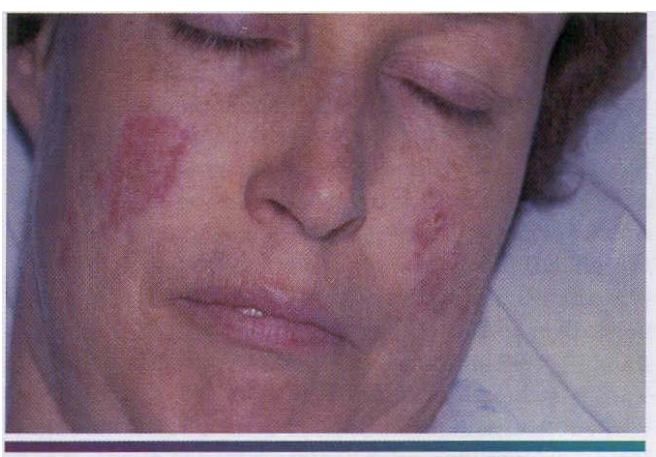


Figure 16-105 • Systemic lupus erythematosus (SIE). The erythematous patches seen in the malar regions are a characteristic sign.

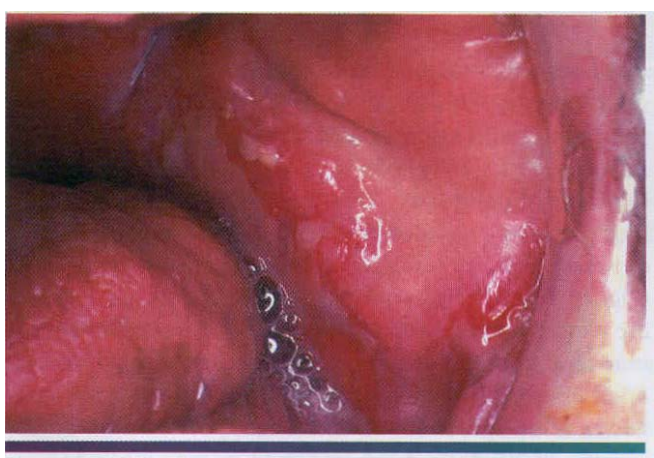


Figure 16-106 • Systemic lupus erythematosus (SlE). Irregulady shaped ulcerations of the buccal mucosa.

Table 16-4 *Clinical Manifestations of Systemic Lupus Erythematosus (SLE)*

FINDING	AFFECTED PATIENTS (%)
Nonerosive polyarthrjtis	60%
Malar rash	50%
Discoid rash	15%
Photosensitivity	70%
Oral ulcers	40%
Hematologic Abnormalities	
Anemia of chronic disease	70%
Hemolytic anemia	10%
Leukopenia «4000/mm')	65%
Lymphopenia «1500/mm')	50%
Thrombocytopenia « 100,000/mm')	15%
Neurologic Symptoms	
Psychosis	10%
Seizures	20%
Cardiopulmonary	
Pleurisy	50%
Pericarditis	30%
Myocarditis	10%
Renal	
Proteinuria (> 500 mg!24 hr)	50%
Cellular casts	50%
Nephrotic syndrome	25%
Renal failure	5% to 10%

From Hahn BH: *Harrison's principles of internal medicine,* ed 14, New York, 1998, Mcqraw-Httl.

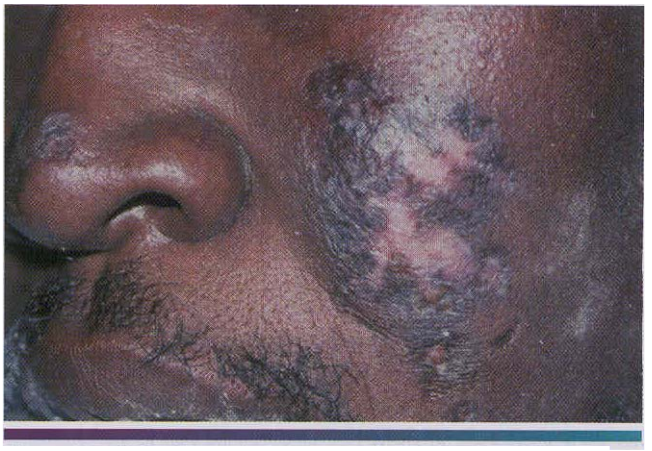


Figure 16-107 . Chronic cutaneous lupus erythematosus (CCIE). The skin lesions are characterized by scaling, atrophy, and pigmentary disturbances, which are most evident on sun-exposed skin.

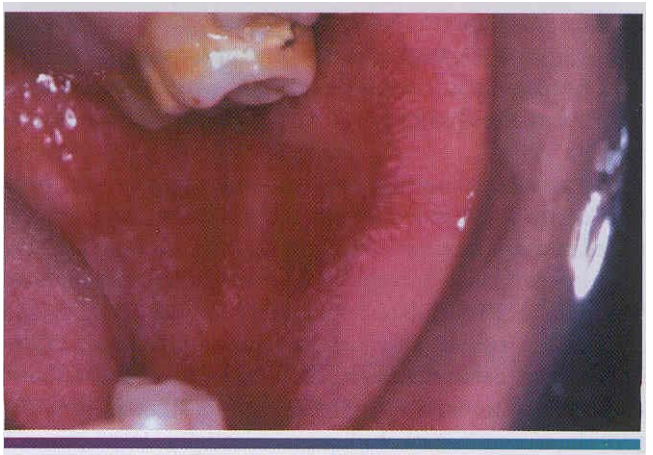


Figure 16-108 • Chronic cutaneous lupus erythematosus (CCIE). Erythematous zones of the buccal mucosa are surrounded by radiating keratotic striae, These features are similar to those of erosive lichen planus.

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 are known 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 (Figure 16-107). 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.

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 rarely 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 (Figures 16-108 and 16-109). 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 subacute cutaneous lupus erythematosus 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 photo-

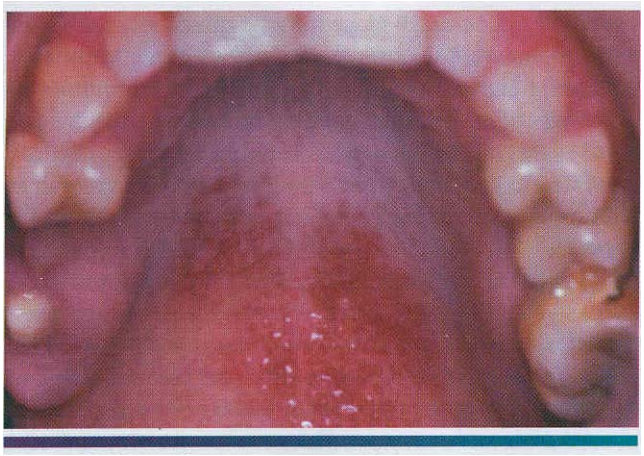


Figure 16-109 . Chronic cutaneous lupus erythematosus (CCLE). Oral involvement may also include relatively nondescript erythematous patches, such as this one in the palate.

sensitivity 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, usually, the renal or neurologic abnormalities associated with SLE are not present either, with most patients having arthritis or muscuioskeletal problems.

Histopathologic Features

The histopathoiogic features of the skin and orai lesions of the various forms of lupus erythematosus 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 iupus erythematosus, degeneration of the basal cell layer is frequentiy observed, and the underiying connective tissue supports patchy to dense aggregates of chronic inflammatory cells (Figure 16-110). in the deeper connective tissue, the inflammatory infiltrate often surrounds the small blood vessels (Figure 16-111 J.

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 lupus erythematosus 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 inflammatory infiltrate, often in a perivascular orientation. Some authorities, however, feel that differentiating lichen planus from lupus erythematosus is best done by direct immunofluorescence studies or histopathologic examination of the cutaneous lesions.

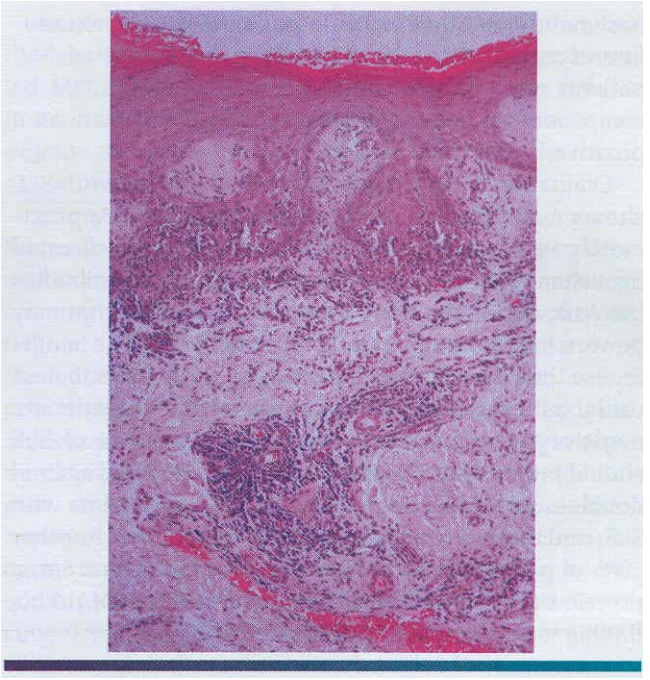


Figure 16-110 . Lupus erythematosus (LE). Low-power photomicrograph showing hyperparakeratosis with interface mucositis and perivascular inflammation.

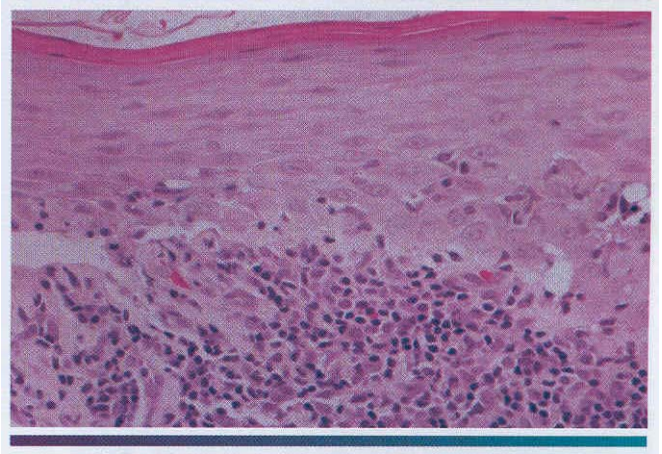


Figure 16-111 • Lupus erythematosus (LE). High-power photomicrograph of the interface mucositis.

Diagnosis

In addition to the clinical and microscopic features, a number of additional immunologic studies may be helpful in making the diagnosis of lupus erythematosus.

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.

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 (antinuclear antibodies [ANAsJ). Although this is a nonspecific finding that may be seen in other autoimmune diseases. as well as in otherwise healthy elderly individuals, it is nevertheless useful as a screening study. Furthermore, if results are negative on multiple occasions, 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 SIE.

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 ultraviolet light may precipitate disease activity. Mild active disease may be effectively managed using nonsteroidal antiinflammatory agents 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 agents. If oral lesions are present. they typically respond to the systemic therapy.

As with SlE patients. patients with CCIE should avoid excessive sunlight exposure. Because most of the manifestations of CCLE are cutaneous, topical corticosteroids are often reasonably effective. For cases that are resistant to topical therapy, systemic antimalarial drugs or low-dose thalidomide may produce a response. Topical corticosteroids are also helpful in treating the oral lesions of CCIE.

The prognosis for the patient with SlE is variable. For patients undergoing treatment today. the 5-year survival rate is approximately 95%; however, by 15 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. For reasons that are poorly understood, the prognosis is worse for men than for women.

The prognosis for patients with CCIE is considerably better than that for patients with SlE, although transformation to SlE may be seen in approximately 5% of CCIE patients. Usually, CCIE remains confined to the skin. but it may persist and be quite a nuisance. For about 50% of CCIE patients. the problem eventually resolves after several years.

Table 16-5 *Selected Abnormal tmmunologic Findings ill Lupus Erythematosus*

FINDING	FREQUENCY	SIGNIFICANCE
Direct immunofluorescence, leslonal skin	CCIE: 90% SlE 95%	May help distinguish among the various types of lE
Direct immune-fluorescence. normal skin	CCIE: 0% SlE: 25%-60%	lupus band test
Antinuclear antibodies	CCIE: 0%-10% SlE: 95%	Very sensitive for SlE, however. not very specific; not useful for CCIE diagnosis
Antidouble-stranded DNA antibodies	CCIE: 0% SlE: 70%-80%	Specific for SlE; may indicate disease activity or kidney involvement
Anti-Sm antibodies	CCIE: 0% SlE: 10%-30%	Specific for SLE

CCLE. Chronic cutaneous lupus erythematosus: *LE,* lupus erythematosus; *SLE.* systemic lupus erythematosus.

SYSTEMIC SCLEROSIS (PROGRESSIVE SYSTEMIC SCLEROSIS; SCLERODERMA; HIDE-BOUND DISEASE)

Systemic sclerosis is a relatively rare condition that probably has an immunologically mediated pathogenesis. 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 19 persons per million population each year. Women have the condition three times more frequently than men do. 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's phenomenon, a vasoconstrictive event triggered by emo-

tional distress or exposure to cold. Raynaud's phenomenon (see CREST syndrome, on page 696) 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 (aero-osteolysis) and flexion contractures produce shortened, clawlike fingers (Figure 16-112). The vascular events and the abnormal collagen deposition contribute to the production of ulcerations on the fingertips (Figure 16-113).

The skin develops a diffuse, hard texture (*sclera* = 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 (Figure 16-114). Similarly, the nasal alae become atrophied, resulting in a pinched appearance to the nose, called a "mouse" facies.

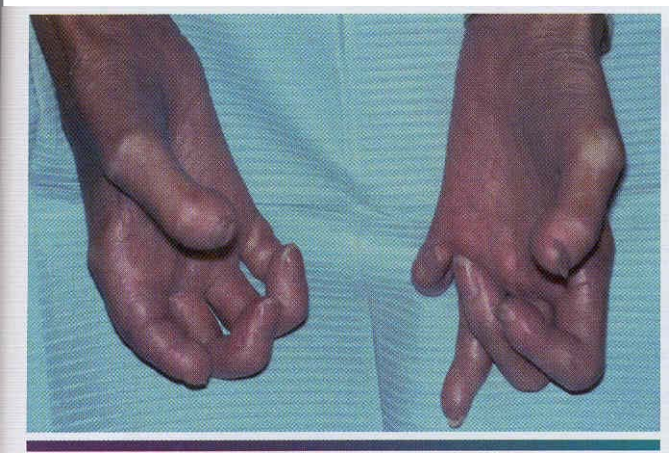


Figure 16-112 • Systemic sclerosis. The tense, shiny appearance of the skin is evident. Note that the fingers are fixed in a clawlike position, with some showing shortening as a result of aero-osteolysis.

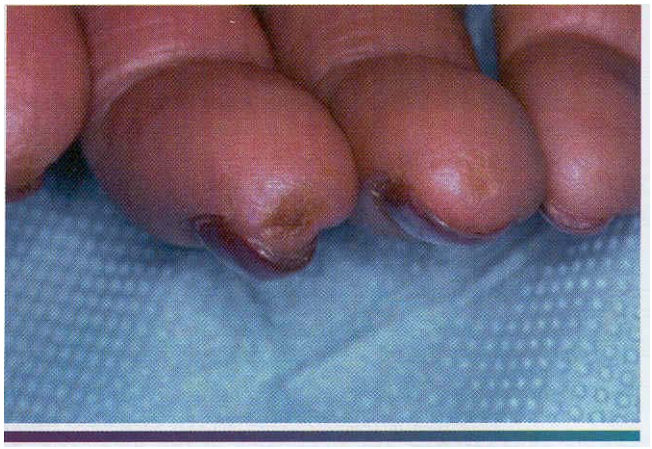


Figure 16-113 . Systemic sclerosis. Ulcerations of the fingertips.

Involvement of other organs may be subtle at first, but the results are more serious. Fibrosis of the lungs, heart, kidneys, and gastrointestinal tract leads to organ failure. Pulmonary fibrosis is particularly significant, leading to pulmonary hypertension and heart failure, a primary cause of death for these patients.

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 (Figure 16-115). 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 Sjogren 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

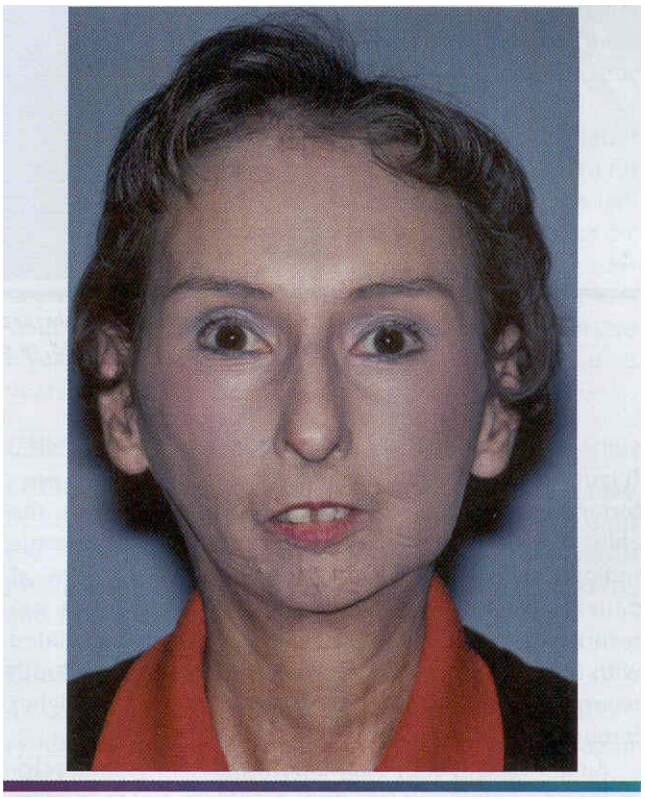


Figure 16-114 • Systemic sclerosis. The involvement of the facial skin with abnormal collagen deposition produces a masklike facies. Note the loss of the alae of the nose.

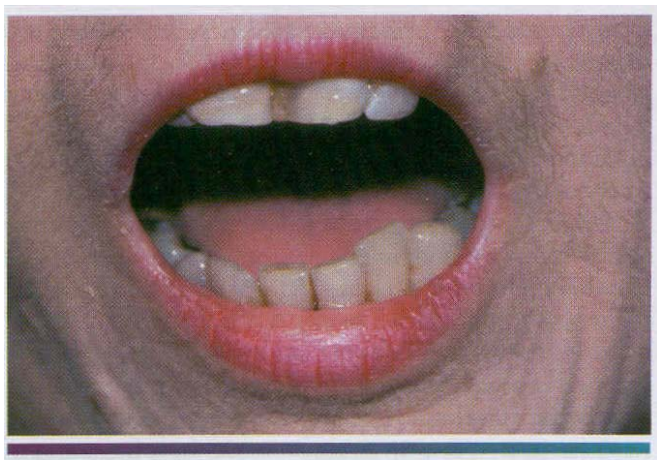


figure 16-115 • Systemic sclerosis. Same patient as depicted in Figure 16-114. Because of the associated microstomia, this is the patient's maximal opening.

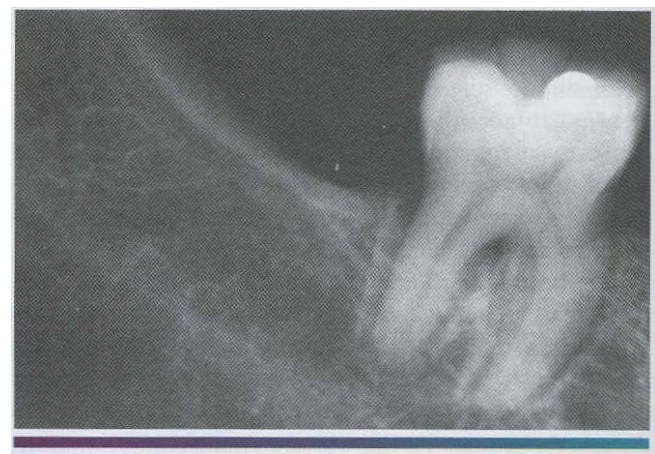


Figure 16-116 • Systemic sclerosis. Diffuse widening of the periodontal ligament space is often identified on evaluation of periapical radiographs.

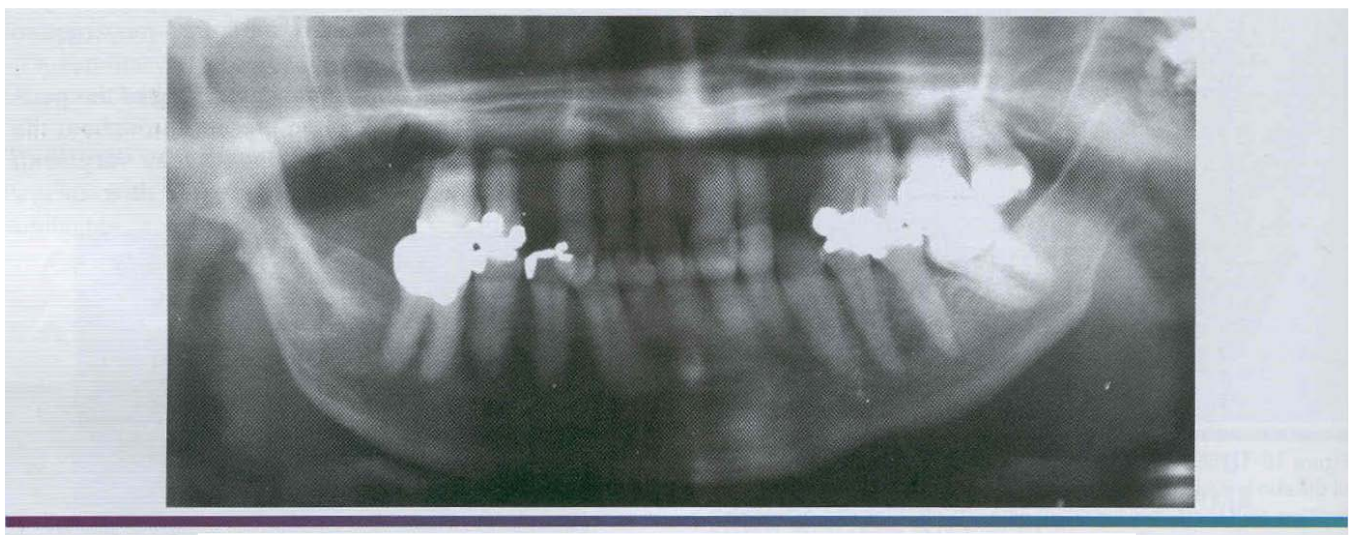


Figure 16-117 • Systemic sclerosis. Panoramic radiographic evaluation may show a characteristic resorption of the ramus, coronoid process, or condyle.

some examples being subtle and others quite dramatic (Figure 16-116). 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 (Figure 16-117). In 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 mild variant of this condition, called localized scleroderma, usually affects only a solitary patch of skin. Because these lesions often look like scars, the name *coup de sabre* ("strike of the sword") is used to describe them (Figure 16-118). This problem is primarily cosmetic and, unlike systemic sclerosis, it is rarely life threatening.

Histopathologic Features

Microscopic examination of tissue involved by systemic sclerosis shows diffuse deposition of dense collagen within and around the normal structures (Figure 16-119). 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's phenomenon are suggestive of the diagnosis. A skin biopsy may be supportive of the diagnoses if abundant collagen deposition is observed microscopically.

Laboratory studies may be helpful to the diagnostic process. If anticentromere antibodies or anti-Scl 70 (topoi-

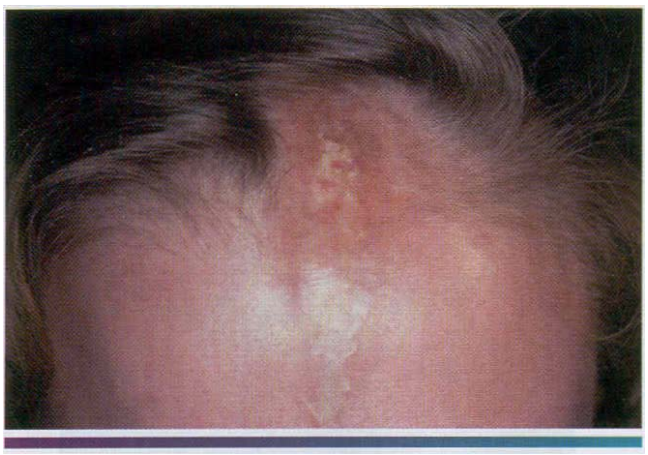


Figure 16-118 • localized scleroderma. The cutaneous alteration on the patient's forehead represents a limited form of scleroderma called *coup de sabre* because the lesion resembles a scar that might result from a cut with a sword.

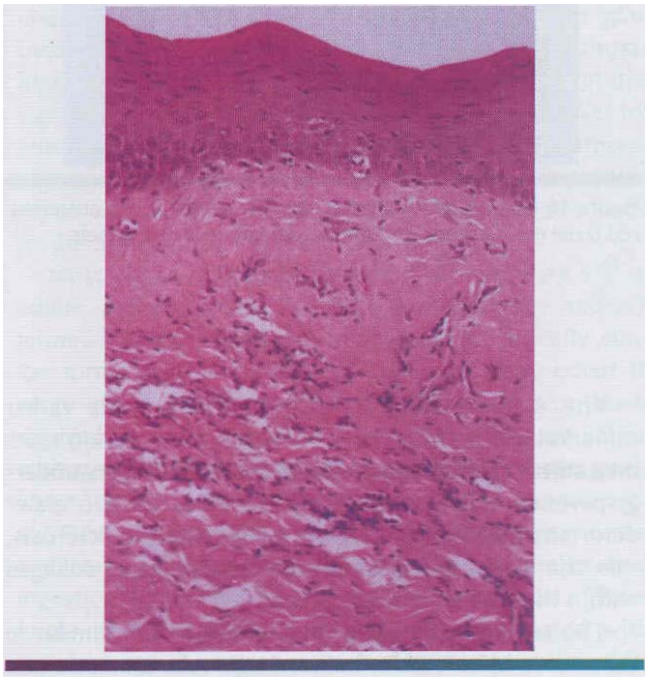


figure 16-119 • Systemic sclerosis. Medium-power photomicrograph of an oral biopsy specimen. Diffuse deposition of collagen is apparent throughout the lamina propria.

sornerase I) is detected. Anti-Sci 70 antibodies are seen more often with systemic sclerosis; antieentromere antibodies are usually associated with more limited forms of scleroderma or CREST syndrome (see next topic). In addition. increasing levels of endothelial cell autoantibodies appear to correlate with disease severity.

Treatment and Prognosis

The management of systemic sclerosis is difficult. Unfortunately, many of the recommended treatments have not been examined ill 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 D-penicillamine, are prescribed in an attempt to inhibit collagen production. Surprisingly. corticosteroids are of little benefit. Extracorporcal photochernotherapy 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's phenomenon. but many patients can reduce episodes by keeping warm 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. For the same reasons, patients may also have problems with maintaining good oral hygiene, and they 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, the prognosis is particularly poor. but most patients die because of pulmonary involvement. Approximately 80% of patients will survive 2 years after diagnosis, but survival drops off with time. Only 30% to 50% will survive 8 years. and the survival rate drops to t5% to 30% at 12 years.

CREST SYNDROME (ACROSCLEROSIS)

CREST syndrome is an uncommon condition that may be a relatively mild variant of systemic sclerosis. The term *CREST* is an acronym for Calcinosis cutis. Raynaud's phenomenon. Esophageal dysfunction, Sclerodactyly. and Telangiectasia.

Clinical Features

As with 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 em in size. which are usually multiple (Figure 16-120).

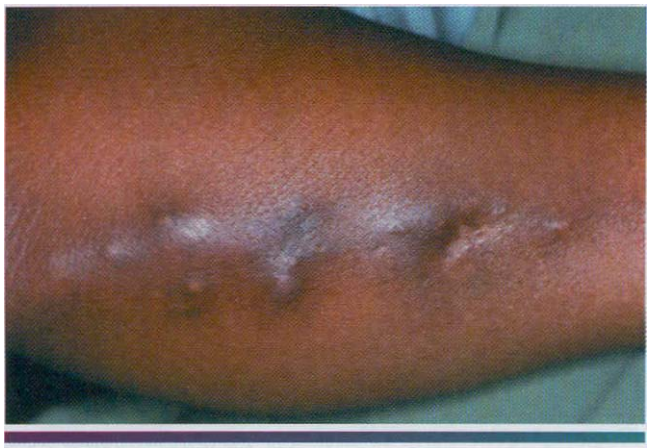


Figure 16-120. CREST syndrome. The subcutaneous nodules on this patient's arm represent deposition of calcium salts (calcinosis **cutis). (Courtesy of Dr. Román** Carlos.)

Figure 16-121 • CREST syndrome. (lawlike deformity affecting the hands (sclerodactyly).

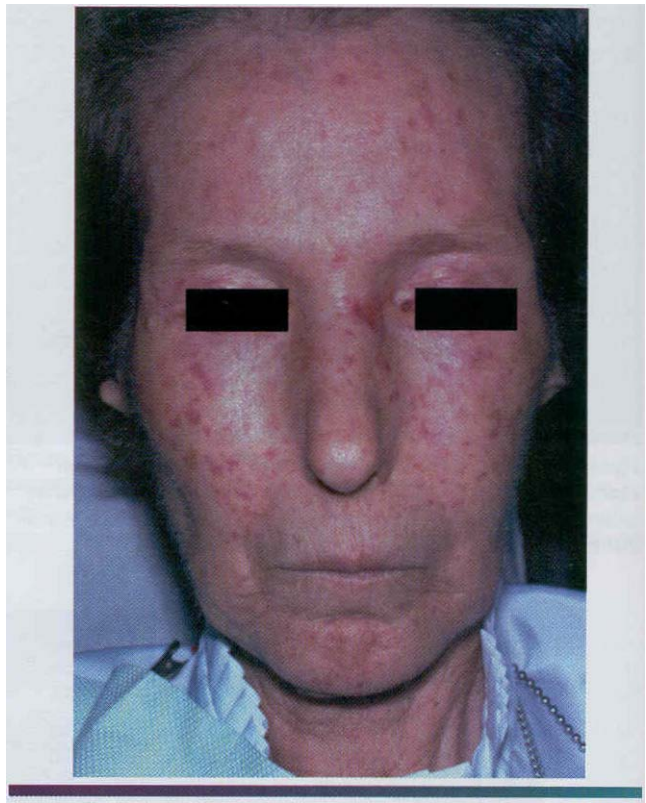


Figure 16-122 • CREST syndrome. The patient shows numerous red facial macules representing telangiectatic blood vessels.

Raynaud's 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 (Figure 16-121). As with systemic sclerosis, this change is due to abnormal deposition of collagen within the dermis in these areas.

The telangiectasias in this syndrome are similar to those seen in hereditary hemorrhagic telangiectasia (see page 654). 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 (Figure 16-122).

Diagnosis

Sometimes, hereditary hemorrhagic telangtectasla may be considered in the differential diagnosis if the history is unclear and the other signs of CREST 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.

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.

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. The prognosis **is much better than that for systemic sclerosis, with** 80% of these patients surviving 6 years after diagnosis **and 50% alive after 12 years.**

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 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 benign forms of acanthosis **nigricans may be inherited or may occur in association with various endocrinopathies, such as diabetes mellitus,** Addison's disease, hypothyroidism, and acromegaly. Furthermore, **benign acanthosis nigricans may occur with certain syndromes** (e.g., **Crouzon syndrome) or drug** ingestion (oral contraceptives, corticosteroids). These forms of the condition are typically associated with resistance of their tissues to the effects of insulin, **similar to the insulin resistance seen in** noninsulin-dependent diabetes mellitus. 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. Approxi**mately 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.

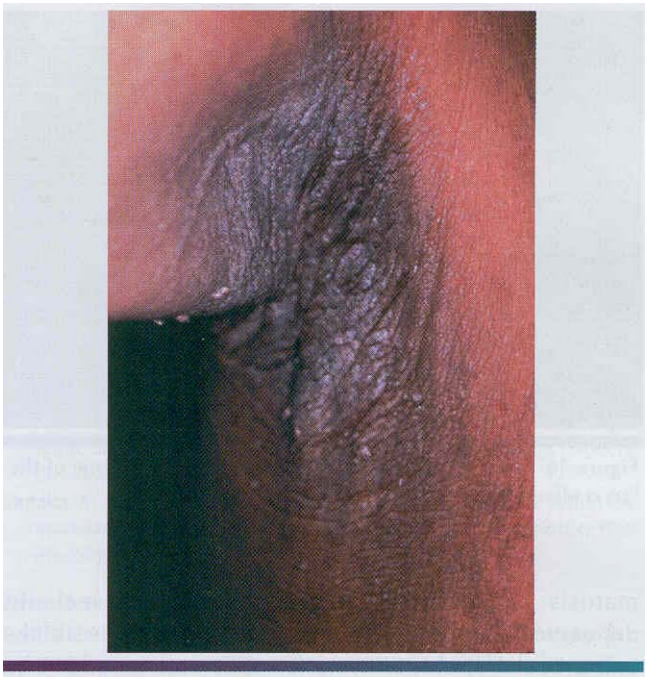


Figure 16-123 • Acanthosis nigricans. **The lesions are characterized by numerous fine, almost velvety, confluent papules. The lesions most often affect the flexural areas, such as the axilla depicted in this** photograph. (From Hall) M, Moreland A. Cox GJ, Wade TR Oral acan**thosis nigricans: report of a case and comparison of oral and cuta**neous pathology, *Am J Dermatopatho/1O:68-73, 1988.)*

Both forms of acanthosis nigricans affect the flexural areas of the skin predominantly, appearing as finely papillary, hyperkeratotic, brownish patches that are usually asymptomatic (Figure 16-123). 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, 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 (Figures 16-124 and 16-125). 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 papillo-

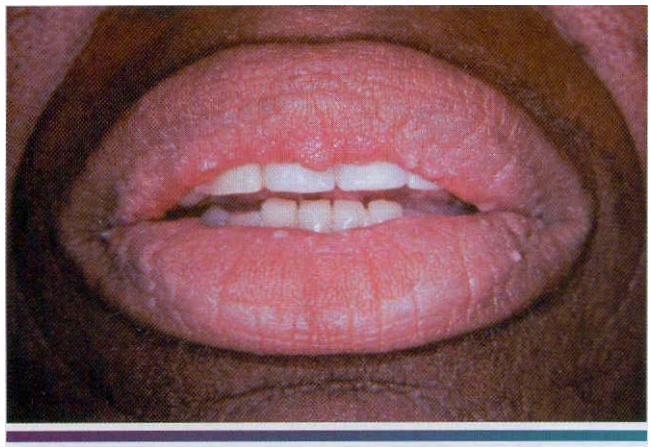


Figure 16-124 . Acanthosis nigricans. The vermilion zone of the lips is affected. (Courtesy of Dr. George Blozis.}

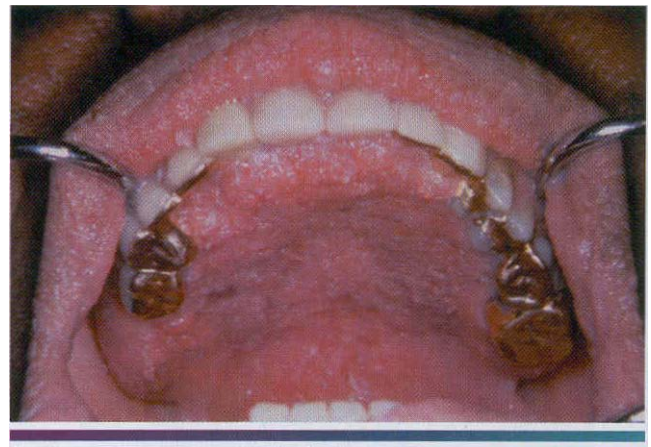


Figure 16-125 • Acanthosis nigricans. Same patient as depicted in Figure 16-124. Note involvement of the palatal mucosa. (Courtesy of Dr. George Blozis.)

matosis. 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 (Figure i6-i26).

Treatment and Prognosis

Although acanthosis nigricans itself is a harmless process, the patient should be evaluated to ascertain which form of the 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.

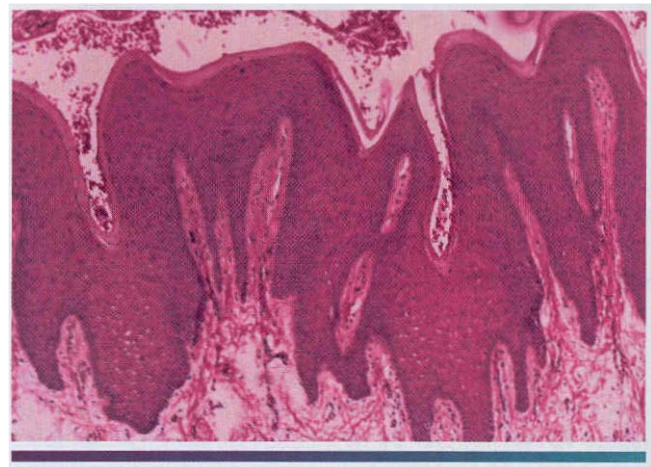


Figure 16-126 • Acanthosis nigricans. Medium-power photomicrograph of an oral lesion showing papillomatosis, mild hyperkeratosis, and acanthosis of the epithelium.

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CHAPTER 17

Oral Manifestations of Systemic Diseases

CHAPTER OUTLINE

MUCOPOIYSACCHARIDOSIS

The mucopolysaccharidoses are a heterogeneous group of metabolic disorders that are usually inherited in an autosomal recessive fashion. These disorders are ail characterized by the lack of anyone 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 foilowing:

- Heparan sulfate
- Dermatan sulfate
- Keratan sulfate
- Chondroitin sulfate

The type of mucopolysaccharidosis that is seen c1inically depends on which of these substrates lacks its particular enzyme. The mucopolysaccharidoses occur with a frequency of approxtmately I in 15,000 persons.

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 display some degree of mental retardation. Often, the facial features of affected patients are somewhat coarse, with heavy brow ridges (Figure 17-1), and there are other

Table 17-1 *Features of Selected Mucopolysaccharidosis Syndromes*

TYPE	EPONYM	INHERITANCE	ENZYME DEFICIENCY	STORED SUBSTRATE	CLINICAL FEATURES
I-H	Hurler	AR	Alpha-L-iduronidase	HS and DS	Appears in infancy, cloudy corneas, growth retardation. reduced intelligence, coronary artery disease. rarely live 10 years
1-5	Scheie	AR	Alpha-Liduronidase	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 retardation, stiff joints
III-A	Sanfilippo-A	AR	Sulfamidase	HS	Appears at 4 to 6 years of age, clear corneas, reduced intelligence, mild skeletal changes, death in adolescence
III-B	Sanfilippo-B	AR	Alphe-N. acetylglucosaminidase	HS	Generally same as Sanfilippo-A
V-A	Morquio-A	AR	Galactose-6-sulfatase	KS. CS. GalNAc6S	Appears at 1 to 2 years of age. cloudy corneas, normal intelligence, lax joints. may survive to middle age
IV-B	Morquio-B	AR	Beta-0-galaetosidase	KS	Generally similar to Morquio-A
VI	Maroteaux-lamy	AR	N-acetylgalactosamine-4-sulfatase	DS. CS. GaINAc4S. GalNAc4.6dis	Appears at 2 to 6 years of age, cloudy corneas, normal intelligence, growth retardation, stiff joints, may survive to adulthood

AR, Autosomal recessive; *CS,* chondroitin sulfate; dis. disulfate; *OS,* dermatan sulfate; *GalNAc.* N-acctylgalactosamine; *HS.* heparan sulfate; *KS,* keratan sulfate; *R.* recessive; 5, sulfate.

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 mucopolysaceharidosis type IV-A. Other dental manifestations include numerous impacted teeth with prominent follicular spaces (Figure 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 mucopolysacchartdoscs. 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 rnucopolysaccharidosis are associated with a markedly reduced life span and with mental retardation. Attempts to improve survival and the quality of life of these patients using allogeneic bone marrow transplantation have met with some success. Unfortunately. not all aspects of the disease are corrected. and the complications associated with transplantation must be addressed. Although the possibility of enzyme replacement has generated a great deal of interest. currently It does not appear to be feasible.

Management of the dental problems of these patients is essentially no different than that of any other patient. However. several factors may have to be taken into account:

- Degree of mental retardation (if anyl
- 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.

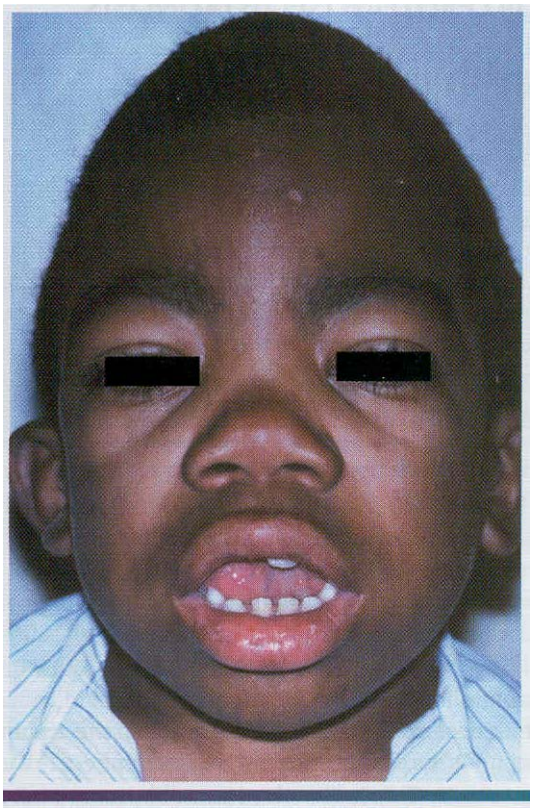


Figure 17-1 • Mucopolysaccharidosis. This patient, affected by Hunter syndrome, exhibits the characteristic facial features of this disorder.

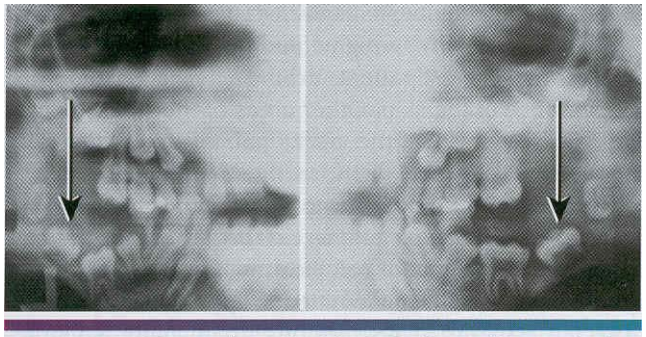


Figure 17-2 • Mucopolysaccharidosis. Radiographic examination of the dentition of a child affected by Hunter syndrome typically shows radiolucencies *(arrows)* associated with the crowns of unerupted teeth.

LIPID RETICULOENDOTHELIOSES

The lipid reticuloendotheliosesare a relatively rare group of inherited disorders. These include the conditions known as the following:

- 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, and 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.

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 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. When the genetic mutation known to cause Gaucher disease was *evaluated* for the Ashkenazi Jewish population, it was found that approximately 1 in 10 persons carried the defective gene. Most of the persons 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 caused by 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 bone marrow of the affected patient. This 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 retardation. Neurologic deterioration may also occur in a few patients. Jaw lesions typically appear as ill-defined radiolucencies that usually affect the mandible without causing devitalization of the teeth or resorption of the lamina dura.

Niemann-Pick disease. Niemann-Pick disease occurs as four different types, each associated with a different clinical expression and prognosis. Types A and B are caused by a deficiency of acid sphingomyelinase, whereas types C and D are due to mutations of NPC-1, a gene involved with cholesterol processing. Types A, C, and D have neuronepathic features, characterized by psychomotor retardation, 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.*** Fay-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 retardation, 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 resembiing 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 macrophage-targeted glucoccrebrosidase is used; however. this is quite expensive. often costing over $100,000 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. 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, A case-control study showed that adults with Gaucher disease have an increased risk for hematologic mallgnancies, 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 populatlon screening for the gene that causes Tay-Sachs disease has resulted in a marked decrease in affected patients during the past 3 decades.

LIPOID PROTEINOSIS (HYALINOSIS CUTIS ET MUCOSAE; URBACH-WIETHE SYNDROME)

A rare condition, lipoid protcinosis 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 protetnosis was by Urbach and Wiethe in 1929. and more than 300 patients. most of whom are of European background, have been reported to date. The precise nature of the biochemical defect associated with this disease is still controversial and essentially unknown.

Clinical Features

The laryngeal mucosa and VOCJI cords are usually the sites that are initially affected by lipoid proteinosis. Therefore, the first sign of the disease may be:

- An inability of the infant to make a crying sound,
- A hoarse cry in infancy, or
- 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 invoive the pharynx, esophagus, tonsils. vulva. and rectum. Skin lesions also develop early in life, appearing as thickened. yellowish, waxy areas that often affect the face. particularly the lips and the margins of the eyelids. Some lesions may begin as dark-crusted vesicles. which heal as atrophic hypcrplgrncnted patches.

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. symmetric intracranial calcifications of the medial temporallobes 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 mUCOSJ become nodular. diffusely enlarged, and thickened because of infiltration with waxy, yellowish-white plaques and nodules. 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 protrude the tongue. Gingival enlargement appears to be an infrequent finding.

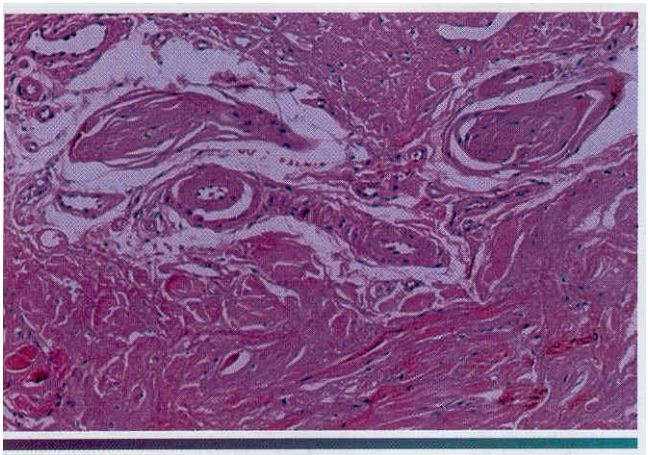


Figure 17-3 • lipoid proteinosis. This medium-power photomicrograph shows perivascular deposition of a lamellar, acellular material.

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 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 (Figure 17-3).

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.

JAUNDICE (ICTERUS)

Jaundice is a condition characterized by excess bilirubin in the blood stream. 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 blood stream 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 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. Because most of these examples of jaundice occur with impaired processing of bilirubin, laboratory studies usually show unconjugated bilirubin in the serum.

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 blood stream.

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 (Figure 17-4). The yellow discoloration caused by hypercarotenemia (caused by excess inges-

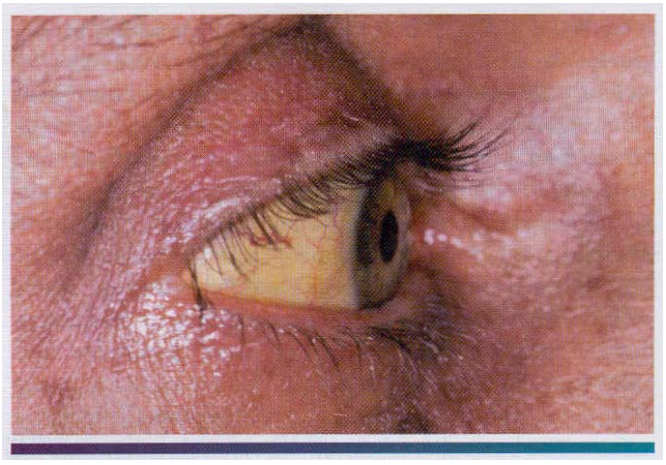


Figure 17-4 • Jaundice. The yellow color of the sclera represents a common finding.

tion 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, although if the infant is placed under special lights 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, 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 starchlike material (*amyl* = starch: *aid* = resemblingl. We now understand that amyloid can be formed in a variety of settings, each with its own specific type of amyloid protein. Although amyloid may have several sources, all types of amyloid have the common feature of a ß-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 impact 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 our knowledge of this unusual condition increases. None of the classifications is completely satisfactory. In this discussion, we attempt to be as concise and direct as possible.

Essentially, amyloidosis may be divided into organ-limited and syslemic forms.

Organ-limited amyloidosis, Although organ-limited amyloidosis may occur in a variety of organs, it has rarely been reported in the oral soft 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 and 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. 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 (Figure 17-5l. the retroauricular region, the neck, and the lips. The lesions are often associated with petechiae and

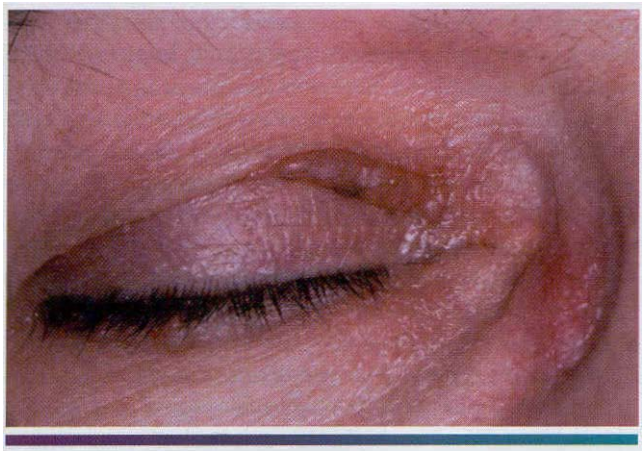


Figure 17-5 . Amyloidosis. This patient exhibits a firm, waxy nodular lesion in the periocular region, a finding characteristic for this condition.

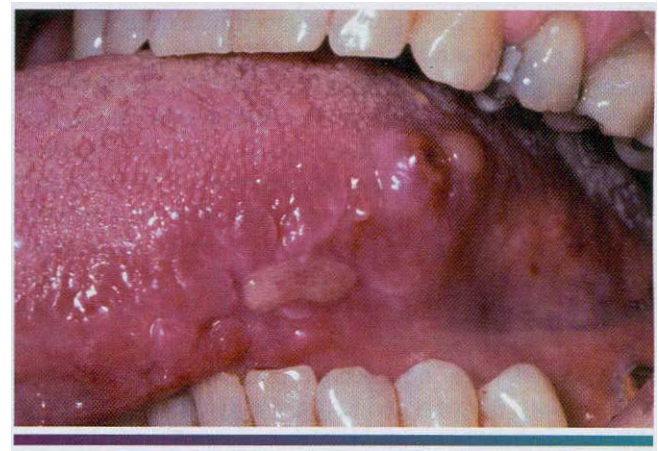


Figure 17-6 . Amyloidosis. Same patient as depicted in Figure 17-5. Note amyloid nodules of lateral tongue, some of which are ulcerated. The patient's amyloidosis was due to previously undiagnosed multiple myeloma.

ecchymoses. Macroglossia has been reported in 10% to 40% of these patients and may appear as diffuse or nodular enlargement of the tongue (Figure 17-6). 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. 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 rare.

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 ß-2 microglobulin. This normally occurring protein 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.

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 autosomal recessive form, known as familial Mediterranean fever, has also been described. Most 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 an 85% yield has been reported. 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 (Figure 17-7). Labial salivary gland tissue shows deposition of amyloid in a periductal or perivascular location in more than 80% of the cases.

A standard means of identifying amyloid uses 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 is viewed with polarized light, it exhibits an apple-green birefringence (Figure 17-8). 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. 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. Familial Mediterranean fever may respond to systemic colchicine therapy. Treatment of primary amyloidosis 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.

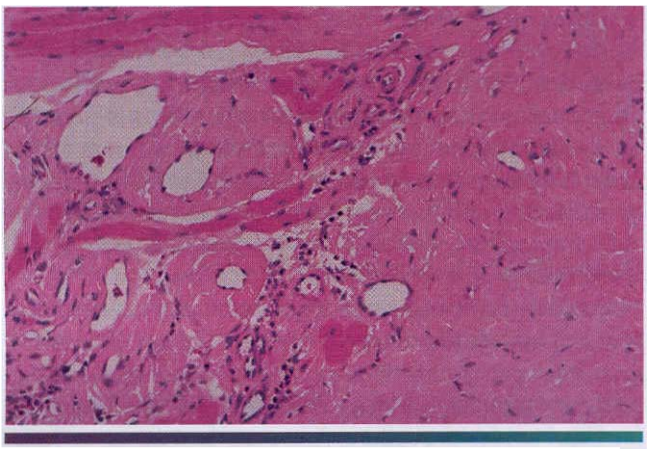


Figure 17-7. Amyloidosis. This medium-power photomicrograph shows the eosinophilic, acellular deposits that are characteristic of amyloid deposition.

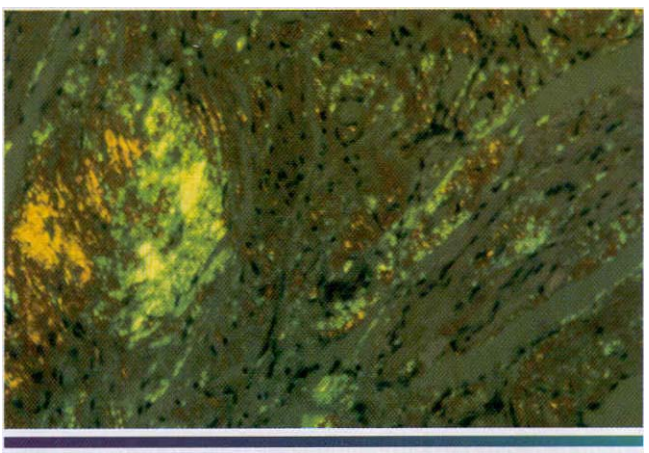


Figure 17-8. Amyloidosis. High-power photomicrograph of a Congo red-stained section, demonstrating characteristic apple-green birefringence when viewed with polarized light. (Courtesy of Dr. John Kalmar.)

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 or milk, or the body can synthesize it from beta carotene, which is abundant in red and yellow vegetables.

Vitamin B] (thiamin) acts as a co-enzyme 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, meat (especially liver), fish, and eggs.

Vitamin B_3 (niacin) acts as a co-enzyme for oxidation-reduction reactions. Rich sources include food from animal sources, especially lean meat and liver, and peanuts, yeast, and cereal bran or germ.

Vitamin B_6 (pyridoxine) serves as a co-factor 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 (a-tocopherol) is a fat-soluble vitamin that is widely stored throughout the body. It probably functions as an antioxidant. Vegetable oil 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; it is also produced by intestinal bacteria. 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 (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 except in alcoholics or other individuals who do not receive a balanced 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, edema) and neurologic problems (including peripheral neuropathy and Wernicke's encephalopathy). Patients with Wernicke's 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, which may occur in populations that use corn as a principal component of their diets. 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 dis**tributed symmetrically; sun-exposed areas, such as the face, neck, and forearms, are affected most severely. 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 dis**ease may evolve and persist over a period of years, even**tually 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 defi**ciency 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 elderly edentulous men, particularly those who live alone.

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 (Figure 17-9>' If untreated, scurvy may ultimately lead to death, often as a result of intracranial hemorrhage.

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

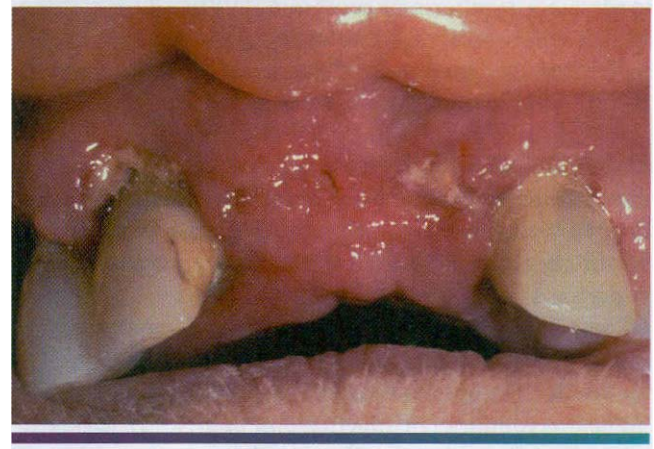


Figure 17-9 . Scurvy. The gingival inflammation and ulceration (scorbutic gingivitis) are due to severe vitamin C deficiency.

vitamin 0 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, 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 retardation, 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.

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 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 dlcurnarol 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 uncorrected. 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 kidney stones in some individuals.

IRON-DEFICIENCY ANEMIA

Iron-dcficicncv anemia is the most common cause of anemia in the United States andthroughout 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. This type 01 anemia develops under four conditions:

i. Excessive blood loss
2. Increased demands for red blood cells
3. Decreased intake of iron
4. Decreased absorption of iron

It is estimated that 200/0 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 biood 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 elderly people may be deficient if their dental condition prohibits them from eating the proper foods or if they cannol afford iron-rich foods, such as meats and vegetables.

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 compiete blood count with red blood cell 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 red blood cells in addition to reduced numbers of erythrocytes.

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. parenteral iron may be given periodically. The response to therapy is usually prompt. with red cell parameters returning to normal within t 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 incidence 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.**

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 (Figure t7-10). Marked atrophy of the lingual papillae. which produces a smooth. red appearance of the dorsal tongue. is seen clinically (Figure l7-u).

Patients also frequently complain of difficulty in swallowing (dysphagia) or pain on swallowing. An **evaluation with endoscopy or esophageal barium contrast radio**graphic 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.

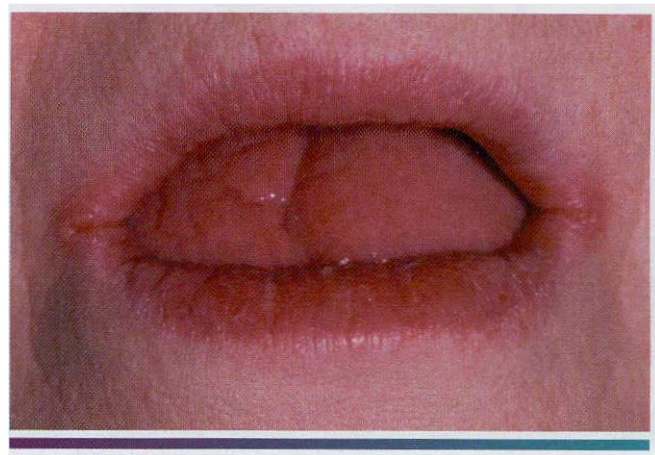


Figure 17-10 . Plummer-Vinson syndrome. Patients often show angular cheilitis.

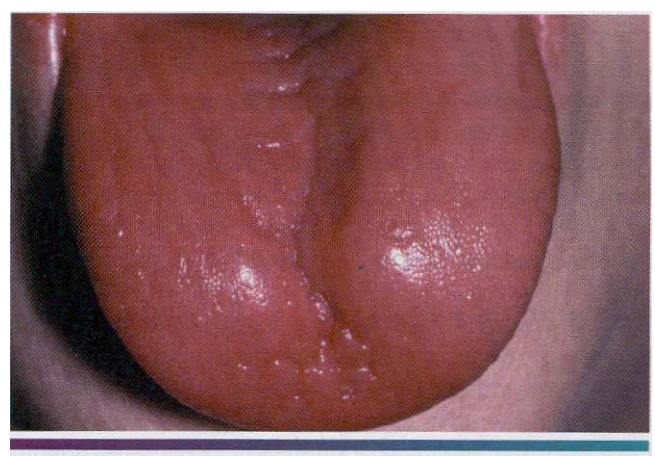


Figure 17-11 • Plummer-Vinson syndrome. The diffuse papillary atrophy of the dorsal tongue is characteristic of the oral changes. (From Neville BW, Damm DO, White OK: *Coloratlas of cfinical oral pathology,* ed 2. Philadelphia. 1999. Lippincott. Williams & Wilkins.)

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.

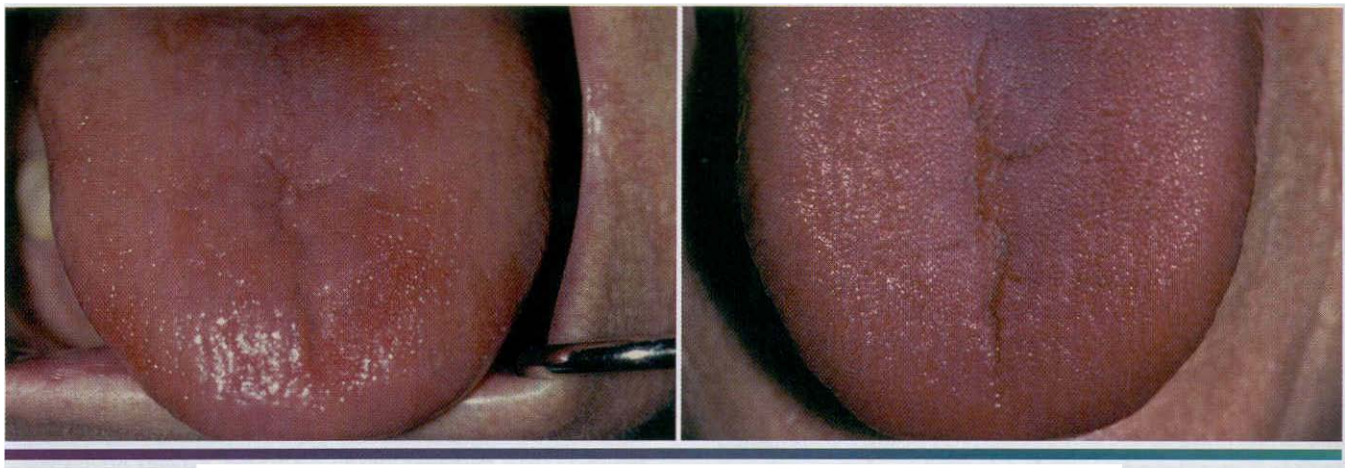


Figure 17-12 • Pernicious anemia. A. The dorsal tongue shows erythema and atrophy. B. After therapy with vitamin B_{12}, the mucosal alteration resolved.

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 elderly patients of northern European heritage, although recent studies have identified the disease in black and Hispanic populations as well. 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, and this results in decreased absorption of cobalamin. A decreased ability to absorb cobalamin may also occur after gastrointestinal bypass operations. Because cobalamin is primarily ***derived*** **from animal sources, some strict vegetarians** 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. In addition, many patients report paresthesia, tingling, or numbness of the extremities. Difficulty in walking and diminished vibratory and positional sense may be present.

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 (Figure 17-12) 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, and prominent nucleoli (Figure 17-13). This pat-

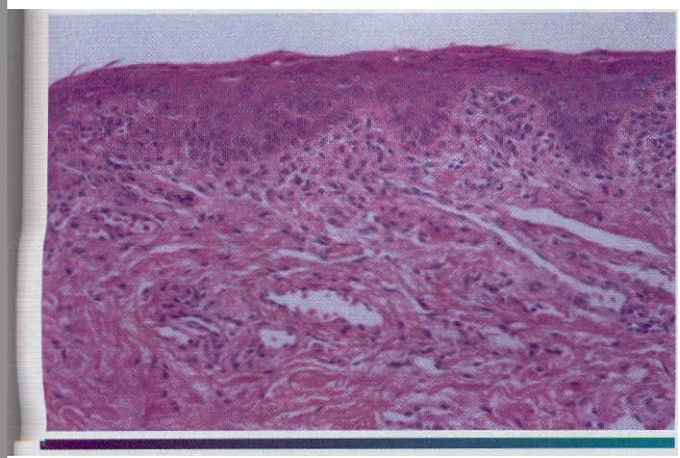


Figure 17-13 . Pernicious anemia. This medium-power photomicrograph shows epithelial atrophy and atypia with chronic inflammation of the underlying connective tissue. These features are characteristic of a megaloblastic anemia. such as pernicious anemia.

tem 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.

Laboratory Findings .

Hematologic evaluation shows a macrocytic anemia, and serum cobalamin levels are reduced. The Schilling test is used to determine the pathogenesis of the cobalamin deficiency by comparing absorption and excretion rates of radiolabeled cobalamin.

Treatment and Prognosis

Once the diagnosis of pernicious anemia is established, treatment usually consists 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 effective treatment, with advantages being its cost-effectiveness and the elimination of painful injections. One study has confirmed an increased risk of malignancy, particularly gastric carcinoma, a complication that affects between 1% and 2% of this population.

PITUITARY DWARFISM

Pituitary dwarfism is a relatively rare condition that results from either the diminished production of growth hormone by the anterior pituitary gland 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: (I) intrinsic defects in the patient's tissues (e.g., certain skeletal dysplasias, chromosomal abnormalities, idiopathic short stature) or (2) alterations in the environment of the growing tissues (e.g., malnutrition, hypothyroidism, 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, 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 thy-**roid 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 I 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.

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. 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.**

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 hypoadreno**corticism. it 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 555) 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.

The life span of patients with gigantism is usually markedly reduced. Complications associated with hypertension, peripheral neuropathy. osteoporosis. and pul**monary 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 believed to be 66 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 (Figure 17-14) and in the membranous bones of the skull and jaws is typically observed. Patients may complain of gloves or hats becoming "too small." The soft tissue is also often affected. producing a coarse facial appearance (Figure 17-15). 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 nearly 9 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

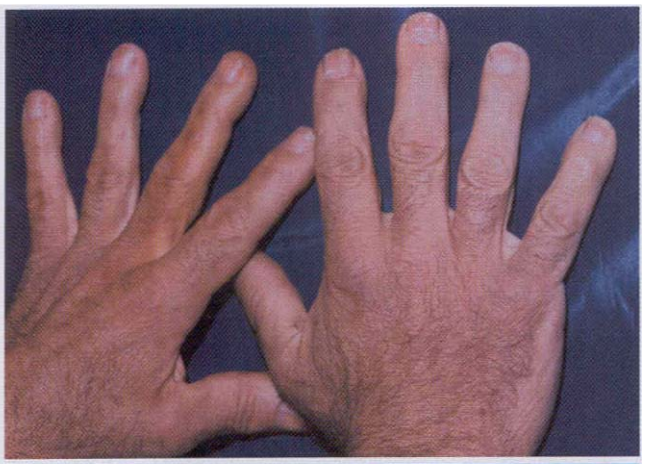


Figure 17-14 • **Acromegaly. Enlargement of the bones of the hands. (Courtesy of Dr. William** Bruce.]

growth of the mandible (Figure 17-16). which may cause apertognathla (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.

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 (octreotlde. lanreotlde. vapreotide) helps to control acromegaly if surgical treatment is unsuccessful or if surgery is contraindicated. 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, respl-

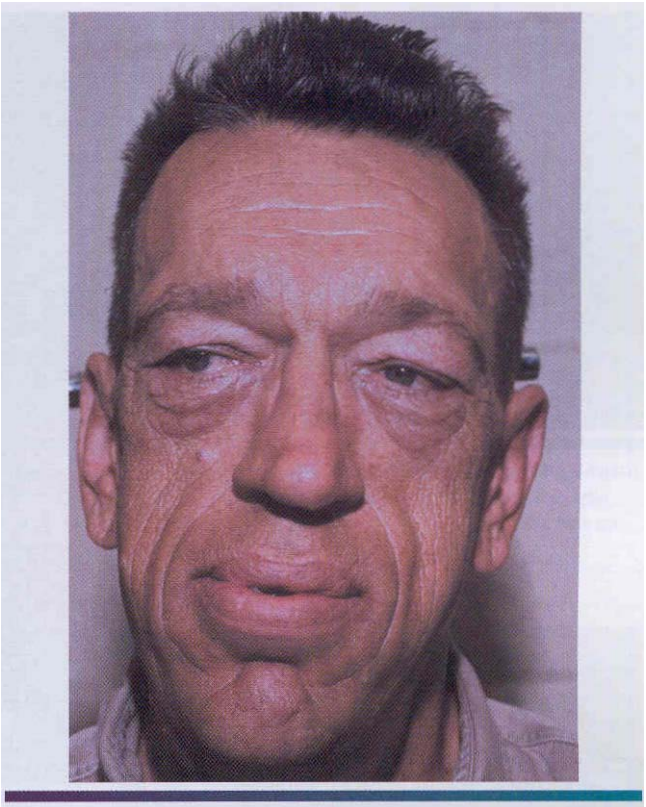


Figure 17-15 • **Acromegaly. This patient shows the typical coarse facial features. (Courtesy of Dr. William Bruce.)**

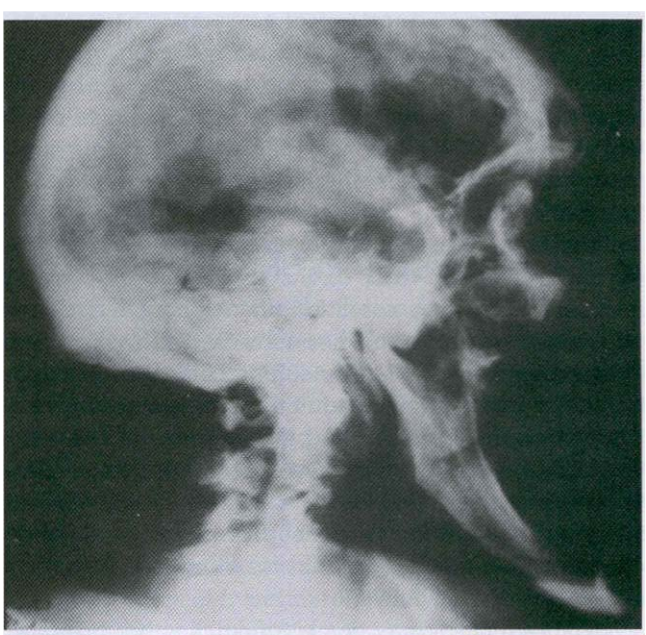


Figure 17-16 . **Acromegaly. This lateral skull film shows the dramatic degree of mandibular enlargement that mayoccur.**

Figure 17-17. Hypothyroidism. A. The facial appearance of this 5-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.

ratory 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.

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, 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 adults, hypothyroidism is often caused by autoimmune destruction of the thyroid gland (known as Hashimoto's 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, coarse skin; swelling of the face (Figure 17-17) and extremities; husk-

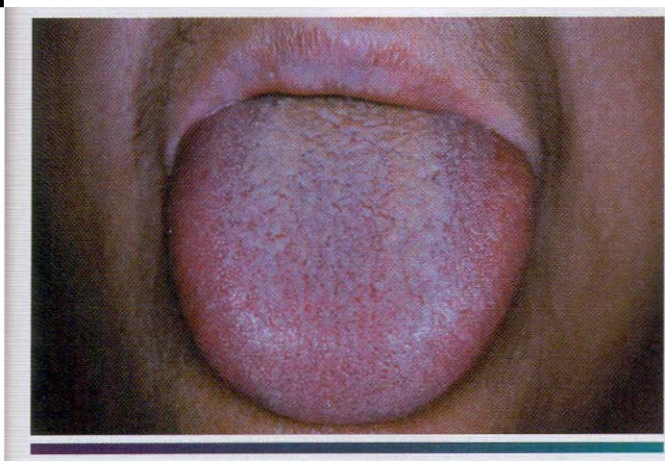


Figure 17-18 . Hypothyroidism. The enlarged tongue (macroglossia) is secondary to edema associated with adult hypothyroidism (myxedema). (Courtesy of Dr. George Blozis.)

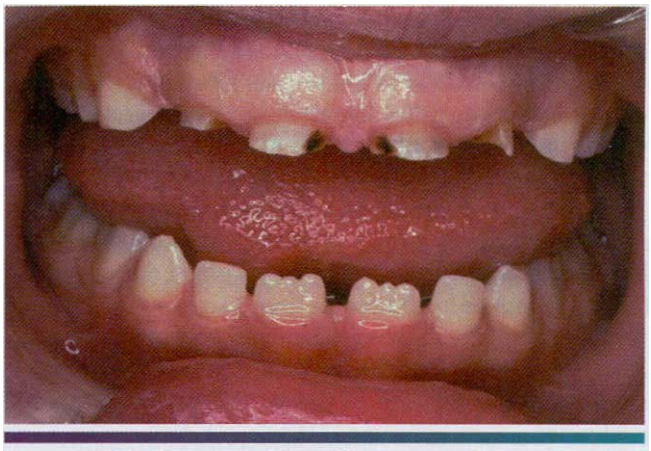


Figure 17-19 • Hypothyroidism. Photograph of the same patient depicted in Figure 17·17 before hormone replacement therapy. Note the retained deciduous teeth. for which the patient was initially referred.

iness 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 (Figure 17-18). If the condition develops during childhood, the teeth may fail to erupt, although tooth formation may not be impaired (Figures 17-19 and 17-20).

Laboratory Findings

The diagnosis is made by assaying the free thyroxine (T.) levels. If these levels are low. 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.

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 timeiy manner. however, permanent damage to the central nervous system may occur, resulting in mental retardation. For affected children, thyroid hormone replacement therapy often results in a dramatic resolution of the condition (see Figure 17-17).

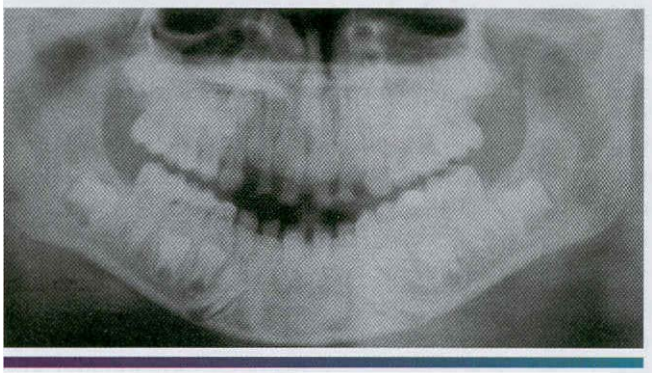


Figure 17-20 . Hypothyroidism. Panoramic radiograph of the same patient in Figures 17-17 and 17-19. Note the unerupted, yet fully developed permanent dentition.

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, which 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.

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 5 to 10 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 (Figure 17-21). 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.

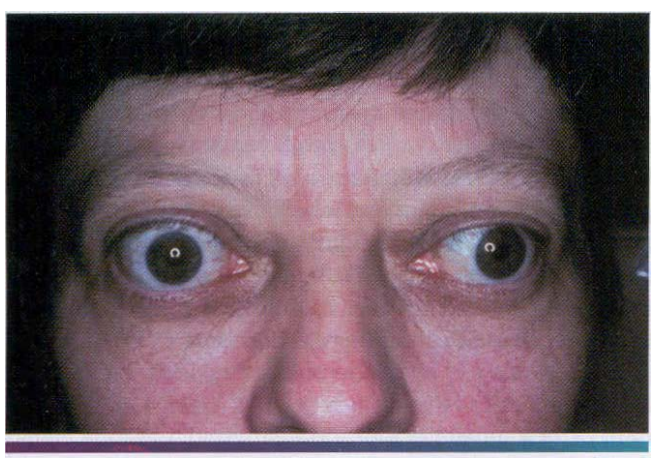


Figure 17-21 • Hyperthyroidism. The prominent eyes are characteristic of the exophthalmos associated with Graves' disease.

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 blood stream because this element is a critical component of thyroid hormone. When radioactive iodine is given to a patient with Graves' disease, the thyroid gland qutckly removes it from the blood stream 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 $^{131}1$ 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 widely used drugs are propylthiouracil and methimazole, At times, they are used before the radioactive iodine therapy. Sometimes they may be administered chronically in the hope that a remission may be induced. In addition. a portion of the thyroid gland may be removed surgically. thereby reducing thyroid hormone **production.**

Drug therapy alone is often unsuccessful in controlling hyperthyroidism, Unfortunately. with radioactive iodine and surgery, the risk of hypothyroidism is relatively great. although thyroid hormone replacement therapy can be instituted. if needed.

In a patient with uncontrolled hyperthyroidism, a def**inite 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, an elevated temperature, and tachycardia. Such individuals should be hospitalized immediately because the mortality rate associated with thyroid storm is 20% to 40%. 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.**

HYPOPARATHYROIDISM

Calcium levels in extracellular tissues are normally regulated by parathyroid hormone (parathorrnone [PTH]) in conjunction with vitamin D. If calcium levels drop below

a certain point. the release of PTH is stimulated. The hormone then acts directly on the kidney and the osteoclasts 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. Osteoclasts are activated to resorb bone and thus liberate 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 endocrine-candidiasis syndrome. 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's 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. a pitting enamel hypoplasia and failure of tooth eruption may occur (Figure 17-22). The presence of persistent oral candidiasis in a young patient may signal the onset of endocrine-candidiasis syndrome (see page 194). Hypoparathyroidism may be only one of several endocrine deficiencies associated with this condition.

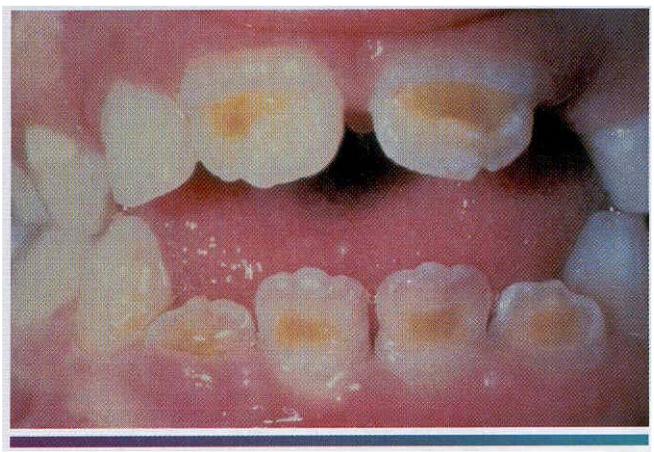


Figure 17-22 . Hypoparathyroidism. Enamel hypoplasia has affected the dentition of this patient. who had hypoparathyroidism while the teeth were forming.

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. a diagnosis of hypoparathyroidism can be made.

Treatment and Prognosis

Patients with hypoparathyroidism are usually treated with oral doses of a vitamin 0 precursor (ergocalciferol. vitamin D_2). Additional supplements of dietary calcium may also be necessary to maintain the proper serum calcium levels. With this regimen, patients can often live a fairly normal life.

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 Gsa 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 Gsa 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. 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 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; how-

ever, 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. which include mild mental retardation. 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 tb and II disease clinically appear normal. aside from their symptoms of hypocalcemia.

Dental manifestations of pseudo hypoparathyroidism 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 0 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). Infrequently (in less than 2% of cases), a parathyroid carcinoma may be the cause of primary hyperparathyroidism.

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 0 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.**

Patients with the classic triad of signs and symptoms of hyperparathyroidism are described as having "stones, bones. and abdominal groans."

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 (Figure 17-23). 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 hyper-

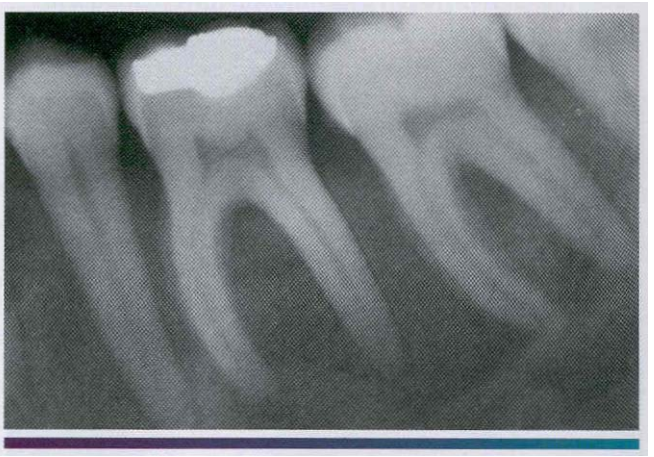


Figure 17-23. Hyperparathyroidism. This periapical radiograph reveals the "ground glass" appearance of the trabeculae and loss of lamina dura in a patient with secondary hyperparathyroidism. (Courtesy of Dr. Randy Anderson.)

parathyroidism. This lesion derives its name from the color of the tissue specimen. which is usually a dark reddish-brown because of the abundant hemorrhage and hemosiderin deposition within the tumor. These lesions appear radiographically as well-demarcated unilocular or multilocular radiolucencies (Figure 17-24). They commonly affect the mandible. clavicles. ribs. and pelvis. They may be solitary but are often multiple, and longstanding 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 longstanding brown tumors. In patients with secondary hyperparathyroidism caused by end-stage renal disease (renal osteodystrophy), striking enlargement of the jaws has been known to occur (Figure 17-25) and produce a ground-glass radiographic pattern (see Figure 17-23).

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 544). Both lesions are characterized by a proliferation of exceedingly vascular granulation tissue, which serves as a background for numerous multinucleated osteoclast-type giant cells (Figure 17-26), 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 (Figure 17-27). This pattern is often 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.

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)

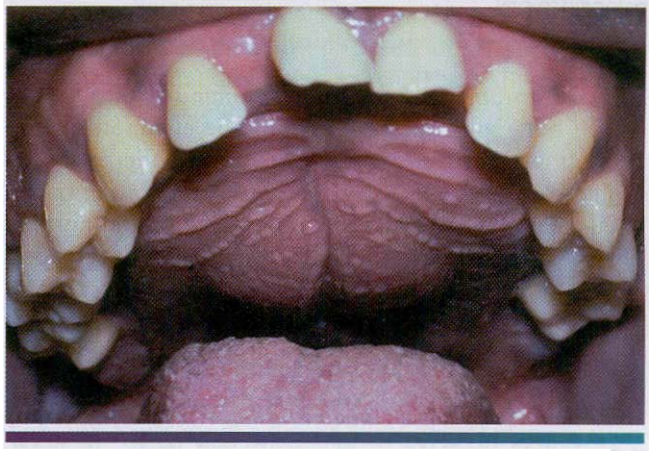


Figure 17-25 • Hyperparathyroidism. Palatal enlargement is characteristic of the renal osteodystrophy associated with secondary hyperparathyroidism.

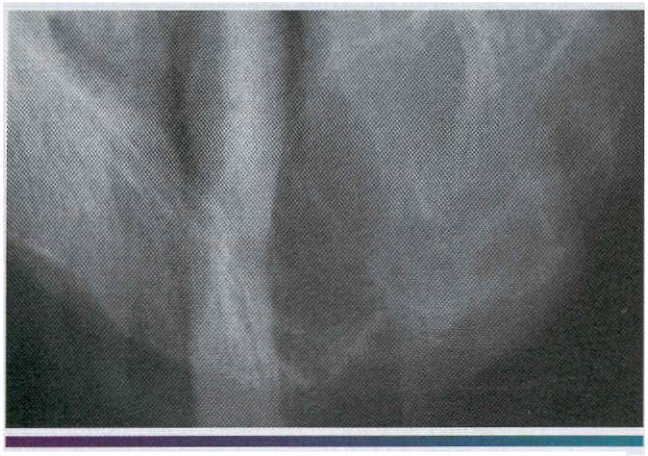


Figure 17-24 . Hyperparathyroidism. This occlusal radiograph of the edentulous maxillary anterior region shows a multilocular radiolucency characteristic of a brown tumor of primary hyperparathyroidism. (Courtesy of Dr. Brian Blocher]

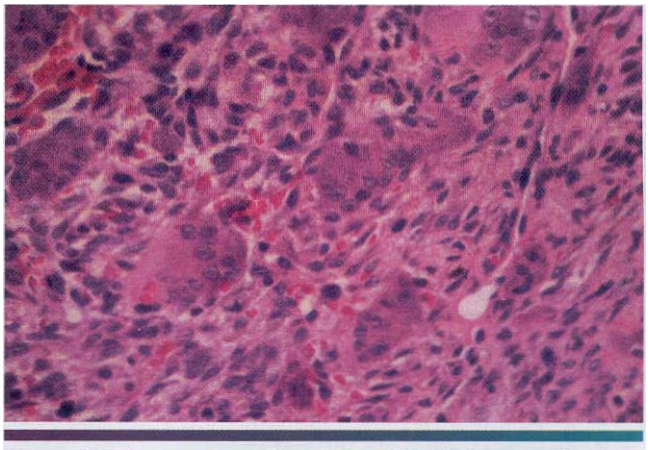


Figure 17-26 . Hyperparathyroidism. This high-power photomicrograph of a brown tumor of hyperparathyroidism shows scattered multinucleated giant cells within a vascular and proliferative fibroblastic background.

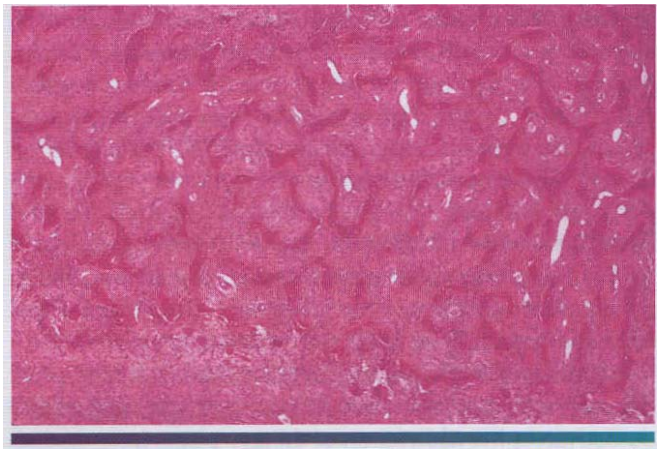


Figure 17-27 • Hyperparathyroidism. This low-power photomicrograph shows delicate, interconnecting trabeculae of woven bone within a background of cellular fibrous connective tissue. These features are characteristic of tissue changes seen in renal osteodystrophy.

may avert problems. 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 is the ideal treatment because it usually restores the normal physiologic processing of vitamin D, as well as phosphorus and calcium reabsorption and excretion.

HYPERCORTISOLISM (CUSHING'S SYNDROME)

Hypcrcortisolism 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. If the increase **is caused by an endogenous source. such as an adrenal** or pituitary (adrenocorticotropic hormone [ACTH]-**secreting) tumor, the condition is known as Cushing's** disease. This latter condition is rather rare and usually affects young adult women.

clinical Features

The signs of Cushing's 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" (Figure** 17-28). Other common findings include the following;

- Reddish-purple abdominal striae
- **Hirsutism**
- Poor healing
- **Osteoporosis**
- Hypertension

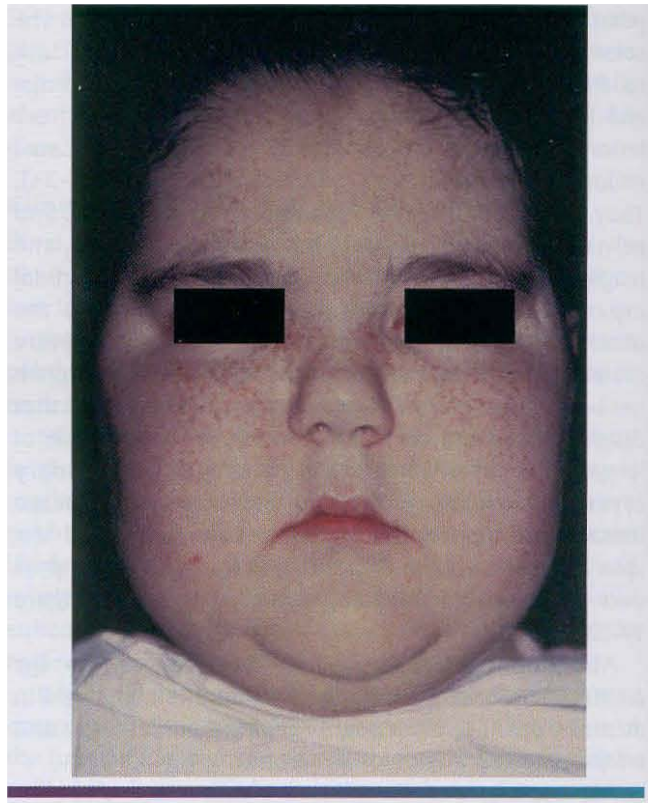


Figure 17-28 . Cushing's syndrome. The rounded facial features ("moon facies") of this patient are due to the abnormal deposition of fat. which is induced by excess corticosteroid hormone. (Courtesy of Dr. George Blozis.]

- 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, 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 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, if 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, particulariy 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 reclpl**ents. 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 *taddlsonian crisis)* may be precipitated. Therefore, the clinician must be aware of the potential side effects of chronic high-dose corticosteroid useand 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 cortico-**steroid 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'S DISEASE (HYPOADRENOCORTICISM)

Insufficient production of adrenal corticosteroid hormones caused by the destruction of the adrenal cortex **results in the condition known as Addison's disease, or primary** hypoadrenocorticism. **The incidence of new** cases diagnosed in the Western hemisphere is 40 to SO per million population per year. The causes are diverse and include the following:

- **Autoimmune destruction**
- Infections (such as 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 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.**

The orai manifestations include diffuse or patchy, brown macular pigmentation of the oral mucosa caused by excess melanin production (Figure 17-29). 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's disease.

Laboratory Findings

The diagnosis of hypoadrenocorticism is confirmed by a rapid ACTH stimulation test and measurement of plasma

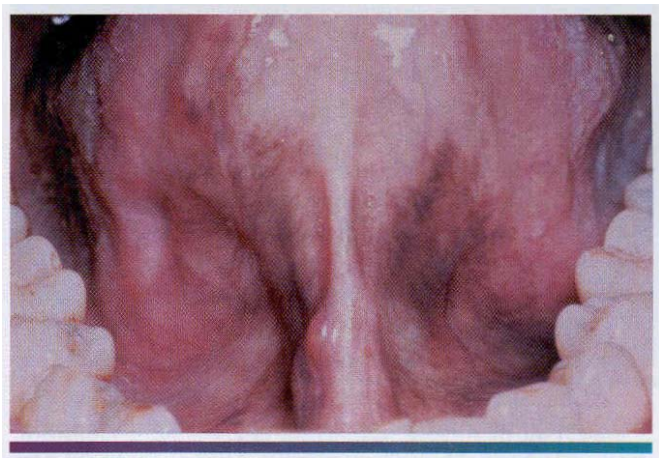


Figure 17-29 • **Addison's disease. Diffuse pigmentation ofthe floor of the mouth and ventral tongue in a patient with Addison's disease. (Courtesy of Dr. George Blozis.)**

ACTH levels. In primary hypoadrenocorticism, the plasma ACTH levels are high (> 250 pg/rnl). In secondary hypoadrenocorticism, the levels are low (D to 20 pg/rnl), as would be expected because the condition results from decreased ACTH production by the pituitary gland.

Treatment and Prognosis

Addison's disease is managed with corticosteroid replacement therapy. The physiologic dose of corticosteroid is considered to be approximately 5 mg of prednisone 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 may be necessary for certain dentai and oral surgical procedures.

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 affected patients can expect to have a normal life span.

DIABETES MEILITUS

Diabetes mellitus is a common disorder of carbohydrate metabolism that is thought to have several causes, aithough the basic probiem 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: insulin-dependent diabetes mellitus (100M) or juvenile-onset diabetes
2. Type Ⅱ: noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes

Type I diabetes mellitus is characterized by a lack of insulin production. Patients usually exhibit severe hyperglycemia and ketoacidosis. The disease is typically diagnosed during childhood, and patients require exogenous insulin injections to survive.

Type II diabetes mellitus is sometimes more difficult to diagnose. It usuaily occurs in older, obese adults. Although hyperglycemia is present, ketoacidosis rareiy develops. Furthermore, patients can produce some endogenous insulin. A few patients may take 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 6% of the population, or nearly 16 million people. Almost 800,000 new cases are diagnosed 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 over 50,000 amputations are performed for the gangrenous compiications 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 biindness in working-age adults in the United States is diabetes, with over i2,000 people affected annually.

The cause of diabetes mellitus is essentially unknown, although evidence is accumulating that many cases of type I diabetes may be precipitated by a viral infection that triggers an autoimmune response. resulting in destruction of the pancreatic islet cells. 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, the chances of a chiid having the disorder is about 40%. Similarly, if one identical twin has type Ⅱ diabetes, 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, this sets into motion a cascade of intracellular molecular events that 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, glucose cannot be absorbed by the body's cells 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** urtnetncreases, **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 postbinding molecular *events* related to glucose uptake results in glucose not being absorbed by the body's cells. Thus, patients are **said to show** "lnsulinresistance" **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 almost never 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.

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 404), 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 (Figure 17-30). In addition, these patients appear to be more susceptible to oral candidiasis in its various clinical forms (see page 189). Erythematous candidiasis, which appears as central papillary atrophy of the dorsal tongue papillae, is reported in up to 30% of these patients. Zygomycosis (see page 206) may occur in patients with poorly controlled type i diabetes. An increased prevalence of benign migratory glossitis has also been associated with type I diabetes. 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.**

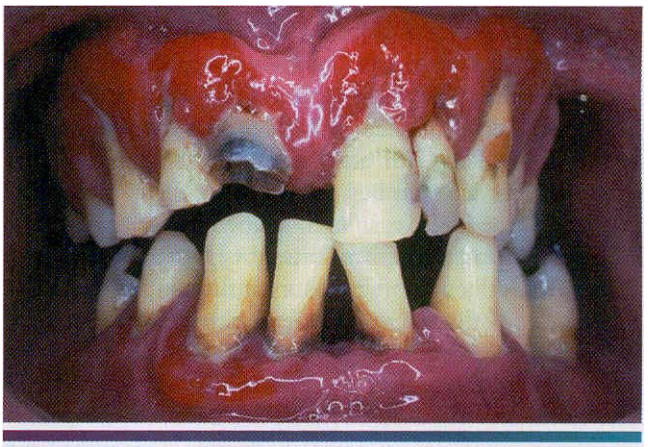


Figure 17-30 . Diabetes mellitus. The diffuse, strikingly erythematous enlargement of the gingival tissues is an oral feature that has been identified in diabetic patients.

Treatment and Prognosis

For patients with type Il diabetes. dietary modification may be the only treatment necessary. Usually. this consists of a reduction in the caloric value of the foods consumed. with the goal being weight loss. The dietary changes may need to be coupled with an oral hypoglycemic agent. such as tolbutamide. chlorpropamide. tolazamide. or glyburide. If these modalities do not control the blood glucose levels. 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 prevtously 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. some pharmaceutical companies have developed brands of insulin that have the molecular structure of human insulin. This human insulin is produced by 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. 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. intravenous 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 (c.g.. blindness. kidney damage. 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 1diabetes who show poor blood glucose control, have active infections, or require extensive oral surgical procedures.

HYPOPHOSPHATASIA

Hypophosphalasia is a rare metabolic bone disease that is characterized by a deficiency of tissue-nonspecific alkaline phosphatase. At least 65 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 arc 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 probabiy are responsible for the clinically observed abnormalities. Alkaline phosphatase is thought to playa role in the production of bone. but its precise mechanism of action is unknown.

Clinical and Radiographic Features

Four types of hypophosphatasia are generally recognized, depending on the severity and the age of onset 01 the symptoms:

1. Perinatal
2. Infantile
3. Childhood
4. Adult

Perinatal *llypol"lOsplmtasia*. The perinatal 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.

tnfantile 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 *tor* these infants. Radiographs show a markedly reduced degree of ossifi-

cation 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 (Figures 17-31 and 17-32). 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 has the appearance of "beaten copper," and it shows uniformly spaced, poorly defined, small radiolucencies. This pattern may be due to 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.

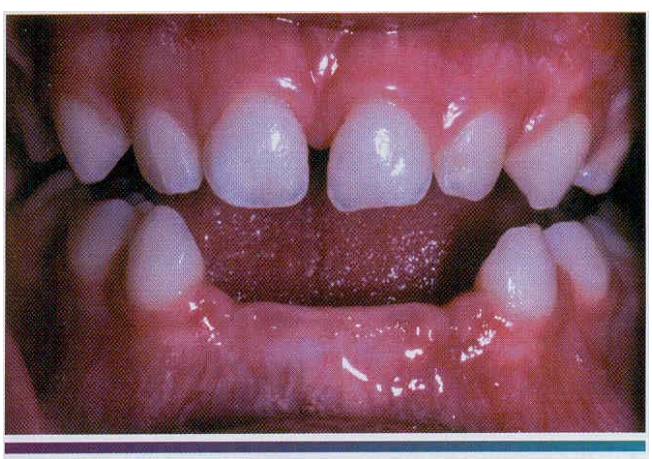


Figure 17-31 • **Hypophosphatasia. Premature loss of the mandibular anterior teeth. (Courtesy of Dr. Jackie Banahan.)**

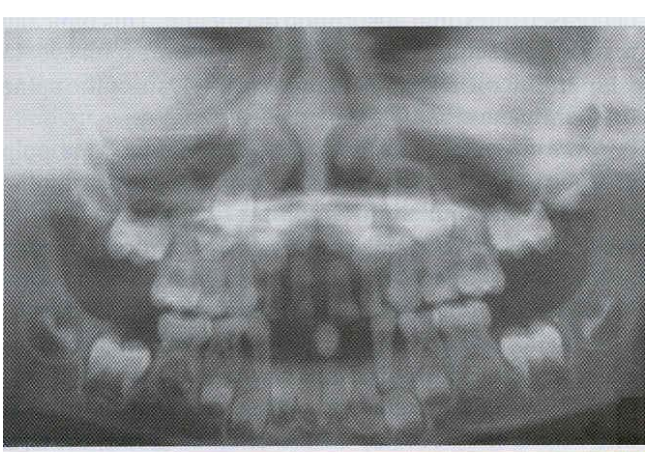


Figure 17-32 • **Hypophosphatasia. This panoramic radiograph shows the loss of the mandibular anterior teeth. (Courtesy of Dr. Jackie Banahan.)**

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 exfoiiated from an affected patient often shows an absence or a marked reduction of cementum that covers the root's surface (Figure 17-33). 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 ceil 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. Because

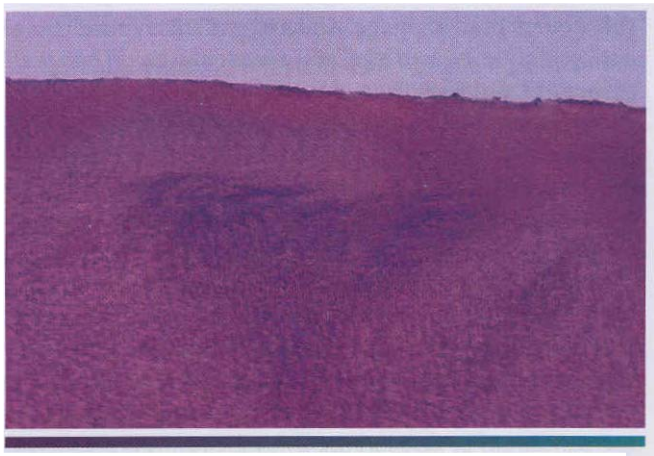


Figure 17-33 • Hypophosphatasia. This medium-power photomicrograph of an exfoliated tooth shows no cementum associated with the root surface.

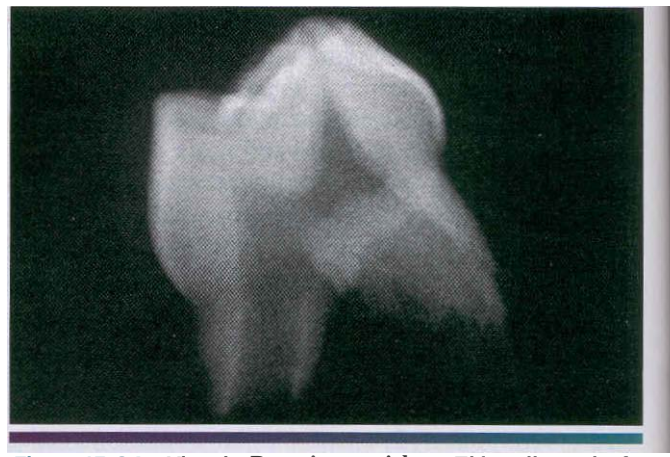


Figure 17-34 . Vitamin D-resistant rickets. This radiograph of an extracted tooth shows a prominent pulp chamber with pulp horns extending out toward the dentinoenamel junction.

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 arc usually affected more severely than females. who presumably have attenuated features because of lyonlzation. In the United States. this condition occurs at a frequency of I 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 PHEX (phosphate regulating gene with endopeptidase activity on the X chromosome). Although the precise mechanisms of action of this gene are unclear. it appears to playa role in vitamin D metabolism.

In contrast. patients affected by the rare autosomal recessive condition known as vitamin D-dcpendent 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 la-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 (calcltrtol).

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 (Figures 17-34 and 17-35). 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 (Figure i 7-36). Recent studies have also shown that rnlcroclefts 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.

Figure 17-35 • Vitamin D-resistant rickets. Ground section of the same tooth depicted in Figure 17-34. A pulp horn extends to the dentinoenamel junction. (Courtesy of Dr. Carl Witkop.)

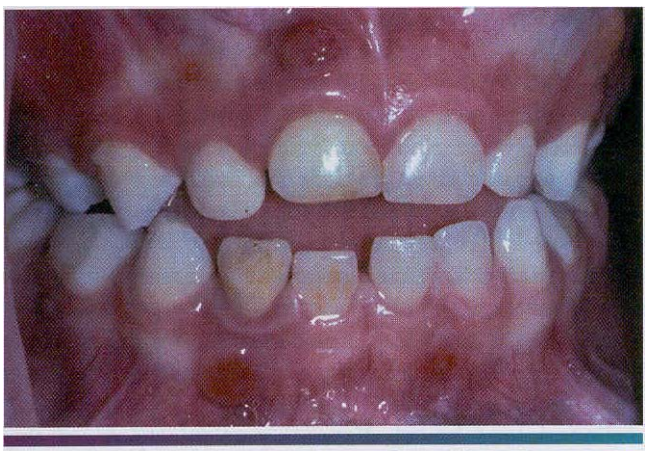


Figure 17-36 . Vitamin D-resistant rickets. This patient exhibits multiple ncnvital teeth with associated parulides. This arose in the absence of caries or trauma.

Histopathologic Features

Microscopic examination of an erupted tooth from a patient with vitamin D-resistant rickets usually shows markedly enlarged pulp horns. The dentin appears abnormal and is characterized by the deposition of globular dentin, which often exhibits c1efting. 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 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. **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'S DISEASE (REGIONAL ILEITIS; REGIONAL ENTERITIS)

Crahn's 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's 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's disease appears to be increasing, but **the reasons for this increase have not been determined.**

Clinical Features

Most patients with Crohn's disease are teenagers when the disease first becomes evident. Gastrointestinai 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.**

A wide range of oral lesions has been clinically reported in Crohn's disease; however, many of the abnormalities described are relativeiy nonspecific and may be **associated with other conditions that cause orofacial** granulomatosis (see page 294). The more prominent findings include diffuse or nodular swelling of the oral and periorai tissues, a cobblestone appearance of the mucosa, and deep, granulomatous-appearing ulcers. The ulcers are often linear and develop **in** the buccal vestibule (Figure 17-37). Soft tissue swellings that resemble denture-related fibrous hyperplasia may be seen, although the lesions occur in dentate individuals. Another manifestation that has been reported is aphthouslike 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's disease. One large study showed no difference in the prevalence of aphthous ulcers in patients with Crohn's disease compared with a control population. Less than 1% of patients with Crohn's disease may develop diffuse stomatitis, with some cases apparently caused by *Staphylococcus aureus*, and others being nonspecific.

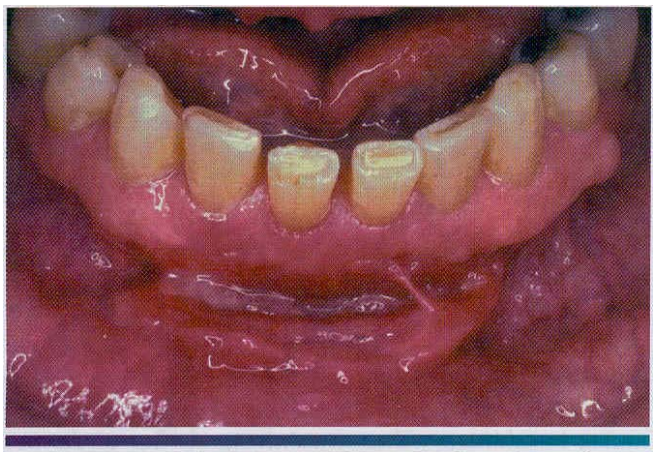


Figure 17-37 . Crohn's disease. This patient has a linear ulceration of the mandibular vestibule. An adhesion between the alveolar and labial mucosae was caused by repeated ulceration and healing of the mucosa at this site.

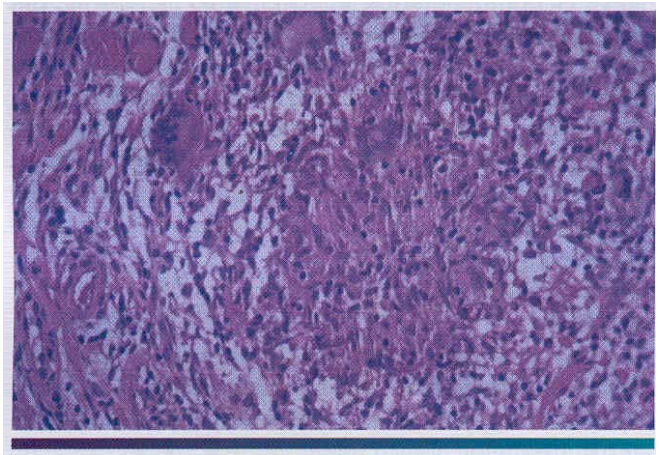


Figure 17-38 . Crohn's disease. This medium-power photomicrograph of an oral lesion shows a nonnecrotizing granuloma in the submucosal connective tissue.

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 (Figure i 7-38). 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 anyone site and time may not necessariiy rule out a diagnosis of Crohns disease. As with the clinical lesions, the histopathologic pattern is relatively nonspecific, resembling orofacial granuiomatosis. Special stains shouid be performed to ruie out the possibtlltv of deep tungai infection, **tertiary syphilis, or mycobacterial infection.**

Treatment and Prognosis

Most patients with Crohn's disease are initiali y treated medicali y with a sulfa type of drug (sulfasalaztne), and some patients respond weil to this medication. With **moderate to severe involvement, systemic prednisone** may be used and is often effective, particularly when combined with the immunosuppressive drug, azathio**prine. Sometimes the disease cannot be maintained in** remission by medical therapy, and complications **develop that require surgical intervention. Complications** may include bowel obstruction or fistuia or abscess *for*mation. if a significant segment of the termin al ileum has been removed surgicaliy or is involved with the disease. **periodic injections of vitamin B12 may be necessary to** prevent megaloblastic anemia secondary to the iack *of* ability to absorb the vitamin. Similar supplementation *at* **magnesium, iron, the fat-soluble vitamins and folate may** also be required because of malabsorption.

Oral lesions have been reported to clear with treatment of the gastrointestinal process in many cases. Occasionaliy persistent oral uicerations wili develop, and these may have to be treated with topicai or intraiesional corticosteroids. Systemic thalidomide has been used successfully to manage refractory oral ulcers of Crohn's 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. particulariy ulcerative colitis or Crohn's disease. The pathogenesis of the condition. like that of inflammatory bowei 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 pus**tules set on an erythematous oral mucosa. The lesions** primarily affect the buccai and labial mucosa. soft palate. and ventral tongue (Figures 17-39 and 17-40). These iesions have been calied "snail track" ulcerations. although in most instances the lesions are probabiy not truly ulcerated. Oral discomfort is variabie 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.**

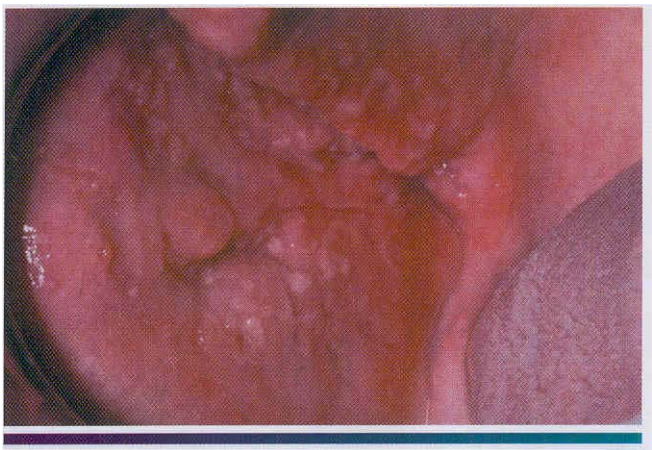
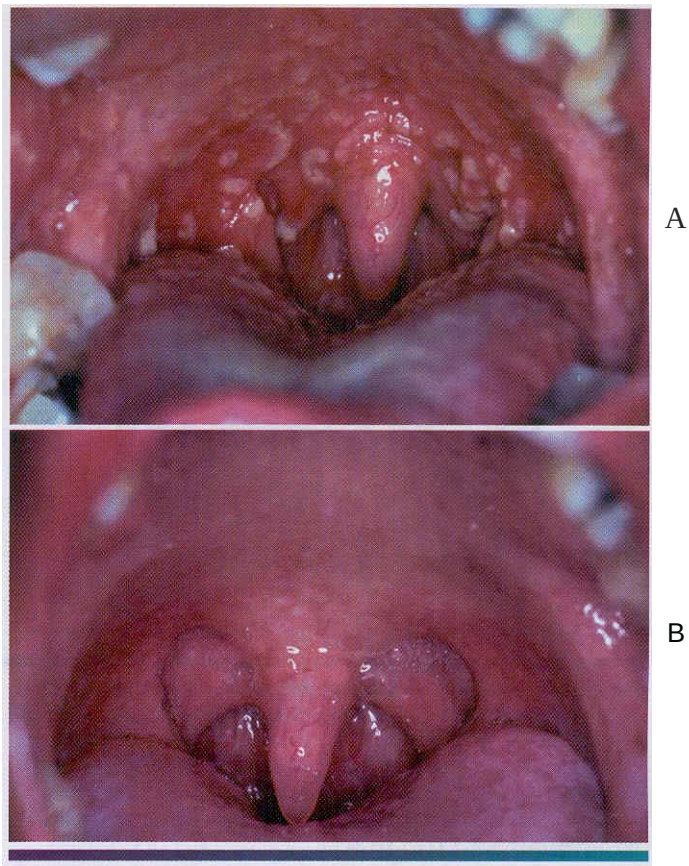


Figure 17-39 • Pyostomatitis vegetans. The characteristic lesions are seen on the buccal mucosa, appearing as yellowish-white pustules.



A

B

Figure 17-40 • 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 Dermatopatho/7:69-77, 1985.)*

Histopathologic Features

A biopsy specimen of an oral lesion of pyostomatitis vegetans usuaily 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 (Figure 17-41). Subepithelial eosinophilic abscesses have been 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 Figure 17-40). Often the oral lesions clear within days after systemic corticosteroid therapy Is begun, and they may recur if the medication is withdrawn. If the bowel symptoms are relatively mild, 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 typicaily show markedly elevated levels of urea and other nitrogenous wastes in the blood stream. 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 (Figure 17-42). 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.

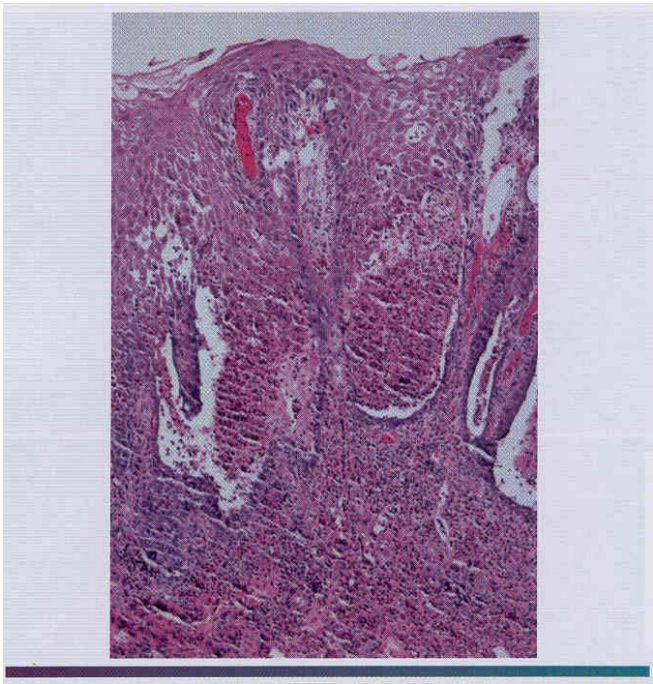


Figure 17-41 • Pyostomatitis vegetans. Medium-power photomicrograph showing intraepithelial abscesses comprised of eosinophils.

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 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.

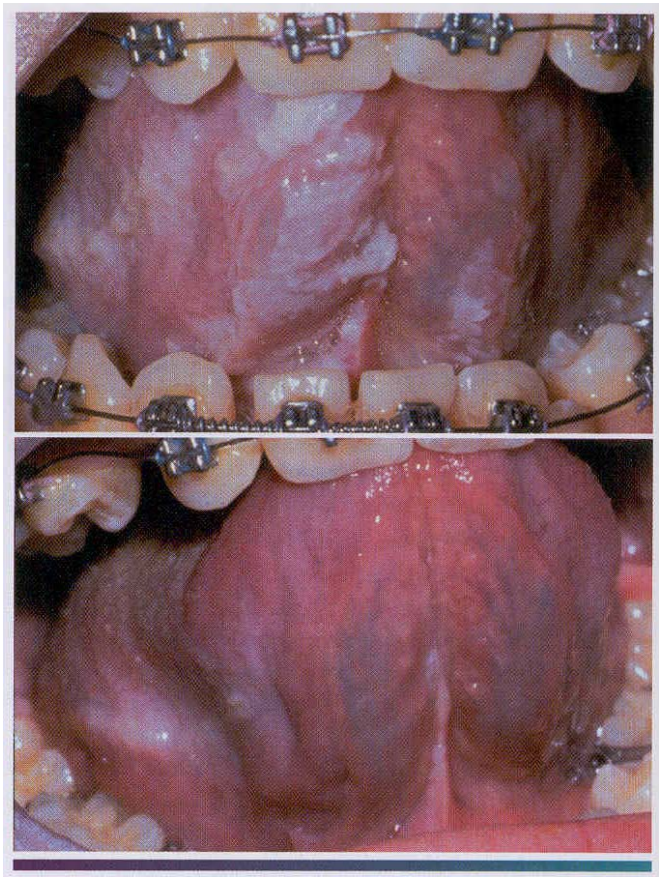


Figure 17-42. Uremic stomatitis. A, Ragged white plaques affect the ventral tongue and floor of the mouth. B, Same patient after renal dialysis. (From Ross WF, Salisbury PL: Uremic stomatitis associated with undiagnosed renal failure, *Gen Dent 42:410-412,* 1994.)

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CHAPTER 18

Facial Pain and Neuromuscular Diseases

CHAPTER OUTLINE

BELL'S PALSY (IDIOPATHIC SEVENTH NERVE PARALYSIS; IDIOPATHIC FACIAL PARALYSIS)

Bell's palsy is a dramatic but self-limiting. unilateral facial paralysis. A variety of potential triggering events are known (Box 18-I), although a trigger cannot be identified in at least one fourth of all cases. The precise cause remains unclear, but familial occurrences have been reported and suspected causes include reactivation of herpes simplex or zoster in the geniculate ganglion. nerve demyelination, nerve edema or ischemia, autoimmune damage to nerves, and vasospasm of vessels associated with *nerves*.

A similar presentation can be seen with obvious damage to the facial *nerve* (e.g.. from facial and salivary gland tumors or from severance of the nerve caused by trauma or surgery). When the cause is known, the term Bell's palsy is not usually used.

Bell's palsy is diagnosed in 24 of every 100.000 persons each year. with increased frequency in the rail and winter seasons. In demyelinating diseases, such as multiple sclerosis (MSJ. it occurs much more frequently (I in 5 cases), usually appearing late in the disease but occasionally being the first symptom. Rarely, *other* anatomic sites also will become paralyzed. usually in persons with Melkersson-Rosenthal syndrome (see page 295), Lyme disease (*Borrelia burgdorferi* infection, Lyme peripheral facial palsy. transient facial nerve palsy), or sarcoidosis.

Box 18-1 ***Triggering Events or Phenomena Related to Bell's Palsy***

- Acute otitis media
- Atmospheric pressure change (diving, flying)
- Exposure to cold
- Ischemia of the nerve near the stylomastoid foramen
- local and systemic infections (viral, bacterial, fungal)
- Melkersson-Rosenthal syndrome
- Multiple sclerosis (MS)
- Pregnancy (third trimester. early eclampsia)

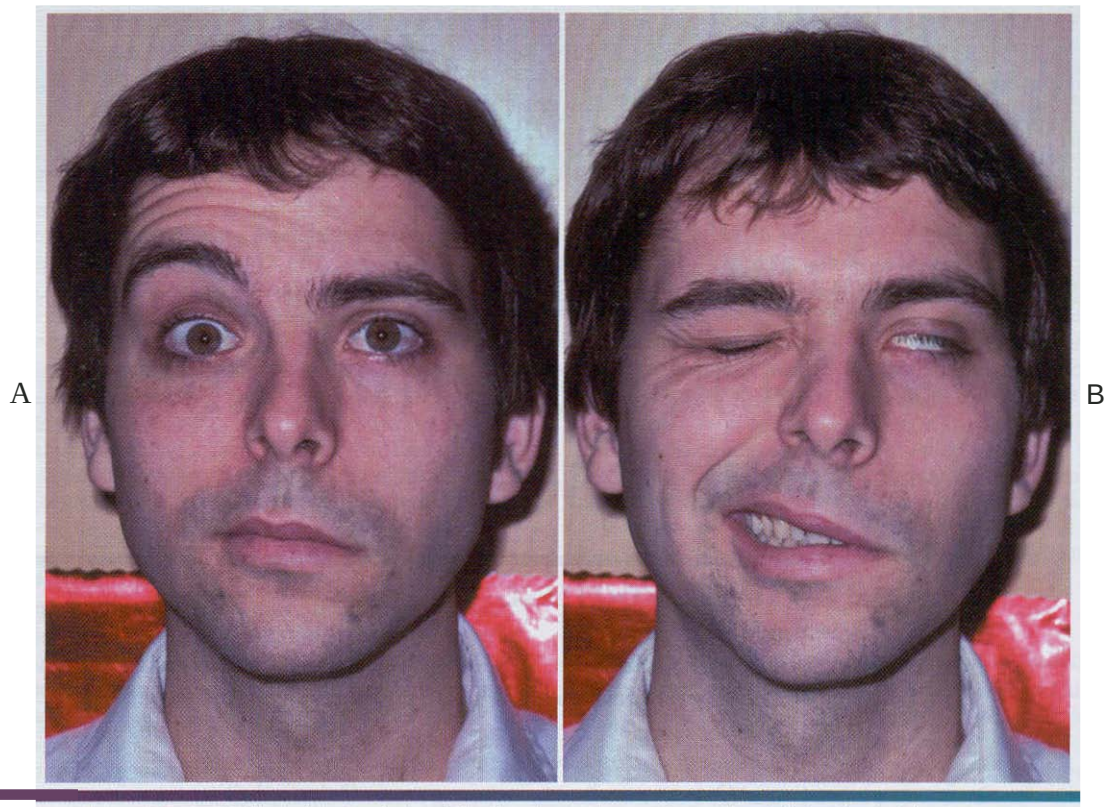

Figure 18-1 • Bell's palsy. Paralysis of the facial muscles on the patient's left side. A. The patient is trying to raise his eyebrows. B, The patient is attempting to close his eyes and smile. (Courtesy of Dr. Bruce B. Brehm.)

Clinical Features

People of all ages are susceptible to Bell's palsy. but middle-aged people are affected most frequently. Women are affected more often (71%) than men. Childhood involvement is usually associated with a viral infection. Lyme disease. or earache.

Considerable variation exists in the severity of signs and symptoms. The palsy is characterized by an abrupt loss of muscular control on one side of the face, Imparttng a rigid mask-like appearance and resulting in the inability to smile. to close the eye, to wink. or to raise the eyebrow (Figure 18-1). A few patients. espectally those with MS. experience prodromal pain on the affected side before the onset of paralysis. Infrequently. bilateral involvement is seen. The paralysis may take several hours to become complete. but patients frequently awaken in the morning with a full-fledged case. When vertigo or tinnitus is a major symptom, an occult herpes zoster ear infection should be suspected. and the diagnosis may be changed to Ramsay Hunt syndrome (see page 223).

The corner of the mouth usually 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.

Treatment and Prognosis

No universally preferred treatment exists for Bell's palsy. Histamine and other vasodilators may shorten the duration. as will systemic corticosteroids and hyperbaric oxygen therapy. Surgical decompression of the intratemporal facial nerve is used in select cases. Topical ocular antibiotics and artificial tears may be required to prevent corneal ulceration. and the eyelid may have to be taped shut.

Symptoms usually begin to regress slowly and spontaneously within I to 2 months of onset: more severe cases take longer. as do those in older patients. Overall. more than 82% of patients recover completely within 6 months. Residual symptoms that remain after I year will probably remain indefinitely. Recurrence is rare. except in Melkersson-Roscnthal syndrome.

TRIGEMINAL NEURALGIA (TIC DOULOUREUX; TIC)

The head and neck region is a common site for neuralgias (pain extending along the course of a nerve) (Box 18-2). 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 of the facial neu-

Box 18-2 *Types of Facial and Cervical Neuralgias*

- Atypical pain/neuralgia
- Geniculate neuralgia
- Glossopharyngeal neuralgia
- Migrainous neuralgia
- Occipital neuralgia
- Paratrigeminal neuralgia of Raeder
- Postherpetic facial neuralgia
- Sphenopalatine ganglion neuralgia
- Superior laryngeal neuralgia
- Trigeminal neuralgia
- Tympanic plexus neuralgia

Box 18-3 *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"), additional attacks usually cannot be brought on by touching the trigger point.
- 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.

ralgias, is characterized by an extremely severe electric shocklike or lancinating (sharp, jabbing) pain limited to one or more branches of the trigeminal nerve. It is often idiopathic but is usually associated with pathosis somewhere along the course of the nerve. Occasionally, trigeminal neuralgia results from a brainstem tumor or infarction.

Trigeminal neuralgia is diagnosed In 6 of every 100,000 persons each year, but it develops in 4% of persons with multiple sclerosis (MS). Moreover, patients with neuralgia-inducing cavitational osteonecrosis (NICO) of the jaws (see page 746), Gradenigo syndrome (suppurative otitis media, trigeminal nerve pain, abducens nerve palsy), and chronic paroxysmal hemicrania-tic syndrome, may have pain so similar as to be indistinguishable from trigeminal neuralgia.

Because so many of its features are consistent with a central nervous system (CNS) disease, trigeminal neuralgia has been called "a pain syndrome with a peripheral cause but a central pathogenesis." The seriousness of the disorder is underscored by the fact that It has one of the highest suicide rates of any disease.

Clinical Features

Trigeminal neuralgia characteristically affects individuals older than 40 years *at* age (average age at onset: 50 years), although it may affect persons as early as puberty. Women are affected slightly more often than men, and the right side is involved more often than the left. Any branch of the trigeminal nerve may be involved, but the ophthalmic division is affected in only 5% of cases. More than one branch may be involved and the pain is *occa*sionally bilateral.

Specific and strict criteria must be met for an accurate diagnosis (Box 18-3). If the pain pattern does not meet these criteria, a different diagnosis should be considered. When these criteria are partially fulfilled, alternative terms such as atypical trigeminal neuralgia, atypical facial pain, and atypical facial neuralgia are applied.

In the early stages, the pain of trigeminal neuralgia is rather mild and is described by the patient as a twinge, dull ache, or burning sensation. There are long, asymptomatic refractory periods between painful attacks. With time, the attacks occur at more frequent intervals and the pain becomes increasingly intense. At this point, patients often state that the pain is like "a lightning bolt" or a "hot ice pick jabbed into the face."

Although individual pains or pain spasms last only a few seconds, several attacks may follow each other for up to 30 minutes of rapidly repeating volleys. 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* ("painful jerking") for this disease. The paroxysmal facial pain is occasionally accompanied by excess lacrimation, conjunctival injection, and intense headache. This presentation may represent the SUNCT (short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing) syndrome rather than trigeminal neuralgia.

When an obvious trigger point is present in trigeminal neuralgia, a pain attack *may* be brought on by a stimulus to the area as mild as a breeze, a gentle movement, or a feather-light touch. Trigger points are found most frequently on the nasolabial fold, the vermilion border of the lip, or the midfacial and periorbital skin. Intraoral trigger points are uncommon but do occur, especially on the alveolus.

Histopathologic Features

No unique histopathologic characteristic to the nerves in trigeminal neuralgia exists, although the trigger points may show fibrosis and Infiltration by small numbers of

Box 18-4 *Intracranial Neurosurgical Therapies for Trigemi'lal Neuralgia*

- 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)
- Repositioning of blood vessels impinging on trigeminal nerve (microvascular decompression)
- 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)

chronic inflammatory cells. Focal areas of myelin degeneration have been reported within the gasserian ganglion and along the course of the cranial nerve itself. but these also have been occasionally seen in persons without trigeminal neuralgia. MS patients with trigeminal neuralgia show unique amorphous plaques in the ganglion.

Treatment and Prognosis

The initial treatment for trigeminal neuralgia is medical. Topical capsaicin cream (a nociceptive substance-P suppressor) over the affected skin may be effective. Anticonvulsant medications (phenytoin, carbarnazeplne, gabapentin) often are effective in pain control. probably because they decrease conductance in Na+ channels and inhibit ectopic (arising from abnormal sites) discharges. These drugs. unfortunately. often have severe side effects and may not be tolerated long. Moreover. the pain usually returns upon discontinuance of the medication.

Various neurosurgical procedures also are effective in severe or refractory cases. especially in younger patients (Box 18-4). and recent reports have shown some success with gamma knife radiosurgery of the gasserian ganglion and its associated nerves.

Neurosurgical methods provide relief for years in the majority of trigeminal neuralgia patients. Repeated surgical procedures often are necessary. however. 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 dolorosal.Overall, long-term success from surgical procedures is 70% to 85%.

GLOSSOPHARYNGEAL NEURALGIA (VAGOGLOSSOPHARYNGEAL NEURALGIA)

Neuralgia of the ninth cranial nerve. glossopharyngeal neuralgia. is similar in every way to trigeminal neuralgia (see previous topic) except in the anatomic location of the pain. Some unfortunate individuals have a combination of giossopharyngeal neuralgia and trigeminal neuralgia.

Glossopharyngeal neuralgia is rare. occurring only once for every 100 cases of trigeminal neuralgia. The pain also may affect sensory areas supplied by the pharyngeal and auricular branches of the vagus nerve. As with trigeminal neuralgia. the cause is unknown.

Clinical Features

The age of onset for glossopharyngeal neuralgia varies from 15 to 85 years. but the average age is 50 years. There is no sex predilection. and only rarely is there bilateral involvement. The paroxysmal pain may be felt in the ear (tympanic plexus neuralgia). infra-auricular 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 (30- to 60-seeond bursts that may repeat for 5 to 30 minutes). 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 difficult to differentiate it from the severe pain of temporomandibular joint dysfunction (TMD).

Patients frequently point to the neck immediately beiow the angie of the mandible as the site of greatest pain. but trigger points are not found on the external skin. except within the ear canal. Rarely. syncope. hypotension. seizures. arrhythmia, or cardiac arrest may accompany the paroxysmal pain. as may coughing or excessive salivation. The clinician should be careful to rule out Eagle syndrome (see page 22) before applying the glossopharyngeal neuralgia diagnosis.

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.

About 80% of patients experience immediate 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. Carbamazepine. oxcarbazeplne, baclofen, phenytoin. larnotrtgine, or resection of the glossopharyngeal

nerve may relieve the neuralgic pain for a long period. but no therapy is considered to be uniformly effective or even adequate.

ATYPICAL FACIAL PAIN (ATYPICAL FACIAL NEURALGIA; IDIOPATHIC FACIAL PAIN; ATYPICAL TRIGEMINAL NEURALGIA; TRIGEMINAL NEUROPATHIC PAIN)

Atypical facial pain is a persistent pain in the maxillofacial region that does not fit the diagnostic criteria of any other orofacial pain and has no identifiable cause. In other words. it is a diagnosis of exclusion and its use by the clinician implies that all potential causes of pain have been ruled out (Box IB-5). Although not the most common facial pain. this condition is the facial disease that most often brings a patient to a pain clinic. No acceptable population studies are available.

Atypical facial pain is such a difficult diagnostic and therapeutic condition that patients travel from one health professional to another and receive many different diagnoses and treatments in a frustrated attempt to find relief. Patients are often described as being neurotic ("hysterteal") and suffering from hypochondriasis. obsessive-compulsive disorder. anxiety disorder. depression. or a "lack of insight." Whether this is true or not. the strong emotional overtones of this condition make it difficult to distinguish functional (psychogenic) from organic (physiologic) pain.

Clinical Features

Atypical facial pain affects women far more frequently than men. It usually develops during the fourth through sixth decades of life. but can occur as early as the teenage years. The pain may be localized to a small area of the face or alveolus (atypical odontalgia. "phantom" toothache) but more frequently affects most of a quadrant and may extend to the temple. neck. or OCCipital area. Patients have great difficulty describing the pain. but most often portray it as a continuous. deep. diffuse. **gnawing ache, an intense burning sensation. a pressure,** or a sharp pain. It is important to differentiate the pain from trigeminal neuralgia (see page 742).

Bilateral involvement occasionally occurs and the pain is frequently initiated or enhanced by oral surgery and restorative dental work. The mucosa of the affected quadrant appears normal but typically contains a zone **of increased temperature, tenderness. or bone marrow** activity (vhot spot" on technetium 99m MOP bone scan). Radiographic changes are not present.

Treatment and Prognosis

Occasional cases of spontaneous remission are noted, but the great majority of atypical facial pain patients will obtain little relief without therapy. Symptoms tend to become more intense gradually. and patients become irritable. fatigued. and depressed. Most patients are not benefited substantially from the drugs used for trigeminal neuralgia. although the new anticonvulsant. gabapcnnn, dramatically reduces the pain in one third of affected patients. Opioid analgesics (codeine. fentanyl, hydrocodone, morphine. oxycodone) may be of considerable benefit but their effectiveness often diminishes **over time and, of course. they are associated with** the risk of abuse and addiction.

The tricyclic antidepressants (amitriptyline. nortriptyline) are popular therapies for neuropathic pain. They appear to block reuptake of norepinephrine and serotonin. transmitters released by pain-modulating systems in the spinal cord and brain stem. thereby allowing long periods of diminished neural activity. Other antidepressants (such as the selective serotonin reuptake inhibitors. paroxetine and citaloprarn) are generally not as effective as the tricyclic antidepressants for managing atypical facial pain. although some patients may respond to this therapy. It is important to remember. however. that antidepressant medications may be quite hazardous to the frail elderly or to patients with coronary disease. When a localized area (usually alveolar) of tenderness can be found in the quadrant of pain. the application of topical capsaicin or injection with local anesthetics may be temporarily beneficial, Psychotherapy, behavior mod**ification, transcutaneous electric nerve stimulation, and** sympathetic nerve blocks are helpful in a subset of patients with atypical facial pain.

The frequent failure of medical treatment for atypical facial pain may lead to surgical intervention. usually the removal of a portion of the affected trigeminal nerve branch or the injection of a caustic solution (phenol. glycerol. alcohol) into the nerve. designed to destroy a

Box 18-5 *Diseases That Must Be Rllled Out Before Making a Diagnosis of Atypical Facial Patn/Neuralgia*

- **Allergy of sinuses**
- **Cracked tooth syndrome**
- **Headache with referred pain to face**
- **Impingement of bone or blood vessel on nerve**
- **Infection: dental, periodontal, sinuses, ear**
- **Ischemic and inflammatory marrow disease**
- **Myofascial pain**
- **Neuralgias. other**
- **Temporomandibular joint disorder**
- **Trauma to nerve (including traumatic neuroma)**
- **Tumors**

portion of the nerve. These therapies often provide relief for several weeks or months, but seldom is there permanent cure. Surgical exploration of the marrow surrounding a large nerve may discover diseased marrow, which, if removed, may reduce the pain, temporarily or permanently (see following topic).

NEURALGIA-INDUCING CAVITATIONAL OSTEONECROSIS (NICO; ALVEOLAR CAVITATIONAL OSTEOPATHOSIS; ISCHEMIC OSTEONECROSIS; BONE MARROW EDEMA)

Ischemic osteonecrosis is a bone disease characterized by degeneration and death of marrow and bone from a slow or abrupt decrease in marrow blood flow. Along with its lesser variants, bone marrow edema and regional ischemic osteoporosis, it is one of the most common bone diseases in humans, but only recently has it been appreciated as a disorder of the head and neck region. Numerous local and systemic factors are associated with ischemic damage to marrow (Box 18-6), the most common being an hereditary (autosomal dominant) tendency toward blood clot formation within blood vessels. Bone is particularly susceptible to this problem, which in the jaws may be accentuated by dental infections and the vasoconstrictors in local anesthetics.

The ischemia and infarctions of osteonecrosis are typically associated with pain, often with an ill-defined neuralgic or neuropathic character. Because of this, presumed examples of this process in the jaws have been referred to as neuralgia-inducing cavitational osteonecrosis (NICO). NICO is Included in this chapter because of its strong association with pain, but it should be remembered that osteonecrosis is not necessarily a painful condition and our understanding of this disease is still incomplete.

Ischemic osteonecrosis most often affects the hips, maxillofacial bones, and knees. NICO has been found in I of every 11,000 adults, a prevalence rate similar to that of hip cases. The NICO prevalence rate for women (I per 2000) Is much higher than the rate for men (I per 20,000).

Clinical and Radiographic Features

NICO characteristically affects women 35 to 60 years of age but has been diagnosed in men and in teenagers. Third molar regions are affected in half of all cases but any alveolar site may become Involved, as may the walls of the sinuses and the mandibular condyle. At least one third of patients have more than one maxillofacial site of involvement. and 10% have lesions in all four alveolar quadrants.

Patients often have trouble describing and localizing their pain, which can be intermittent or constant, deep or superficial, aching or sharp, mild or extremely intense. Most often the pain is described as a deep ache or sharp bone pain. It typically begins as quite mild and vague, increasing slowly in frequency and intensity *over* months and years, but may also have a sudden onset, especially after a dental procedure using vasoconstrictors in the anesthetic. The pain may roam in the general anatomic area or be referred some distance from the affected bone (neck, shoulder). Many describe pressure and deep burning sensations, and local anesthesia typically relieves the pain.

Osteonecrosis is not visualized readily on radiographs, but when visible it usually appears as an area of regional osteoporosis or ill-defined radiolucency, often with irregular vertical remnants of lamina dura representing old extraction sites (Figure 18-2). Occasional lesions show an admixture of irregular sclerotic and radiolucent areas (ischemic osteosclerosis), or there may be a faint central sclerotic oval surrounded by a thick radiolucent circle which is, in turn, surrounded by a thick but faint sclerotic ring (hull's eye lesion). More than 60% of the lesions will exhibit a hot spot of increased isotope uptake with the technetium 99m MDP bone scan (Figure 18-3).

Histopathologic Features

The microscopic appearance of ischemic osteonecrosis depends on the duration and intensity of the diminished marrow blood flow. The features of bone marrow edema include dilated marrow capillaries and slnusoids, serous

Box 18-6 *Diseases and Phenomena Associated With Ischemic Osteonecrosis*

COMMONLY ASSOCIATED
- Coagulation disorders (thrombophilia, hypofibrinolysis)
- Alcohol abuse
- Trauma
- Prednisone, prednisolone
- Estrogen, pregnancy
- Sickle cell disease
- Lupus erythematosus
- Cancer chemotherapy (including prednisone)

LESS COMMONLY ASSOCIATED
- Tobacco use
- Arteriosclerosis
- Deep sea diving ("bends")
- Shwartzman reaction (serum sickness)

RARELY ASSOCIATED
- Osteomyelitis
- Starvation (e.g., anorexia nervosa)

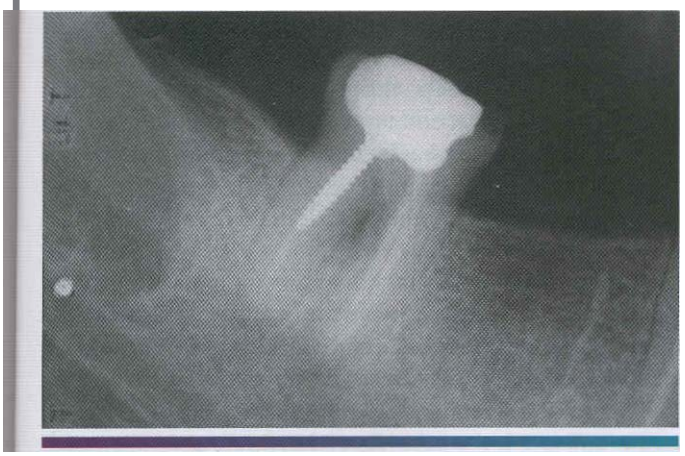

Figure 18-2 • Neuralgia-inducing cavitational osteonecrosis (NICO). Periapical radiograph demonstrates an oval radiolucency in the third molar region and thin lamina dura remnants (residual socket) more anteriorly.

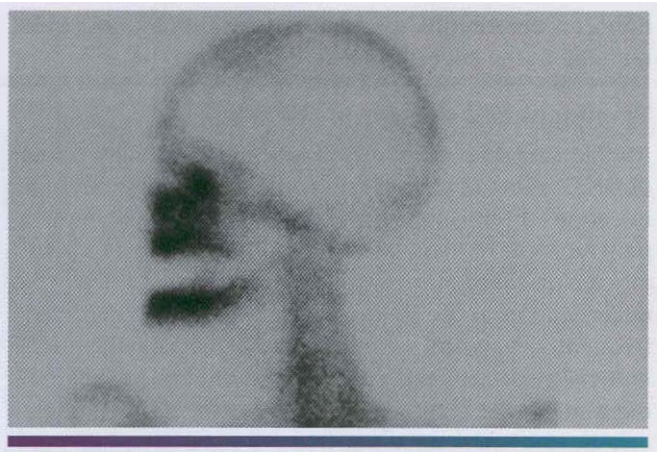

Figure 18-3 • Neuralgia-inducing cavitational osteonecrosis (NICO). Technetium 99m bone scan reveals multifocal and extensive NICO involvement (hot spots) years after extraction of the entire dentition for "atypical facial pain." None of the sites was visualized by routine radiographs. MRI, or CT scans, or other forms of radioisotope bone scans.

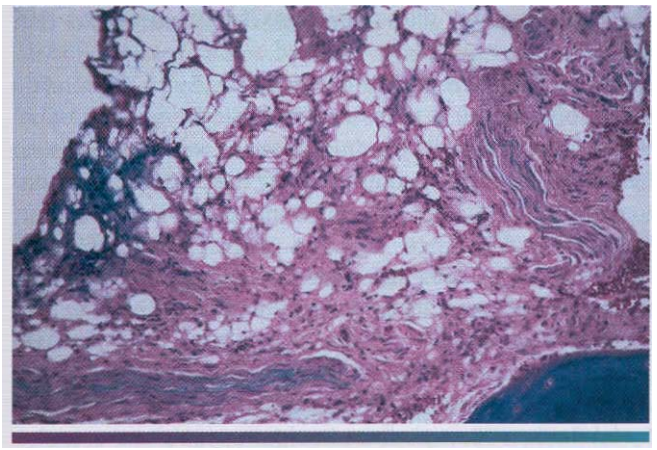

Figure 18-4 • Neuralgia-inducing cavitational osteonecrosis (NICO). Photomicrograph showing ischemic myelofibrosis with a sprinkling of chronic inflammatory cells and serous ooze.

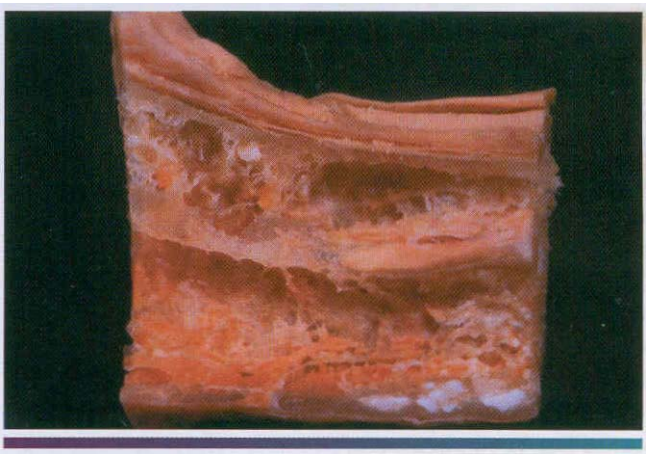

Figure 18-5 • Neuralgia-inducing cavitational osteonecrosis (NICO). Gross photo of section of posterior mandible showing extensive cavitation that has hollowed out most of the bone. (From Bouquot JE, McMahon RE: Neuropathic pain in maxillofacial osteonecrosls.j *Oral Maxillofacial Surg* 58:1003-1020. 2000,)

ooze (plasmostasis) around blood vessels and adipocytes, wispy fibrous streaming (ischemic myelofibrosis) between fat cells. areas of dense fibrosis (intramedullary fibrous scar). and a light sprinkling of chronic inflammatory cells in regions of myelofibrosis (Figure 18-4). Bony trabeculae usually remain viable at this stage but are inactive. thin. and often widely spaced.

Degenerative extracellular cystic spaces (cavitations) are commonly seen and may dominate the picture. eventually coalescing to form spaces large enough to extend from cortex to cortex (Figure 18-5). Focal areas of marrow hemorrhage (microinfarction) are frequently present and considered by some to be pathognomonic **for osteonecrosis.**

Bubbles of coalesced. liquefied fat (oil cysts) may be seen. but because high-speed rotary instruments can produce similar bubbles as an artifact. it is important that only hand-curetted marrow samples be submitted for histopathologic evaluation.

Bone death. when present. is represented by focal loss of osteocytes, but this feature can be evaluated properly only if formic acid or another very weak acid is used for slow. gentle laboratory decalcification. In addition. smudged. globular. often dark masses of calcific necrotic detritus may be seen. These represent destroyed trabeculae that have literally dissolved over time and contributed their calcium to other salts precipitated within necrotic fat. The heat of high-speed rotary instrumenta-

tion can create similar calcific debris, but this debris remains at the edges of tissue fragments.

Treatment and Prognosis

Antibiotics may temporarily diminish the associated pain of NICO in those cases with a superimposed low-grade infection (chronic nonsuppurative osteomyelitis), but the pain typically returns when antibiotics are stopped. Usually the diseased marrow must be *removed* surgically by **decortication and curettage. Once *removed*, the defect** frequently heals and the intense facial pain subsides dramatically or disappears completely, although pain abatement may take several months to occur. Unfortunately, one third of patients thus treated experience no pain relief. In addition, the disease has a strong tendency to recur or to develop in additional jawbone sites. A repetition of the surgical procedure is, therefore, often necessary. Overall. the cure rate (free of pain for at least 5 years) for curettage is better than 70%.

CLUSTER HEADACHE (MIGRAINOUS NEURALGIA; SPHENOPALATINE NEURALGIA; HISTAMINIC CEPHALGIA; HORTON'S SYNDROME)

Cluster headache is an exquisitely painful affliction of the midface and upper face, particularly in and around the eye. The name is derived from the fact that the headache attacks occur in temporal groups or clusters, with extended periods of remission between attacks. Cluster headache is an uncommon disease of unknown origin and has been called "the most severe pain syndrome known to humans." A vascular (vasodilation) cause has been suggested, possibly related to abnormal hypothalamic function, head trauma, or abnormal release of histamine from mast cells. The majority of patients suffer from sleep apnea and diminished oxygen **saturation, but it is not known whether this is a cause or** effect of the disease. Headache can be initiated by alcohol, cocaine, and nitroglycerin; 80% of affected per**sons are cigarette smokers.**

This disorder is diagnosed in iOof every 100,000 persons each year, and there is a predilection for blacks. There is also a strong familiai influence: when a first-degree relative has the headache, there is a fifty-fold increase in the chance that another family member also will be affected.

Clinical Features

Cluster headache may occur at any age. although it usually affects persons in the third and fourth decades of life and is rare before puberty. There is a strong male predilection (a 6:I male-to-female ratio). The pain is almost always unilateral and follows the distribution of the ophthalmic division of the trigeminal nerve.

It is usually felt deep within or behind the orbit, radiating to the temporal and upper cheek regions. However, it may simulate a toothache or neuralgic jaw pain in the anterior maxillary region. Because of this, patients may be treated inappropriately for dental pain with endodontic therapy or tooth extraction, which is thought to be successful when the pain subsequently resolves. **When each successive cluster returns, the next tooth is** treated, sometimes resulting in multiple, repeated episodes of unnecessary dental therapy.

The pain is described as paroxysmal (abrupt onset) and intense. with a burning or lancinating quality and without a trigger zone. The attacks may last from 15 minutes to 3 hours and occur up to eight times daily (or on alternate days). The cluster periods typically last for weeks, with the intervening periods of remission usually lasting for months (sometimes years). The pain often begins at the same time in a given H-hour period (alarm clock headache), with most attacks occurring in the middle of the night.

A chronic form occurs occasionally, with no remissions for years at a time, and episodic forms may convert to the constant, chronic form. In addition, cluster headache is rarely accompanied by the aura so common to migraine headache (see following topic). An important behavioral difference between migraine and cluster headache is that the patient is usually hyperactive during the latter and retreats to a dark, quiet room during the **former.**

In addition to the pain, the patient may experience **autonomic alterations such as nasal stuffiness, tearing,** facial flush, or congestion of conjunctival blood vessels. The latter sign, especially when associated with **increased intraocular pressure. may indicate chronic** paroxysmal hemicrania (Sjaastad syndrome), a rare syndrome with short-duration, highly recurring, nonclustered pain.

Treatment and Prognosis

The proper diagnosis is important to avoid sequential, unnecessary endodontic or extraction procedures. Sys**temic prednisone, ergotamine, lithium carbonate, indo**methacin, methysergide maleate, and verapamil all provide relief in some cases. Sumatriptan (agonistic to 5-HTID receptors) and other drugs of this class shorten the symptoms in 74% of cases. However, no single drug is universally effective. Inhaling oxygen may abort **impending attacks, and various neurosurgical interven**tions to the affected nerve have provided relief in some patients, as has the recently reported use of gamma knife radiosurgery. Overall, only 50% of patients with cluster

headache benefit significantly and permanently from the available therapeutic modalities.

It is important to distinguish cluster headache from chronic paroxysmal hemicrania because the latter disease responds almost universally to indomethacin.

MIGRAINE (MIGRAINE SYNDROME; MIGRAINE HEADACHE)

Migraine is a common. disabling. paroxysmal, unilateral headache that is experienced at least once by more than 14% of teenagers and young adults (lifetime risk: 21%). More than 400 new cases are diagnosed each year for every 100,000 persons. At least 14 different types of migraine exist; they are broadly classified into 2 groups: (I) migraine with aura. and (2) migraine without aura.

The cause of migraine is still unclear, but it appears to be related to vasoconstriction or vasospasm of portions of the cerebral arteries, possibly in response to a chronically reduced activity of serotonin (S-hydroxytryptamine; 5-HT,). The vasoconstriction apparently leads to cerebral Ischemia. which is followed by a compensating vasodilation (mediated by nitric oxide), with subsequent pain and cerebral edema. Many affected persons (mIgraIneurs) have a family history of migraine, sometimes with a clear autosomal dominant inheritance pattern. Common trIggertug events are listed in Table 18-1.

Clinical Features

Migraine affects women three times more frequently than men, and women tend to experience more severe attacks than men. The disease is most prevalent in the third through fifth decades of life. but the first symptoms often begin at puberty or shortly thereafter.

The unilateral headache lasts for 4 to 72 hours and is usually felt in the temporal, frontal, and orbital regions. as well as occasionally in the parietal, postauricular. or OCCipital areas. It begins as a poorly localized discom-*tort* in the head that soon becomes a mild ache and then increases in severity over the next 30 minutes to 2 hours. At its peak. the pain has a throbbing quality. is quite severe, and is typically associated with nausea. vomiting. diarrhea, photophobia. and phonophobia. Usually, the pain is so severe as to be incapacitating, and the patient must lie down in a dark, quiet room. The headache recurs frequently, although the time between attacks varies Widely. Rarely, bilateral examples occur.

It is important for the dentist to remember that referred migraine pain may initially mimic a toothache, especially of the anterior maxilla. Symptoms may also mimic sinusitis or allergic rhinitis.

Many migraineurs experience an "aura" before the actual headache pain. The aura may appear as visual hallucination. "seeing sparks" (scintillation), temporary

Table 18-1 *Common Triggers for Migraine Headache*

TYPE OF TRIGGER	SUBTYPES
Hormonal	Menstruation
	Ovulation
	Oral contraceptives
	Hormonal replacement therapy
Dietary	Alcohol
	Nitrite-laden meat
	Monosodium glutamate
	Aspartame
	Chocolate
	Aged cheese
	Missing a meal
Psychologic	Stress/poststress
	Anxiety/worry
	Depression
Physical!environmental	Glare
	Flashing lights
	Fluorescent lights
	Odors
	Weather changes
	High altitude
Sleep-related	Lackof sleep
	Excessive sleep
Drugs	Nitroglycerine
	Histamine
	Reserpine
	Hydralazine
	Ranitidine
	Estrogen
Miscellaneous	Head trauma
	Physical exertion
	Fatigue

From Campbell IK. Sakai F: Diagnosis and dlfferenttal diagnosis. In Olesen J. Tfelt-Hansen P. Welch KMA: *The headaches*. ed 2. Philadelphia. 2000. lippincott-Williams & Wilkins.

and partial blindness. partial or complete loss of light perception (scotoma). nausea, vertigo. lethargy, mental confusion. loss of the ability to express thoughts (aphasia), or unilateral facial paresthesia or weakness.

Treatment and Prognosis

The treatment of migraine includes a wide variety *at* medications and the two basic forms, with and without aura. respond in a similar fashion. Severe attacks frequently are diminished by ergotamine tartrate. perhaps combined with caffeine, aspirin. acetaminophen. phenobarbital. or belladonna. Less severe attacks arc treated prophylactically by other ergot compounds (e.g.. methcrgtnc), beta-adrenergic agents (e.g.. propranolol or

metoprolol), calcium channel blockers (e.g., nifedipine or diltiazem). or serotonin receptor agonists (e.g.. methysergide or cyproheptadine). Some patients are aided by simple pressure on the ipsilateral carotid artery. The headaches tend to become less severe and less frequent over time, with or without effective therapy.

TEMPORAL ARTERITIS (GIANT CELL ARTERITIS; CRANIAL ARTERITIS)

Temporal arteritis is a multifocal vasculitis of cranial arteries, especially the superficial temporal artery. Its cause **remains unknown, but autoimmunity to the elastic lamina** of the artery has been proposed. The disease most often affects head and neck vessels but it is considered to be a systemic problem. There may be a genetic predisposition.

The annual incidence rate of temporal arteritis in the United States is approximately 6 per 100,000 population. **Incidence rises with age and has been increasing over** time, perhaps because the population is *aging*. There is a strong predilection for whites.

Clinical Features

Women are affected by temporal arteritis somewhat more often than men, and patients are usually older than 50 years of age at the time of diagnosis (average age, 70 years). The disease is most frequently a unilateral, throbbing headache that is gradually replaced by an intense, aching, burning temporal and facial pain. The throbbing frequently coincides with the patient's heartbeat (systole), and the pain may be lancinating. The superficial temporal artery is exquisitely sensitive to palpation and eventually appears erythematous, swollen, tortuous, or rarely ulcerated.

Most patients complain of pain during mastication or the wearing of hats (pressure over the artery). The pain occasionally mimics toothache or a neuralgic jaw or tongue pain. Significantly, ocular symptoms, such as loss of vision or retro-orbital pain, may be the first complaint. **The visual loss may be transient or permanent. unilateral** or bilateral.

Fever, malaise, fatigue, nausea, anorexia, vomiting, sore throat, and earache often occur, perhaps as prodromal symptoms, and the erythrocyte sedimentation rate is usually elevated. A generalized muscle aching and stiffness (polymyalgia rheumatica) frequently follow an **acute attack.**

Histopathologic Features

The diagnosis of temporal arteritis is confirmed by biopsy. 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 intima and tunica media of the involved artery, with narrowing of the lumen from edema and proliferation of the intima. Necrosis of the smooth muscle and elastic lamina is frequent. A variable number of foreign body-type multinucleated giant cells are mixed with macrophages, plasma cells, and lymphocytes. Thrombosis or complete occlusion of the lumen is not unusual.

Treatment and Prognosis

Temporal arteritis responds well to systemic and local corticosteroids: the symptoms subside within a few days. However, many cases are chronic and need treatment for years. In addition, permanent loss of vision occurs in more than 50% of untreated patients, and even in the occasional **patient refractory to treatment. With some individuals, *vas*-**cular involvement is so widespread throughout the body that the disease is fatal, even with corticosteroid therapy.

MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disease that affects the acetylcholine receptors (AChR) of muscle fibers and results in an abnormal and progressive fatigability of **skeletal muscle. Defective neuromuscular transmission** occurs, probably secondary to the coating of the AchRs by **circulating antibodies to those receptors. Such antibodies** are not normally found in humans; hence, the measurement of serum AChR antibody levels is an important diagnostic tool for this disease. The motor end plate itself is **normal. and smooth and cardiac muscles are not affected.**

Many patients demonstrate either thymus hyperplasia or an actual neoplasm (thymoma) of the thymus gland. Conversely, 75% of patients with thymoma have myasthenia gravis, and 90% have circulating AChR antibodies. The infant of an affected mother may be affected for several weeks or months by maternal antibodies that traverse the placenta. Almost half of the patients with myasthenia gravis have at least one additional autoimmune disorder, especially of the thyroid gland. Each year 1 person in every 100,000 is diagnosed with myasthenia gravis.

Clinical Features

Myasthenia gravis is more common in females (1:2 male-to-female ratio). it can begin at any age and congenital cases have been reported. The disease appears as a subtle but progressive muscle weakness that is most frequently noticed first in the small muscles of the head and neck (Box 18-7).

Repeated muscle contractions, in particular, lead to progressively less power in the contracting muscle; hence, affected patients usually become weaker as the day progresses. The muscles of mastication may become so weak from eating a single meal that the jaws literally "hang open." Bite force is especially weak when circulating AChR antibody titers are high. Lateral tongue forces exerted during swallowing, speech, and mastication, are reduced significantly in a number of patients.

Box 18-7 *Head and Necli Mal/ifestatiol/s of Myasthenia Gravis*

- **An inability to focus the eyes (extraocular muscular paresis)**
- Drooping eyelids (ptosis)
- **Double vision (diplopia)**
- **Difficulty in chewing**
- **Difficulty in swallowing (dysphagia)**
- **Slurring of words (dysarthria)**

Diagnosis

The diagnosis of myasthenia gravis is based on the clinical symptoms, an elevated serum AChR antibody level, **and improved strength after intravenous injection of** edrophonium. a cholinesterase inhibitor. Degenerated muscle fibers are the only characteristic histopathologic feature. with fibers appearing much smaller than normal (hypotrophy. atrophy), having fewer nuclei. and showing a loss of the normal rounded cross-sectional appearance.

Treatment and Prognosis

The prognosis for myasthenia gravis is usually good. **Spontaneous remission sometimes occurs, and approx**imately 10% of patients never have more than weak eye muscles. unfortunately. more severe cases often progress, after months or years, to permanent muscular weakness and wasting of the neck. limbs. and trunk. Respiratory paralysis is sometimes a fatal complication.

The defective neuromuscular transmission can be reversed partially by cholinesterase inhibitors (e.g., edrophonlurn, neostigmine). often in combination with intermittent corticosteroid therapy. For patients with evidence of thymoma or with elevated AChR antibody titers, thymectomy is recommended. Complete. permanent recovery often results from thymectomy, and to a lesser extent, from medical therapy.

MOTOR NEURON DISEASE (PROGRESSIVE MUSCULAR ATROPHY; PROGRESSIVE BULBAR PALSY; AMYOTROPHIC LATERAL SCLEROSIS)

First described by Charcot in the 1870s. motor neuron disease is a fatal neurodegenerative disorder that is characterized by progressive weakness and wasting of muscles. The basic defect is progressive degeneration and death of the motor neurons of the cranial nerves, the anterior horn of the spinal cord. and the pyramidal tract.

The three distinct clinical syndromes with considerable overlapping of signs and symptoms are:

1. Progressive muscular atrophy,
2. Progressive bulbar palsy. and
3. Amyotrophic lateral sclerosis (ALS).

Confusion exists over the appropriate terminology. because some authors have used ALS to include all three disease syndromes. Including all subtypes, new cases of **motor neuron disease are diagnosed in 15 of *every*** 100,000 persons each year.

Many cases appear to be genetic defects associated with mRNA processing. Progressive muscular atrophy is. **for example, the most common autosomal recessive dis**order (mutated SMN gene on chromosome sq) lethal to **infants: it now can be identified with a prenatal test for** the involved gene. Likewise. up to 10% of cases of ALS **are inherited as an autosomal dominant trait (mutated** superoxide dismutase-i gene on chromosome 21). Pro**posed causes for the nonhereditary cases include toxic accumulation of the neurotransmitter glutamate. trauma.** and slow viruses. especially the poliovirus.

Clinical Features

Progressive muscular atrophy occurs in childhood. Most cases occur at birth or within the first few months of life. although adult onset is rarely seen. Males and females are affected equally. There is progressive limb weakness and sensory disturbances, which result in difficulty in walking. leg pain, paresthesia, and atrophy of the feet and hands. Facial muscles are spared.

Progressive bulbar palsy typically affects children and young adults and has no gender predilection. It usually begins with a subtle but progressive difficulty in speaking or swallowing (dysphagia). Attempts to swallow food produce bouts of choking and regurgitation. with liquids frequently thrown into the nasopharynx and nasal sinuses because of palatal paralysis. Chronic hoarseness may develop. Atrophy of the facial muscles, tongue, and soft palate eventually occurs, as do weakness and spasticity of the limbs. There are no altered sensory perceptions.

ALS (commonly called *Lou Gehrig disease.* named after the professional baseball player who died of the disease). affects males more frequently than females and begins to manifest itself in middle age (average age of onset: 59 years). The disease begins with difficulty in walking because of bilateral, generalized leg stiffness. Occasionally, one leg is affected more than the other. forcing the patient to drag it behind the other. Swallowing difficulty develops early in 29% of cases.

The physical examination in ALS reveals spastic quadriparesis. often with a remarkable increase in the tendon reflexes of all four limbs and with extensor plantar responses. Small. synchronous, subcutaneous muscle contractions (fasciculation) of the shoulders and thighs are an early symptom. with muscle atrophy eventually developing at affected sites. Central reflexes. such as those of the abdomen, are not altered until late in the disease. and there are no changes in sense perception. Dysfunction of the muscles controlled by the medulla

oblongata (bulbar paralysis) appears late in the disease, predominantly as spasticity and weakness. Patients become completely disabled. often requiring respiratory support and gastrostomy.

Treatment and Prognosis

Although each of these conditions may have temporary remissions, the course of motor neuron disease is invariably fatal. Progressive muscular atrophy and progressive bulbar palsy almost always result in death within 2 years, usually from respiratory distress caused by weak intercostal muscles.

AIS usually results in death within 5 years of diagnosis. most often from respiratory failure or cachexia, although 20% of patients survive more than 10 years without ventilator use. The antiglutamate agent, rlluzole. has shown some promise in slowing the progression of AIS and improving the morbidity in patients with disease of bulbar onset. but in general there is no cure at this time. Palliative and rehabilitative strategies are used to ease sufferi ng.

BURNING MOUTH SYNDROME (STOMATOPYROSIS; STOMATODYNIA; GLOSSOPYROSIS; GLOSSODYNIA; BURNING TONGUE SYNDROME)

Burning mouth syndrome is a common dysesthesia (distortion of a sense) typically described by the patient as a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations. Although the tongue is most commonly affected (glossopyrosts). other mucosal surfaces may be symptomatic (stomatopyrosis). In addition to the burning sensation. some patients also experience mucosal pain (stomatodynia, glossodynial. Idiopathic burning and painful sensations (the "dynias") also can affect the urogenitai (vulvodynia) and intestinal mucosa. The scalded mouth syndrome is an apparently unrelated immune response to certain medications. especially angiotensin-converting enzyme (ACE) inhibitors.

Various local and systemic factors have been postulated to cause this condition (Box 18-8), but none have been proven. The fact that most patients are postmenopausal women has led to the common belief that estrogen or progesterone deficit is responsible, but a strong correlation between such deficits and burning tongue syndrome has not been established. Some evidence exists for an autoimmune origin. Abnormal levels of antinuclear antibody (ANA) and rheumatoid factor (RF). for example. are found in the serum of more than 50% of patients, although these may also be found in older persons without burning mouth syndrome. The disorder has been reported to be strongly associated with depression and anxiety states. leading some authorities to consider it a psychosomatic disease. Well-controlled comparison studies. however, are lacking.

Box 18-8 *Local and Systemic Factors Reportedly Associated with Burning Tongue Syndrome (Glossopyrosts)*

LOCAL FACTORS	SYSTEMIC FACTORS
Xerostomia	Vitamin B deficiency
Chronic mouth breathing	Vitamin B_1 or B_2 deficiency
Chronic tongue thrust habit	Perniciou s anemia (6_{12})
Chronic mechanical trauma	Pellagra (niacin deficiency)
Referred pain from teeth or tonsils	Folic acid deficiency
Trigeminal neuralgia	Diabetes mellitus
Atypical facial pain or neuralgia	Chronic gastritis or regurgitation
Angioedema (angioneurotic edema)	Chronic gastric hypoacidity
Oral candidiasis	Hypothyroidism
Temporomandibular dysfunction	Mercurialism
Oral submucous fibrosis	Estrogen deficiency
Fusospirochetal infection	Anxiety, stress, depression
Contact stomatitis (allergy)	Parkinson's disease
Trauma to lingual nerve	Acquired immunodeficiency syndrome (AIDS)

Burning tongue syndrome affects 2% to 3% of adults to some degree (14% of post-menopausal 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 problems encountered in the clinical practice of oral and maxillofacial pathology.

Clinical Features

Women are 4 to 7 times more likely to have 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.

This disorder also has a typically spontaneous onset. although it may be quite gradual. Thedorsum ofthetongue develops a burning sensation, usually strongest in the anterior third. Occasionally, patients will describe an irritated or raw feeling. Mucosal changes are seldom visible. although some patients will show diminished numbers and size of filiform papillae, and individuals who rub their 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.

Close questioning often determines that additionai 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 liquids often intensifies the symptoms. A minority describe a constant degree of discomfort.

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 Prognosls

If an underlying systemic or local cause can be identified and corrected. the lingual symptoms should disappear. Almost two thirds of patients with idiopathic disease show at least some improvement of their symptoms when they take one of the moodaltering drugs (e.g.. chlordiazepoxide). Additional therapies that have been used include clonazepam, alpha-lipoic acid (thloctlc acid. a neuroprotective drug). amitriptyline. transcutaneous electrical nerve stimulation. analgesics. antibiotics. antifungals. vitamin B complex. and psychologic counseling. However. none of these treatments has been proven to be effective in a double-blind. placebo-controlled trial.

The long-term prognosis for idiopathic burning tongue or mouth syndrome is variable. Some patients experience a spontaneous or gradual remission months or years after the onset of symptoms. However. other patients may 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 it is benign and not a symptom of oral cancer.

DYSGEUSIA AND HYPOGEUSIA (PHANTOM TASTE; DISTORTED TASTE)

Dysgeusia is defined as a persistent abnormal taste. It is much less common than simple deficiencies in smell thvposmta, anosmia) and taste (hvpogeusia, ageusia) perception. which are found in approximately 2 million adult Americans. Dysgeusia is less tolerated than hypogeusia or hyposrnia, explaining why it accounts for more than a third of patients in chemosensory centers.

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 18-9). Trauma. tumors. or inflammation of the peripheral nerves of the gustatory system usually produce transient hypogeusia rather than dysgeusia. In contrast. relatively

Box 18-9 *Local and Systemic Factors Associated With Altered Taste Sensations (Dysgcusia) or Diminished Taste Sensations (Iiypogeusia)*

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
- line deficiency
- Iron deficiency
- Nutritional overdose (zinc, vitamin A, pyridoxine)
- Food sensitivity or allergy
- Sjogren syndrome
- Chorda tympani nerve damage
- Anorexia, cachexia, bulimia
- Severe vomiting during pregnancy
- liver dysfunction
- Crohn's disease
- Cystic fibrosis
- Familial dysautonomia
- Addison's 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 infection
- Chronic gastritis or regurgitation
- Bell's palsy
- Radiation therapy to head and neck

common upper respiratory infections produce a temporary and mild dysgeusia In almost one third of cases, although they seldom produce hypogeusia. eNS neoplasms predominantly produce dysgeusia, not hypogeusia or ageusia, and taste hallucinations are fairly common during migraine headaches, Bell's palsy, or herpes zoster of the geniculate ganglion. Ischemia and infarction of the brainstem can lead to ageusia of oniy 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 18-2). Even without medication-induced alterations, 40% of persons with clinical depression complain of dysgeusia. 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. The latter may produce a salty taste because of the high sodium chloride content of oozing crevicular fluids.

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, 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 (e.g., sweet, sour, salty, 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 llquids. in which case the taste is said to be distorted. lf no stimulus is required, the dysgeusia is classified as a "phantom" taste.

Treatment and Prognosis

[f 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 or surgical therapy. Dysgeusia in particular tends significantly to affect lifestyles and interpersonal relationships, 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). ldlopathlc hypogeusia is less of a problem for the patient, but tends to slowly become worse over time. Occasionally, even this will undergo spontaneous resolution.

Table 18-2 *Exam/lies of Pharmaceutical Agents that May Be Associated With Altered Taste*

PHARMACEUTICAL ACTION	EXAMPLES
Anticoagulant	Phenindione
Antihistamine	Chlorpheniramine maleate
Antihypertensive or diuretic	Captopril, diazoxide, ethacrynic acid
Antimicrobial	Amphotericin B, ampicillin, griseofulvin, idoxuridine, lincomycin, metronidazole, streptomycin, tetracycline, tyrothricin
Antineoplastic or immunosuppressant	Doxorubicin, methotrexate, vincristine, azathioprine, carmustine
Antlparklnsonian agent	Badofen, chlormezanone, levodopa
Antipsychotic or anticonvulsant	Carbamazepine, lithium, phenytoin
Antirheumatic	Allopurinol, colchicine, gold, levamisole, penicillamine, phenylbutazone
Antiseptic	Hexetidine and chlorhexidine
Antithyroid agent	Carbimazole, methimazole, thiouracil
Hypoglycemic	Glipizide, phenformin
Opiate	Codeine, morphine
Sympathomimetic	Amphetamines, phenmetrazine
Vasodilator	Oxyfedrine, bamifylline

FREY SYNDROME (AURICULOTEMPORAL SYNDROME; GUSTATORY SWEATING AND FLUSHING)

First described by Baillarger in 1853, the Frey syndrome is characterized by facial flushing and sweating along the distribution of the auriculotemporal nerve. These signs occur in response to gustatory stlmuli. and the syndrome results from injury to the nerve.

This 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.

More than 40% of patients with parotidectomies develop Frey syndrome as a complication of surgery. The **condition is rare in infancy but has been seen after forceps delivery. Neonatal cases do not typically occur until the child begins to eat solid foods, at which time it is usually interpreted as an allergy. Additionally, more than one third of diabetics with neuropathy will experience gustatory sweating, especially those who also have severe kidney damage. The nerve damage in this case is presumably from chronic ischemia and immune attacks.**

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 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 (hypoesthesla) or hyperesthesia are common **features.**

To detect sweating, Minor's 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 (Figure 18-6). 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

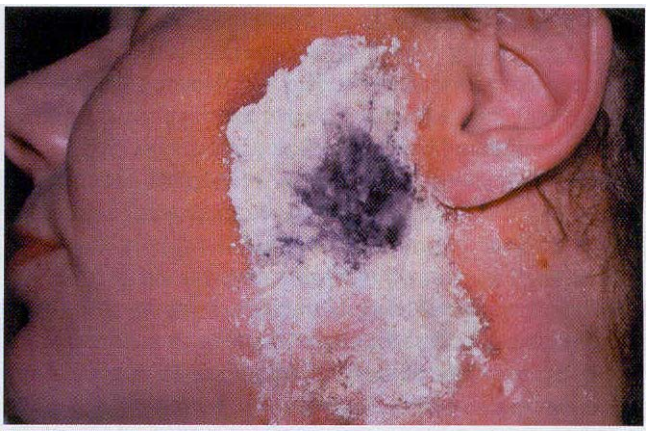

Figure 18-6 • Frey syndrome. This patient received an injury to her auriculotemporal nerve during orthognathic surgery 3 years earlier. Notice the region of sweating detected during mastication by a **color change of the starch in the Minor's starch-iodine test.**

and almost all affected infants experience spontaneous resolution of the syndrome. About 5% of Frey syndrome patients with diabetically damaged kidneys will show considerable improvement or complete resolution of the facial problem after renal transplant.

Severing the auriculotemporal or glossopharyngeal nerve on the affected side inhibits or abolishes the sweating and flushing reaction of auriculotemporal syn**drome, as may atropine injections, botulinum toxin injections, scopolamine creams, and the systemic use of oxy**butynin chloride, an antimuscarinic agent. The risk of this syndrome is greatly diminished by positioning a temporoparietal fascia flap between the gland and the overlying skin of the cheek at the time of parotidectomy.

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. It is now known to have a** strong inflammatory component as well, especially in small joints, such as the temporomandibular joint (TMj), where there appears to be little association with the aging process. The disease represents approximately 10% of patients evaluated for TMj pain.

Osteoarthritis is thought by some to be unavoidable; almost everyone older than 50 years of age is affected to some extent. The TMj is less affected than the heavy weight-bearing joints, but even that joint is involved at the microscopic level in 40% of older adults and at the radiographic level in 14%. Although osteoarthritis is definitely an aging phenomenon, recent research also has identified osteoarthritis in a majority of young persons referred to a TMJ clinic for joint pain and dysfunction.

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 (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 TMI is affected, except that patients seldom experience stiffness of the TMI. 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).

On radiography. joints affected by osteoarthritis demonstrate a narrowing or obliteration of the joint space, surface irregularities and protuberances (exostoses. ostcophyres). 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 tomographic (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 visible.

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 TM] is unique because of its fibrocartilage covering and its meniscus. The disk may be centrally destroyed. and there is little vertical c1efting 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. Arthroplasty and joint replacement often are required for heavy weight-bearing joints and are used occasionally In the TMI. Occlusal adjustment and occlusal splints may reduce 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) recently 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 recent 30-yearfollow-up investigation found radiographic evidence of continued joint destruction. but the clinical signs and symptoms were no more severe than they had been initially.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic. presumably autoimmune disorder characterized by nonsuppurative inflammatory destruction of the joints. It may result from a cross-reaction of antibodies generated against hemolytic streptococci or other microorganisms, or it may represent an antibody attack against bacterial cell walls or viral capsule fragments deposited within the synovium. The cause is still unknown, although some examples show a familial pattern.

This disease affects 3% of people in the United States to at least some degree, and approximately 200,000 new cases are diagnosed yearly. The TMI eventually becomes

involved in 75% of patients, although the involvement is usually so mild as to be clinically insignificant.

In contrast to osteoarthritis (see *previous* topic). rheumatoid arthritis begins as an attack against 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

Rheumatoid arthritis affects women three times more frequently than men, although the condition in men is usually 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 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 hip joint, the joint most often affected by osteoarthritis, is the joint least affected by rheumatoid arthritis. Twenty percent of patients have firm. partially movable. nontender rheumatoid nodules beneath the skin near the affected joint. These are pathognomonic for the disease.

Ioints involved with rheumatoid arthritis 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 TMI is affected to some degree in more than 40% of persons with rheumatoid arthritis. When present, TMI involvement is usually bilateral and occurs late in 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 TMI rheumatoid arthritis 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 TMIs than in other joints, but gross destruction of the condylar heads may be so severe that mandibular micrognathia causes a receding chin and malocclusion. Permanent TMI subluxation has been reported.

Radiographically, involved TMIs 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 TMI radiographs. CT scans, scanning arthrography, and arthroscopy are excellent tools for assessing TMJdamage. Thermography is used commonly in Europe to detect early disease. Ultrasonography is valuable for larger joints but has been used little in TMI disease. Nuclear medicine scans that use scintigraphy have, in recent years. been largely replaced by MRI scans. The latter are sensitive and have become the diagnostic tool of choice.

Laboratory Values

Approximately 80% of patients with rheumatoid arthritis 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 antibody (ANA) can be detected in about 50% of the patients with rheumatoid arthritis, 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. In addition, some affected patients** have mild anemia.

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 TMJinvolvement.

Microscopically, early cases of rheumatoid arthritis demonstrate hyperplasia of the synovial lining cells with deeper portions of the membrane showing hyperemia, edema, and infiltration by lymphocytes. macrophages, and occasional neutrophils. Neutrophils are the predominant inflammatory cell in the synovial fluid. 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 finger-like projections. These projections occasionally undergo necrosis, producing rice bodies, small whitish villi fragments composed of cellular debris admixed with fibrin and collagen. When the TMJis 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. Neutrophils are frequently seen in the center.

Treatment and Prognosis

No cure exists for rheumatoid arthritis, and current treatments strive only to suppress the process as much as possible. Drug therapy in early and mild cases consists of nonsteroidal antiinflammatory drugs (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 corticosteroids. gold injections, penicillamine. cyclophosphamide. and methotrexate are the commonly used second-line medications; all are associated with significant side effects. Severely damaged joints may have to be replaced surgically.

TEMPOROMANDIBULAR JOINT DYSFUNCTION

Pain and dysfunctiop of the TM) are common and have been proposed to result from a wide variety of etiologic factors, both traumatic and nontraumatic (Box 18-10). The syndrome of signs and symptoms (pain, altered function. joint noises) is termed temporomandibular joint dysfunction (TMD). TMD is a problem of the entire masticatory system; teeth. jaws. joints. and muscles. All facets must be evaluated to arrive at the most specific diagnosis and management protocol. Because of the extreme complexity of this disease, the present discussion is limited to a brief overview of those facets of the disorder that are appropriate to the production of pain.

Almost 15% of U.S. adults experience facial and cervical pain, facial tenderness, and headache from TMD, but less than I% of those have symptoms severe enough to warrant professional evaluation or intervention.

Clinical and Radiographic Features

TMD is seen primarily in middle-aged women, but it may affect any age and either sex. Most patients have some degree of pain, which Is the primary reason for seeking professional help. The pain is usually localized to the preauricular area but may radiate to the temporal. frontal, or occipital areas. The pain may be a headache, a ringing in the ears (tinnitus). an earache (otalgia). or a toothache.

Box 18-10 *Classification of Temporomandibular Disorders*

MUSCULAR DISORDERS
- Hyperactivity, spasm, and trismus
- Inflammation (myositis)
- Trauma
- Myofascial pain and fibromyalgia
- Atrophy o' 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, aplasia
- Neoplasia

Nonarthritic inflammatory disorders of the TM) 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 TM]s may be involved. at the same time or at differing times.

The pain may be associated more with the surrounding musculature and soft tissue than with the TMI 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 seldom Is noted in other TMI disorders. It is characterized by circumscribed regions within the muscle ("trigger points"). which 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 eNS excitatory effects.

Derangements of the condyle and meniscus complex are more often associated with dysfunction than with joint pain (arthralgia). When present, the pain associated with a deranged joint may be localized. nonspecific. or referred. It is not a reliable finding for diagnostic purposes. For TMD associated with internal joint damage or

Box 18-11 *Medications Used to Treat the Symptoms of Temporomandibular Joint Dysfunction*

- Aspirin
- Acetaminophen (with or without codeine)
- Other nonsteroidal anti-inflammatory agents
- Centrally acting muscle relaxants (methocarbamol, chlorzoxazone)
- Benzodiazepine derivatives (diazepam, chlordiazepoxide)
- Glucocorticoids (cortisone, prednisone)

derangement. CT and MRI provide excellent diagnostic images of the TMJ. Transcranial and cephalometric radiographic images are much less detailed, but are usually adequate and are used more commonly. The bone itself frequently appears normal, but a widened joint space, anteriorly displaced meniscus, or altered meniscus shape are common findings. Irregular joint surfaces with protuberances (osteophytes) are more likely to relate to arthritis than TMD (see previous two topics). Joint effusions seen with MRI are useful markers of arthritic degeneration.

Treatment and Prognosis

Therapies for TMD are numerous and should be recommended based on the exact pathogenesis of the pain. 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 18-11), 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 75% to 88% experience significant or complete reduction of symptoms.

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. For joints with pain from anterior disk displacement (with or without reduction), *however,* diskectomy is recommended within 6 months of TMD diagnosis; for those with ankylosis, surgery should occur *even* sooner. The indications for surgery are strict. Of all patients sent to a specialist for TMD surgery, less than 1% actually has the surgery.

TEMPOROMANDIBULAR JOINT ANKYLOSIS

Ankylosis refers literally to a "fusion" of body parts, in this case the opposing components of a joint. The fusion can be fibrous or bony in nature—usually fibrous when the TMJ is involved. Joint infection, usually after trauma, accounts for 50% of all TMJ ankylosis cases, but 30% result from aseptic trauma. The remaining cases are idiopathic or produced by rheumatoid arthritis.

The ankylosis may be intra-articular or extra-articular. Intra-articular ankylosis is characterized by the destruction of the meniscus and the temporal fossa, thickening and flattening of the condylar head, and a narrowing of the joint space. Opposing joint surfaces then develop fibrous adhesions that inhibit normal *movements* and may become ossified. Fibrotic intra-articular ankylosis is the most common type seen in the TMJ, especially after trauma-induced hemorrhage (hemarthrosis). Osseous ankylosis is more likely with nonhemorrhagic infections of the joint.

Extra-articular involvement is less frequently seen and produces an external fibrous or osseous encapsulation with minimal destruction of the joint itself.

Clinical Features

TMJ ankylosis occurs predominantly in the first decade of life, and males and females are equally affected. Almost all cases are unilateral. The condition results in a gradually worsening inability to open the jaws, with the mandible shifting toward the affected side on opening. Pain, tenderness, and malocclusion may be present, but this is not usually the case.

In severe examples, there is almost complete immobilization of the mandible and the mandible may protrude forward as the excess tissues occupy the joint space. In very young children, unilateral micrognathia (hemifacial microsomia) may result from diminished growth on the affected side. Malocclusion may be severe in such cases.

Histopathologic Features

TMJ ankylosis is characterized by an excessive amount of dense, rather avascular fibrous connective tissue or new bone formation. Intra-articular ankylosis demonstrates irregular destruction of cartilage and bone with a sparse lymphocytic infiltration.

Treatment and Prognosis

Surgical osteoplasty of the joint with *removal* of excessive fibrous or calcific tissues is the treatment of choice for TMJ ankylosis. For severe cases, complete joint replacement may be necessary.

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CHAPTER 19

Forensic Dentistry

EDWARD E. HERSCHAFT

CHAPTER OUTLINE

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 the 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 necessary to identify the patient and to reduce the potential for malpractice litigation.
- **Identification of human remains, through the comparison** of antemortem and postmortem dental **information, in cases that involve individual** deaths, or multiple deaths In mass disasters.

- Collection and analysis of patterned marks (bite marks) in inanimate material or injured tissue which can be compared, and potentially matched, with a specific human or animal dentition.
- Recognition of the signs and symptoms of human abuse (including domestic or spousal abuse, elderly abuse, and child abuse) and the dental health care worker's rights and responsibilities 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 and containing all subjective and objective information about the patient. Initially, this information is secured when the patient's medical and dental history 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 data base, 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., a daily log of the actual treatment rendered) should contain information about the restorative and therapeutic procedures provided. Unusual physiologic and psychologic 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.

It is becoming more common for dental records to be maintained electronically, and numerous commercial and individually designed programs have been marketed to assist the dentist in collecting and preserving the patient's dental information. The obvious advantage of computer-generated dental records is that they can be easily networked and transferred for routine professional consultation or forensic cases requiring dental records for identification.

However, the use of electronically managed dental records has also created an ethical issue concerning the maintenance of patient privacy. Additionally, there is a potential for insurance fraud associated with the computer enhancement of dental lesions or restorations on electronically generated dental radiographs.

Whether preserved in written form or on a computer data base, the principles of record management describe a mechanism ensuring 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.

IDENTIFICATION

Legal situations often revolve around the establishment of a person's proper identity. The official who is responsible for establishing identification, determining the mode and manner of death, and issuing a death certificate is the coroner or medical examiner. The coroner is an elected official and, depending on the laws of each state, may not necessarily be a physician or have advanced training in death investigation. A medical examiner is an appointed official who is a pathologist specifically trained in forensic medicine.

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 medical examiner and assist in this aspect of a death investigation.

Besides analysis of the teeth, the most common methods of identification include personal recognition, fingerprinting, physical anthropologic examination of bones, and serologic and genetic (DNA) comparison techniques. Each method has its advantages and disadvantages. However, all rely on the principle that identi-

fication 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 data bases, and no major differences are observed.
2. *Presumptive (possible) identification.* There are commonalities among the comparable items in the antemortem and postmortem data bases; 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 data bases. 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, which can occur in mass-disaster situations or when there is criminal intent to create a misidentification.

Even when a body is viewed shortly after death, distraught relatives can inadvertently misidentify the remains. After the occurrence of postmortem changes associated with soft tissue decomposition, insect damage, burn artifact, or dismemberment, this method of identification may be precluded.

FINGERPRINTING

By the beginning of the twentieth century, forensic science had recognized that the ridgelike 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 pattern. A principal variation in the fingerprints of twins is that they appear as mirror images of each other. The variation in combinations of loops, arches, and whorls permits a scientific comparison of fingerprint records with the prints 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 the clinician 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.

Unlike dental records, which are principally retained in private dental offices in North America, fingerprint information is maintained by governmental agencies. The Identification Division of the Federal Bureau of Investigation (FBI) contains approximately 200 million fingerprint records. The recent development of computerized automated fingerprint identification systems (AFISs) even permits input, matching, and retrieval of a single fingerprint image for identification.

Fingerprint nomenclature is standardized, and the same terminology is used by all fingerprint experts worldwide. This advantage is not observed in dental identification, in which numerous charting and tooth numbering systems are employed. Because soft tissues decompose after death, the fingerprint may not be retrievable. This is the principal disadvantage of fingerprint identification.

PHYSICAL ANTHROPOlOGIC EXAMINATION OF BONES

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. This anatomic material can be used to determine the race, age, and sex of a person (Table 19-1).

In addition, the teeth can be studied clinically and radiographically to determine the age of the decedent based on eruption patterns and calcification times. This information, combined with analysis of the calcification centers of the hand and wrist, can be used to determine the precise age of a person who is younger than 20 years of age.

Laboratory procedures used to determine the age of teeth include the study of ground sections of teeth for variations in the following patterns:

- Attrition
- Periodontal attachment
- Secondary dentin
- Cementum apposition
- Root resorption
- Transparency

Table 19-1 *Skeletal Anthropologic variations Associated With Racial and Sexual Characteristics of the Sk,,11*

	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	
		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

This technique, developed by Gustafson in 1947. has recently been supplemented by methods that rely on an analysis of the rate of racemization of aspartic acid in enamel and dentin to determine an exact age. Occlusal tooth wear also may be used to provide reliable estimates of age to within 3 to S years, Often, anthropologic analysis is helpful In arriving at a presumptive identification based on these criteria.

Positive identification is achievable when the skull and facial bones are used as a foundation to reconstruct the facial soft tissues (Figures 19-1 to 19-3). Three-dimensional computer images. computed tomography (CT) images. and radiographs have been used in the replication of the face of a SCOO-year-old person whose remains were removed from glacial ice on the Austrian and Italian border.

With a knowledge of the anatomic relationships between the skull and face. antemortem facial photographs or radiographs can be superimposed and matched with the skull. Video superimposition with two television cameras and an electronic mixing device has been used successfully in overlaying a photograph of a human face on an image of a skull for identification. When the anterior dentition of the skull can be overlayed and matched with a smiling antemortem photograph, the shapes and positions of the individual teeth and their relationships to each other have been considered distinctive enough on which to base an identification. Prosthetic joint replacements. intraosseous implants. and radiographic signs of prior bone fracture are additional anthropologic findings that can be used to facilitate identification.

SEROLOGIC AND GENETIC (DNA) COMPARISON

A comparison of antigenic markers found on red blood cells and in body fluids of people who secrete these markers has traditionally been a source of exculpatory (exclusionary) evidence. This type of evidence is used to exclude a suspect or victim when negative results are achieved. Positive comparisons can only place the suspect or victim in a population of individuals who have similar serologic antigens.

Antigenic substances A. B. and H of the ABO system; M, N. and 5 of the MN system; and various components of the rhesus (Rh) system and the Lewis system are accepted for medicolegal comparison. The ability to secrete the ABH antigens in saliva and other body fluids is genetically determined. More than 80% of people are secretors. With appropriate iaboratory tests. even dried samples of fluid and blood can be analyzed for these markers.

Although each person is a unique individual by virtue of his or her DNA. it was not until 1986 that this "ulti-

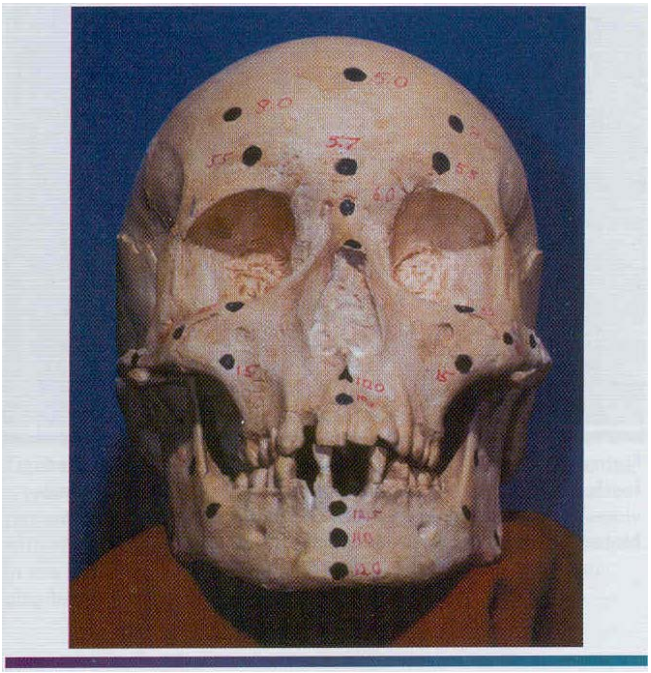

Figure 19-1 • Reconstruction of the facial soft tissue uses predetermined, standard anthropologic thickness measurements for specific points around the face. These measurements are based on variables that are related to racial and sexual characteristics. (Courtesy of Dr. Cleve Smith.)

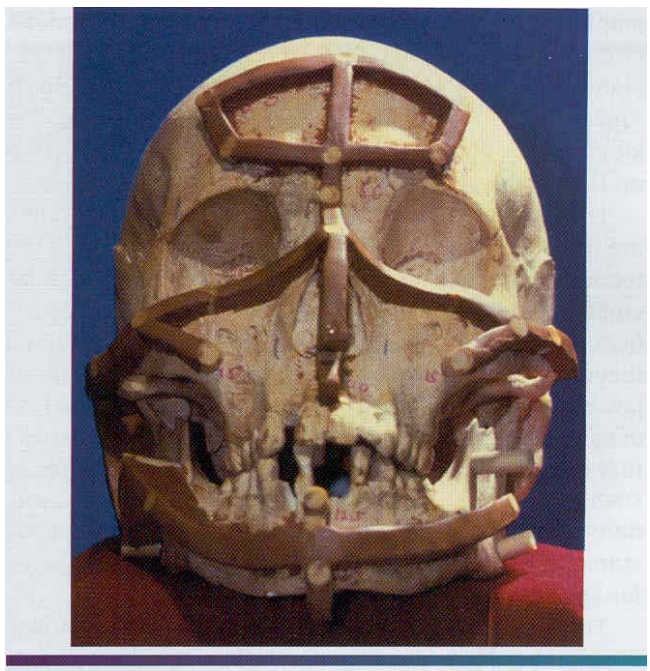

Figure 19-2 • The soft tissue thickness points can be connected with sculpting clay or digitized on a computer screen. The ultimate result of these techniques is a recreation of the contour of the soft tissue features that permits a visual identification. (Courtesy of Dr. Cleve Smith.)

mate identification material" was used in law enforcement to obtain a conviction. The principal laboratory techniques used to compare and evaluate fragments of DNA material from a suspect or victim are restriction fragment length polymorphism (RFLP) and polymerase chain reaction (PCR) analyses. They are both extremely accurate, precise, and reproducible and 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. Fragment size varies among individuals related to the variable number of tandem repeats (VNTR) of base pairs. A match of four or more VNTR loci is consistent with a positive match between DNA evidence gathered from suspect and victim. The RFLP method requires large amounts of high molecular weight DNA, a major disadvantage. When analysis of small samples or degraded evidence in which the DNA has become denatured because of extreme heat or pH variation is required, an analytic method other than RFLP may be indicated.

The evaluation of minute quantities of DNA or denatured DNA can be accomplished with PCR, which is a highly sensitive test. using this laboratory technique, a few copies of a specific DNA sequence can be amplified into enough copies for sufficient analysis. In 1997, a DNA

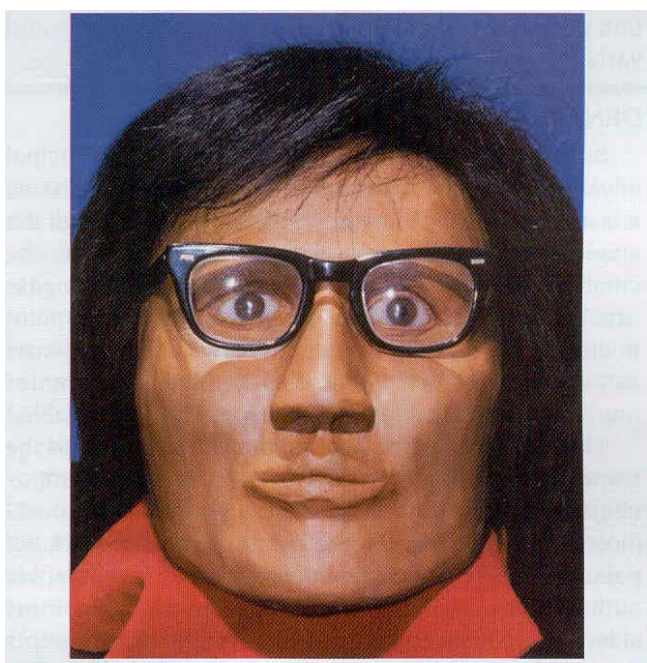

Figure 19-3 • The width of the mouth is related to the interpupillary distance. The length and shape of the nose are determined by the relationship between the inferior and superior nasal spines. If known, the addition of a specific hairstyle, eyeglasses, and eye color can further individualize a facial reconstruction. (Courtesy of Dr. Cleve Smith.)

amplification and typing kit known as the AmpliType PM PCR amplification and typing kit (PM kit) underwent validation studies among 26 forensic laboratories in North America. The results of this testing concluded that this kit meets the guidelines of the Technical Working Group on DNA Analysis Methods.

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 employed for the collection of DNA evidence, 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 can evaluate chewed gum. cigarette remains, licked envelopes. stamps. or similar inanimate objects as potential sources for DNA evidence.

The U.S. Department of Defense has initiated a policy of obtaining DNA samples on all military personnel. This DNA "fingerprint" would significantly reduce 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** principtes.* In identification cases, 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 data base for the antemortem and postmortem comparison (Figure 19-4). The pattern of the palatal ridge, ridges on the lip surface, and radiographic outline of the maxillary and frontal sinuses are also considered unique. In addition, the legal community accepts the fact that dentists can recognize procedures that they have performed.

Problems associated with dental identification information are often related to acquirlng 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).

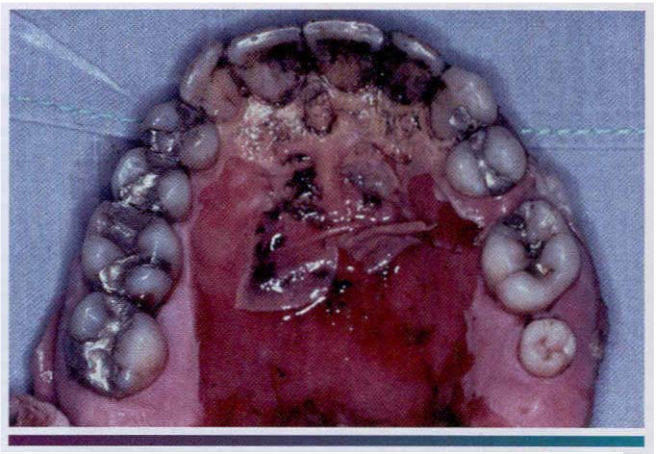

Figure 19-4 • The combination of decayed, missing. and filled teeth, along with unique anatomic *and* pathologic findings, Prvvides the data base for comparison in a dental identification. Note the microdont in the maxillary left quadrant.

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, and child abduction can now be identified without the need to determine a putative identification.

The Armed Forces. Department of Veterans Affairs, and many states require that identifying markings be placed on removable dental prostheses (Figure 19-5). This policy is also supported by the American Dental Association. 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

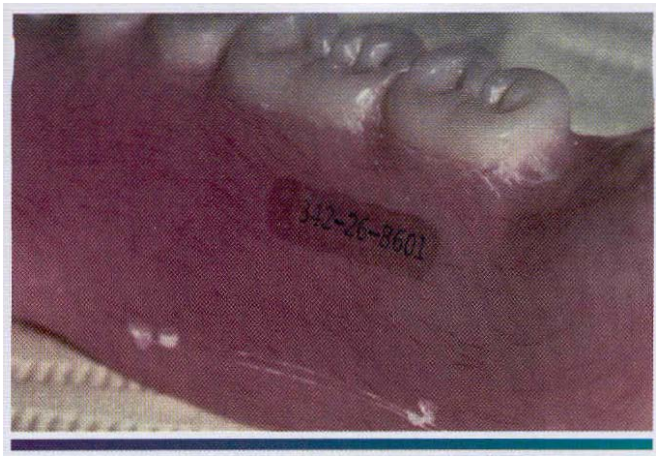

Figure 19·5 • Denture identification is accomplished by inserting a typed name or code number (Social Security number. hospital patient number) in an area of the denture that will not interfere with the aesthetics of the prosthesis. This procedure is performed in the laboratory during the final acrylic pack. Information can also be engraved in the framework of an all-metal appliance.

person can be obtained. they may not reflect the current status of the ridges and alveoiar bone. Commoniy used information for identifying marking in removable dental prostheses includes the person's name. driver's license number, or Social Security 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** that have not been retreated by the current dentist are often not charted. 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, 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.

Table 19-2 *Dental Numbering Systems*

PERMANENT TEETH

Maxillary Right ***MaxUlary 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 65 4 32 | 1 1 2 3 4 5 678
876 5 4 3 2 | 1 1 2 3 4 5 6 7 8

Federation Dentat-e 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 5 R Q P 0 N M l K

Alternate Universal Numbering System

4D	5D	6D	7D	80	9D	lOD	11 D	120	13D
290	280	270	260	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 Intemationale Two-Digit System

55	54	53	52	51	61	62	63	64	65
85	84	83	82	81	71	72	73	74	75

Other tooth numbering methods include the Zsigmondy/Palmer System and the Federation Dentaire Internationale (FDO Two-Digit System. Each uses a different coding technique to identify dental quadrants and specific teeth.

The Zsigrnondy/Palrner 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 I 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 and Canada. The first digit represents the quadrant. Quadrants I 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 cJock-

wise direction. beginning with the maxillary right. The second digit designates the permanent tooth type from I to 8. or deciduous tooth type from I 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. Panoramic radiographic duplicating film, however, does contain a series of notches on one side to indicate that the film is not an original.

With the advent of aesthetic materials for posterior restorations and the reduction in the incidence 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. medical examiner, 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.

Guidellnes [or del/tal identificatton. 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:

- 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 data bases, and
- Development of a written report listing conclusions and an opinion regarding the strength of the identification (e.g.. positive. presumptive. insufficient, or exculpatory).

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 single-lens reflex 35-mm camera and appropriate electronic flash and lens sys-

Box 19-1 ***Suggested*** *instrument Kit [or Forensic Idel/ti[icatiol/*

- **Dental explorers**
- **Dental mirrors**
- Bite blocks
- **Tissue scissors**
- **Osteotome**
- Rubber air/water **syringe**
- **Cotton swabs**
- **Photographic mirrors**
- **Writing instruments**
- **Periodontal probes**
- Scalpels and blades
- Cheek retractors
- ABFO no. 2 ruler
- Bone mallet
- Flashlight or head lamp
- Single lens reflex **camera**
- Case labels
- Rubber gloves
- Radiographic **film**
- TIssue forceps
- **Tissue clamp**
- Tongue clamp
- **Disclosing solution**
- Stryker saw
- **Gauze**
- Film
- Appropriate charts
- Masks

terns for close-up photography should be used. Routinely, both color and black-and-white film is recommended for use in each case.

Dental impressions and jaw resection may also be required after the initial full head photographs have been obtained. If requested by the coroner or medical examiner. the dental specimens from the autopsy may have to **be retained and preserved in a 10% formalin solution.**

The gutdclmcs 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 medical examiner. Therefore. it is only with the permission of these individuals that techniques involving post**mortem 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. **Resection or soft tissue dissection may be necessary in** visually recognizable bodies when the oral cavity is inaccessible because of rigor mortis.

When the jaws are removed with a reciprocating (Stryker) saw or osteotome and mallet, a Le Fort type I fracture of the maxilla is created. The dissection instru**ments are placed *above* the inferior nasal spine** and **malar processes to ensure that the apices of the maxil**lary teeth are not transected. Similarly, if the mandible **is not *removed* by disarticulation, cuts into the mandib**ular 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 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.

Rigor mortis in partially decomposed bodies and charting of dental evidence in fourth-degree burn and cremation cases may prevent the positioning of intraoral periapical films. Occlusal films, 5 X 7 lateral plates. and panoramic radiographs are often used in these sit**uations. With the coroner's or medical examiner's per**mission, the entire skull can be placed in a panoramic radiographic machine. This technique is usefui in cremation cases, when dental evidence may be lost or compromised by the manipulation associated with orai **dissection.**

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. IO-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. Films of the opposite side of the arch are made by simply flipping the mandible and repeating the exposure procedure.

The charting (odontogrami) of the postmortem dentition should provide for situations in which teeth are missing after death. If such a discrepancy remains unexplained, 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** (Figure 19-6). 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 police recovery efforts. When this phenomenon occurs

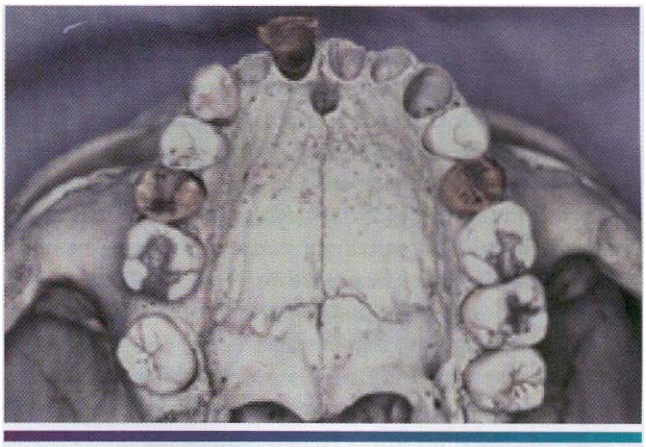

Figure 19-6 • Postmortem tooth loss results in an alveolar socket with unfractured margins and no reossification. **In this example, teeth nos. 7, 9, 10, and 11 represent postmortem tooth loss. Tooth no. 2 is a result of antemortem loss. Teeth nos. 4, 8, and 13 were found near the body and reinserted into their respective sockets.**

and is recognized, the charting abbreviation MPPA (Missing Postmortem, Present Antemortem) is used in that tooth's position in the dental odontogram.

Antemortem record examination. Antemortem records are usually obtained directly from the police, coroner, or medical examiner. 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, many 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 rechart all information obtained from the radiographs, progress notes, and odontograms on a standardized form. This form 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 computers in mass-disaster 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.

Furthermore, the forensic dentist must routinely rely on the belief that premortem 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 effect the misidentification of Hitler and his bride.

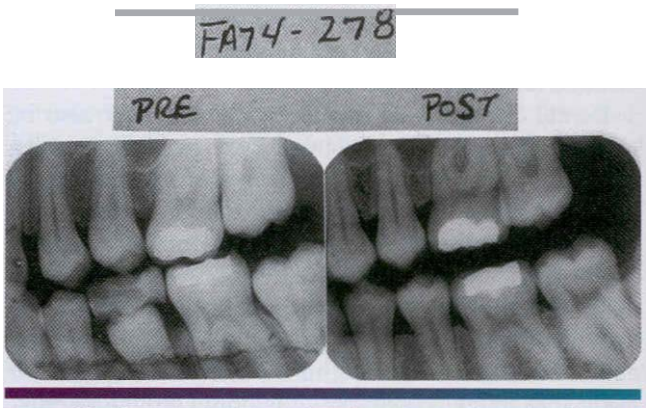

figure 19-7 • Antemortem and postmortem radiographs demonstrating the fluid, changing nature of dental information.

The case demonstrated in Figure 19-7 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.

Dental restorations can be separated from the teeth or melted in a fire. Acrylic melts below 540° C (1000° F), gold and amalgam melt by 870° C (1600° F), and porcelain can withstand temperatures above 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 indi-

cated 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 ill mass-disaster identification. The term "mass disaster" *evokes* images of a chaotic event. initiated by a destructive force, which results in multiple fatalities necessitating identification. Mass disasters can be classified in one of three ways:

I. Natural
2. Accidental
3. Criminal (e.g.. serial homicide, bombings)

Each variety of mass disaster results in the death of multiple victims. However, the problems faced by the forensic dental team responsible for identifying the decedents may vary, depending on the type of mass disaster.

Natural disasters. Natural mass disasters include earthquakes, tornadoes, hurricanes, volcanic eruptions, fire storms, 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 disasters may be unknowns who cannot be presumptively identified. Transients, homeless individuais, and tourists who arc visiting an area involved in a natural mass disaster are often difficult to identify.

In a natural disaster, the principal problem for the dental identification team is that the environmental infrastructure is often compromised. Dental offices containing antemortem records may be destroyed. Communication lines and roads are damaged, preventing the retrieval of any available antemortem records. All of these factors can delay or preclude the prompt identification of victims.

Accidents. Accidental mass disasters are most often associated with transportation accidents, fires, industrial and mining accidents, and military accidents. These events usually occur over short periods. They are associated with closed populations, exemplified by the passengers on an airplane or a shift of workers in a mine. The airline has a list of individuals who are supposed to be on the plane. The mining company can document those who have reported for work. In these examples, the victims of accidents should logically come from the closed population. Therefore, antemortem records are first solicited from the families of these individuals.

Problems can be associated with the identification of victims of industrial and military accidents because these populations are often of similar age and sex, may be ethnically similar, and may wear similar clothing. 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 mass disasters, criminal mass disasters may occur *over* extremely long periods (r.c., years) and wide ranges of territory (l.e.. different cities or states). The remains of the victims of serial killers can be hidden, dismembered, and mutilated. Dental structures in these situations may not be available for postmortem *review.*

Law enforcement agencies are often unaware of the victims 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.

Responsibilities. Regardless of the type of mass disaster, the local coroner or medical examiner 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; members of the FBI fingerprint team; representatives of the National Disaster Medlcal System (NOMS); and the clergy.

The forensic dentists who are responsible for identification and their support personnel should also be organized into a team. *Several* state dental associations (including California, Washington, Michigan, New York, South Carolina, and Iowa) have developed, supplied, and trained such groups in preparation for emergencies requiring their expertise. Training sessions include mock mass-disaster exercises. These drills can prepare the dental team members fordealing with the technical problems of mass-disaster cases.

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 psychologic insults encountered by the dentist who is dealing with human death on a large scale.

During a mass-disaster incident, the NOMS, 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 Disaster Mortuary Teams (DMORTs) administered by the

NDMS. Each DMORT is composed of funeral directors. medical examiners, 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 medical examiner. 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.

Dividing the team into subsections responsible for each of the three identification domains 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 should be directly responsible to the coroner or medical examiner. This person is the only member of the team authorized to release the results of the dental identification process to appropriate investigative agencies.

The advent of computer software has assisted mass-disaster 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 foliowing:

- The FBI-NCIC program, based on the California Dental Identification System, developed by Dr. Norman Sperber and Dr. Robert Siegel
- CAPMt-4 (Computer-Assisted Postmortem Identification-version 4.0), developed by Dr. Lewis Lorton of the U.S. Army Institute of Dental Research and maintained by the Armed Forces Institute of Pathology (AFIP)
- WINtD. developed by Dr. james *McGivney* (St. Louis, MO)
- ToothPics Identification System. developed by Class I tnc. (Tempe, AZ)

Each of these systems is user friendly, can be run on readily available and accessible hardware, is capable of networking, and relies on objective data entry. However. identification is the result of human thought processes. To arrive at correct conclusions based on the evidence. individual dental team members must evaluate computer matches.

BITE PATTERN EVIDENCE

BASIC PRINCIPLES

Animal bites account for most bite injuries reported annually, Bites represent approximately I% of all emergency visits that require medical attention. Of these. most are associated with dog bites. 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 pattern injuries that can be mistakenly interpreted as antemortem trauma. Postmortem bites from rats and scavenging dogs and cats are often avulsive and of narrower or smaller diameter than human bites.

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 *verbai* communication fails. Biting injuries in children can result from piayground 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-Itnked, *recessively* transmitted disease manifesting-among other signs-insensitivity to pain and self-mutilation by chewlng 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.

tnjuries 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 animai bites. Infectious complications include tetanus, tuberculosis, syphilis. actinomycosis, and those infectious complications related to streptococcal and staphylococcal organisms.

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.

Rabies is the most serious infectious complication that results from 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.

The concept of accepting evidence related to the analysis of patterns created by the dentition is relatively new to the United States justice system. In 1954, *Doyle v. State of Texas* became the first modern case in which a conviction was based on evidence relating a suspect's dentition to pattern marks in an inanimate object (a piece of cheese).

However, 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 and the remaining 80% of state courts and all federal courts under the Federal Rules of Evidence 702-705. These are special rules that deal with the admissibility of scientific evidence. 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 *Frye* 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 United States Supreme Court ruled on the admissibility of scientific evidence in *Daubert v. 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 sale, 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 employed 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 techniques employed.
- Consideration is given to acceptance of scientific principles that have gained general acceptance within the scientific discipline to which they belong.

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. In addition, studies indicate that, like fingerprints, the human dentition is unique for each person. Variations in size. wear. and fractures; position in the dental arch; diastemata; and restored surfaces contribute to this principle.

Thus, bite mark evidence is 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, no challenge to the scientific basis of bite mark evidence has been successful under either set of standards.

Characteristics of Bite Marks

To evaluate a pattern 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 individual marks are described as internal characteristics of the entire bite mark. Human incisors make rectangular marks. Depending on the amount of attrition observed on the cuspid's incisal edge, incisal surfaces of cuspids may be associated with points or triangular patterns. Bicuspid teeth are often associated with marks that resemble 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. Round, ovoid, or elliptical patterns are usually observed, but variations may be associated with tapered, square, and U-shaped arches. 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 em (Figure t9-8).

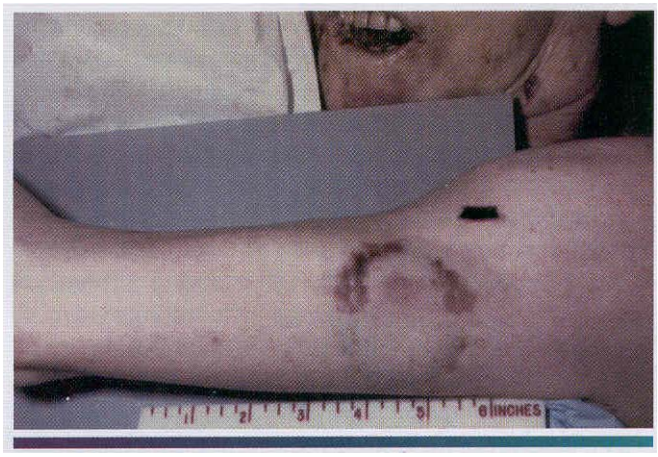

Figure 19-8 • A bite mark pattern demonstrating the internal and class characteristics associated with impressions made by the human dentition. An ecchymotic area in the center of the ovoid pattern is observed, which is not always related to the sucking action of a sexual bite. Therefore, this finding should not be overinterpreted to imply sexual intent on the part of the biter. The impressions made by the teeth of the mandibular arch are more delicate.

Internal 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 internal 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. Shieldlike imprints of the palatal surfaces are generated in the bite mark rather than the rectangular patterns routinely associated with these teeth.

Aberrant muscle forces associated with tongue thrusting can alter the way the teeth contact a bitten surface. Temporomandibular joint dysfunction (TMD) can also contribute to variations in bite patterns. TMD can be associated with midline shifts or inability to achieve maximum opening while biting.

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 19-3). Color changes in the bitten tissue, associated with the degradation of hemoglobin from lysed red blood cells, can be used only to broadly estimate the time of occurrence.

Contusions and areas of ecchymosis are not unusual in bite marks made in living tissue. The absence of bleeding 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 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.

GUIDELINES FOR BITE MARK ANALYSIS

In 1984, the American Board of Forensic Odontology established Guidelines for Bite Mark Analysis. Additional workshops of the Board, held in 1993 and 1994, 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 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.

Description of the bite mark. Demographic information (e.g., 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.

Table 19-3 *Histopathologic and Clinical **Changes** Used to Monitor **the** Time Elapsed (Aging)* ***ill Skill** Iniuries Associated **With Bite Marks***

TIME	PREDOMINANT CELLULAR INFILTRATE AND DEPOSITS	IIEALING	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**

The shape. color. size. and type of injury arc recorded. **Metric measurements of the horizontal and vertical dimensions of the bite mark are determined. Irregularities** and variations from the standard round. *ovoid,* and **crescent shapes associated with human bite marks are** no[illegible] **Injury** [illegible] motic 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's lines).

Evidence ***collection***

Examination of the victim and suspect. Both the victim and the suspect are examined. and evidence from each is gathered for comparative study and evaluation. Col**lection 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.**

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. a knowledge of the suspect's medical history relative to systemic problems associated with cardiovascular dis**ease. allergy. seizure disorder. or requirements for** antibiotic prophylaxis is medicolegally important.

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** [illegible] and provide for due process. as guaranteed by the Fourth and Fourteenth Amendments. respectively, to the U.S. **Constitution.**

Bite marks are considered similar to such physical evidence as fingerprints; hair, blood, and semen samples; and sobriety tests. Therefore, this material is not protected under provisions of the Fifth Amendment, which deal with self-incrimination.

Photography. Ideally. standard photographic techniques include the usc of a 3S-mm single-lens reflex camera with a flat-field macro lens and electronic flash. Numerous photographs employing different camera positions. lighting, exposure settings. and types of film should be obtained. Orientation positions and close up **views with a reference scale are required. The scale** should be positioned next to. and in the same plane as. the bite mark. The scale should be omitted from at least **one view to document that no marks or other injuries** have been hidden by the scale.

A reference scale permits the bite mark photographs to be measured and prepared as life-size (i.e.. I:I) representations of the injury. They can then be compared with casts and other exemplars obtained from the suspect. The ABFO no. 2 reference ruler (Figure 19-9) was developed by the ABFO for use in bite mark photography.

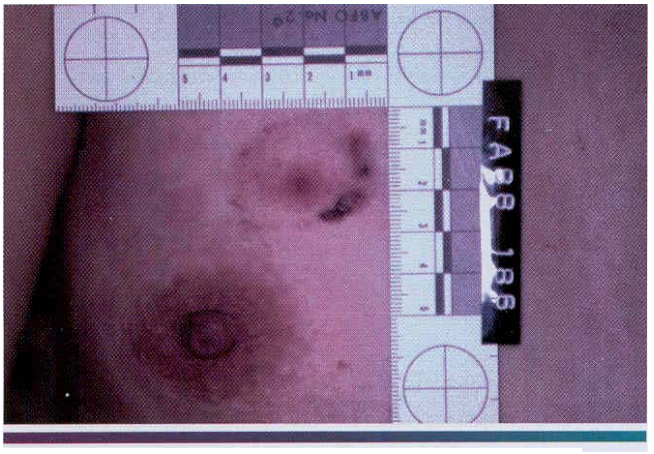

Figure 19-9 • The American Board of Forensic Odontology (ABFO) No. 2 Reference Scale.

This instrument contains two metric scales, an 18% color gray scale, circular symbols, and rectifying grids. Each of these components is used to account for potential photographic distortions, which can negate the value of the photographic evidence.

With living victims, serial pictures are taken over several days. This series provides documentation of the color changes associated with healing of the wound. In addition, special photographic techniques, including the use of reflective ultraviolet (UV) photography, can be used to identify latent images of the teeth. These may remain after the bite mark has clinically disappeared.

Reflective UV photography enhances the bite mark image by selectively identifying photoactive melanin pigment in the injured tissue. Variations in the amount of melanin in the traumatized tissue are observable. This is based on the fluorescence created when the skin is exposed to UV light in the 320- to 450-nm wavelength range. UV photography requires special films, illumination sources, or lens filters, such as the Wratten Filter no. iSA (visibly opaque glass filter), to work within the desired wavelengths. In addition, there may also be focusing problems associated with ultraviolet photography. 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.

As previously stated, photographs of the suspect should involve the same attention to technical quality control. Extraoral, Intraoral, and occlusal photographs are taken. Additional films of wax or acrylic test bites and measurements of maximum interincisal opening are also recorded.

Saliva evidence. Collection of saliva trace evidence from the surface of the bite injury and a control skin surface of the victim is performed to identify blood group antigens and DNA. These samples can be used for comparison with saliva obtained from the suspect. A saliva sample should be collected on a cotton swab that has been moistened in sterile saline. The bite mark is rubbed with the cotton, which is then permitted to air dry. After the sample dries, the cotton swab is placed in a test tube and refrigerated until it can be analyzed. The control sample is obtained from an area of the victim's skin surface that is not associated with the bite. Because a victim may be bitten through the clothing, areas of garments that approximate a bite pattern injury should also be retained and evaluated for saliva.

Unfortunately, many victims of sexual abuse wash the area of a bite mark before reporting for treatment. Emergency room personnel should be trained to identify bite mark injuries and instructed not to wash or disinfect these areas until saliva evidence can be obtained.

Impressions and study casts. The Guidelines for Bite Mark Analysis deliberately do not dictate which impression materials should be used to create exemplars of a bite mark. Vinyl polysiloxanes are dimensionally stable impression materials that 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 and nonexothermic resins have been used to create the rigid trays for bite mark impressions. All impression trays and study casts should be appropriately labeled. Originals are retained for 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,

Tissue samples. Tissue samples of a bite mark can be retained from decedents. With the permission of the medical examiner or coroner, the dermis and underlying muscle and adipose tissue can be removed for transillumination analysis. Before excision, an acrylic ring or stent must be secured within i 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 (Figure 19- 10).

***Evidence** analysis,* 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 forensic dentist first determines whether the pattern is truly a result of biting or whether it is artifactual. Patterns of blood

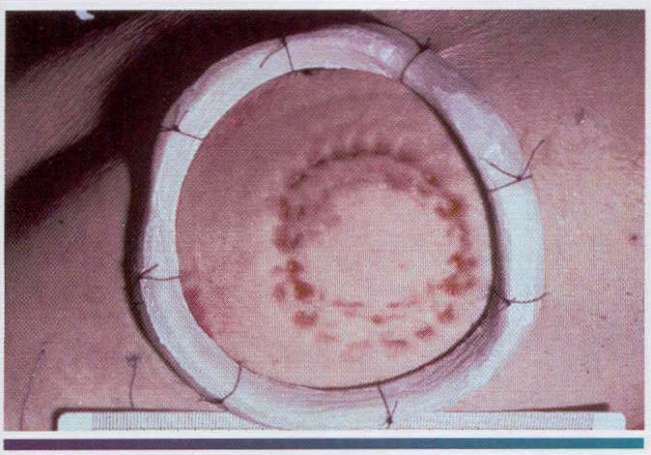

Figure 19-10 • An experimental bite pattern injury on a cadaver. This bite mark has had an acrylic stent glued and sutured around its circumference before dissection and fixation in 4% formalin. (Courtesy of Dr E. Steven Smith.)

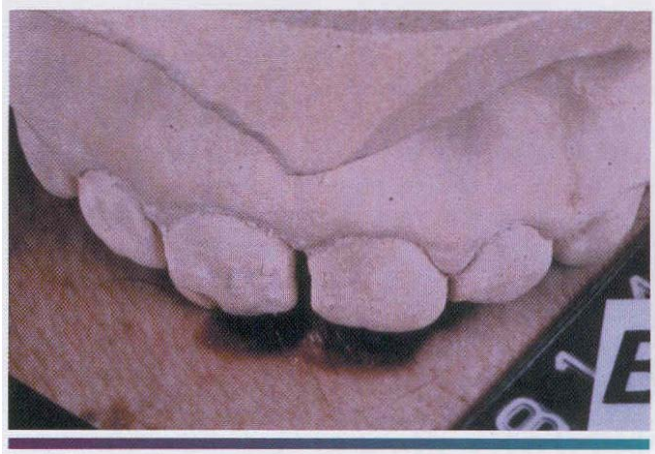

Figure 19-11 • An overlay of the maxillary cast of a suspect's dentition on a photograph of a bite pattern injury. Note the diastema between the central incisor teeth. The distal incisal surfaces of the lateral incisor teeth are not in the plane of occlusion.

splatter around a wound or other tool marks unrelated to the teeth may be mistaken for bite marks.

Once it is established that the pattern is related to the teeth, it can be matched to the suspect's dentition 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.

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.

Clear overlays of the chewing surfaces of the teeth can be 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 achieves the same end. A similar effect is 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 are then superimposed over the bite mark for comparison (Figures 19-11 and 19-12).

A recent study indicates that there are limitations to the accuracy of the various overlay techniques. It is suggested that subjective, hand-traced overlay methods be discontinued. Among the other techniques, computer-generated bite mark overlays are the most reproducible and accurate for analysis. The area of the biting edges of the teeth is best measured using overlays constructed from radiopaque material in wax dental Irnpressions. Photocopiers, calibrated to create 100% images, are best employed to record tooth rotation.

In court, bite mark evidence must be able to withstand legal challenges based on its scientific validity and the

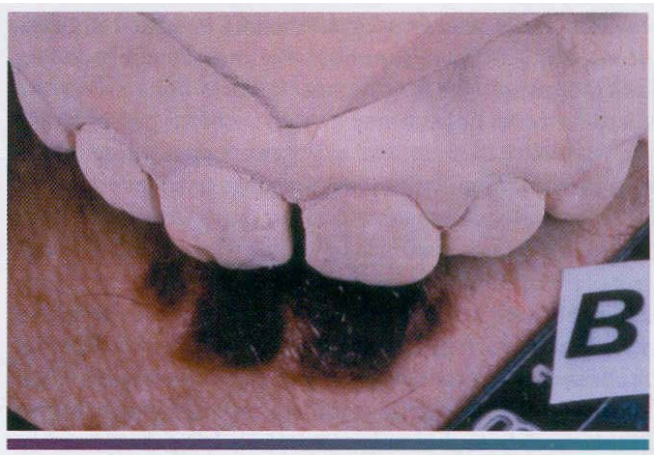

Figure 19-12 • A repositioned overlay of the maxillary cast of a suspect's dentition on a photograph of a bite pattern injury (same case as depicted in figure 19-11). The drag marks. diastema space, and mesial contact points of the lateral incisor teeth become apparent in the pattern. (from Nuckles DB, Herschaft EE, Whatmough IN: forensic odontology in solving crimes: dental techniques and bite mark evidence, *Gen Dent* 42:210-214, 1994.)

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.

HUMAN ABUSE

EPJDEMIOWGY AND CLASSIFICATION

Dental professionals are likely to encounter more victims of physical, neglective, sexual. and psychologic 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 2.5 million cases of child abuse. 2 million cases of elder abuse. and 4 million spousal abuse victims annually.

Child abuse is the nonacctdental, 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. baby-sitter. teacher. or other person acting *in loco parentis.* Elder abuse is similar in all regards except that **it deals with geriatric victims who require care or have** been institutionalized.

Victims of spousal abuse are unique and differ from those of child or elder abuse because they often have **autonomy to choose their circumstances. Unlike the** abused child or geriatric resident in a nursing home, **the abused spouse can make choices to leave the traumatic. violent environment.**

Of the 2.5 million annual cases of child abuse, 2000 to 4000 cases result in death. 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.

Many abusive individuals were themselves abused as children. Criminal charges are often lodged against an abusing caretaker. It is recognized. however, that counseling and psychologic and emotional support can also help to stabilize a violent, dysfunctional family unit.

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 and health care and safety neglect among pediatric and elderly dental patients. Of the children and elderly who are physically abused. 50% manifest orofacial injuries (Figure 19-13l. These unexplained injuries are inappropriately reported by the caretaker or are inconsistent with the history provided. Abusive trauma to the face and mouth 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
- Bilaterai contusions of the lip cornrnlssures from the placement of a gag

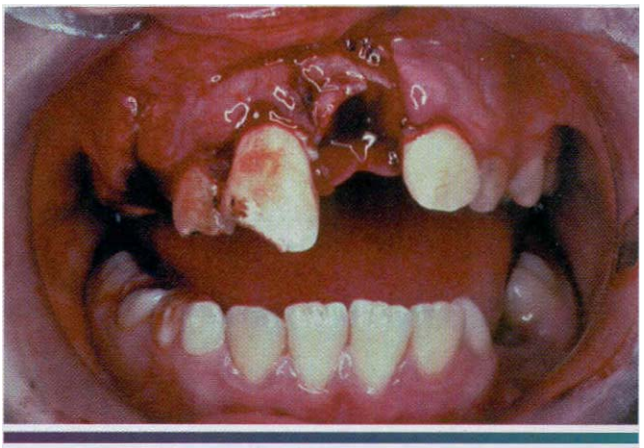

Figure 19-13 . An avulsed tooth. a fractured tooth. and a torn labial frenum associated with oral facial injuries in physical child abuse.

Pattern injuries can be associated with the semicir-cular 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 round. 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 (Figures 19-14 and 19-15l.

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 and geriatric dental patient. Suspicion of abuse is increased when the child or elderly 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. 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 268).

Among siblings. "milk bottle caries" is a sign of neglective abuse and indicates the caretaker's inattention to the dental needs of the children. The dentist may become aware of other abusive behavior directed to a child or elderly 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.

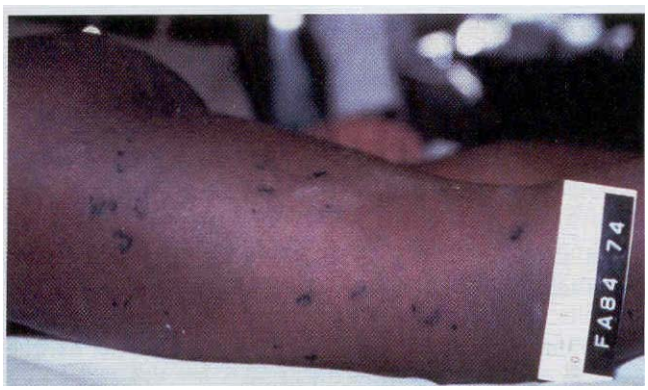

Figure 19-14 • Multiple circular ulcerated injuries are associated with intentional burns from a cigarette. When a child is accidentally burned by a cigarette. only one elliptical ulcer is observed.

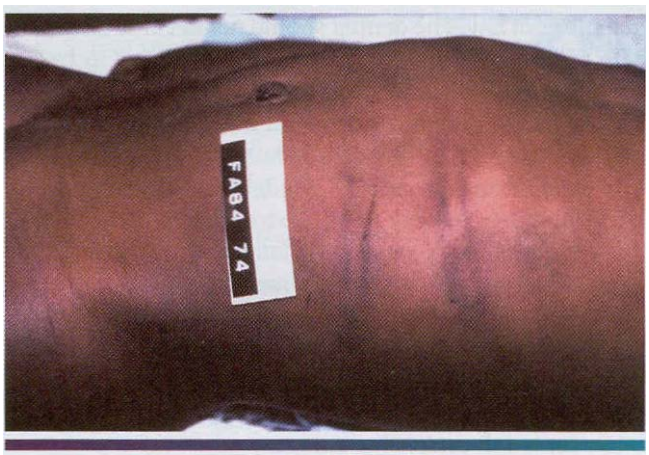

Figure 19-15 • Parallel linear **("railroad** track"} **pattern s are associated with blows to the skin with such straight-edged objects as a belt. a hanger; an electrical cord. and a ruler.**

THE 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, New **York State 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 **spousal abuse 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 spousal abuse 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** counterprosecution 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 below the age of majority.

THE DENTIST AS AN EXPERT WITNESS

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, judges, and ultimately juries (the triers of fact) 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.* Temporomandibular joint (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 mass-disaster victims.*

In criminal court, dental expertise is requested in identification of homicide victims and in bitemark 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 jury 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 a dentist's knowledge of the law. Appreciation of forensic dental problems permits clinicians to maintain legally acceptable records and assist legal authorities in the identification of victims of disasters and crimes.

The pursuit of justice in cases of rape and child abuse often relies on dental testimony to interpret bite pattern injuries. New photographic techniques, computer software development, and laboratory and clinical procedures have permitted forensic dentists to provide objective, scientific evidence in these types of cases.

The legal community's reliance 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.

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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 gutdellnes 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 such items 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 very 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 our colleagues, the clinician should be familiar with the following terms:

Macule. Focal area of color change which is not elevated or depressed in relation to its surroundings.

Papule. Solid, raised lesion which is less than 5 mm in diameter.

Nodule. Solid, raised lesion which isgreater 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 exhibitlng numerous surface projections.

Verrucous. Describing a tumor or growth exhibiting a rough, warty surface.

Vesicle. Superficial blister, S 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 fiat 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 such additional characteristics as prevalence, patient race or nationality, patient age at diagnosis, patient gender. 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 **(..**'J; rare lesions are marked with a single asterisk ('J. 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 I
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	
▪••	**Pseudomembranous candidiasis**	"Milk curd" or "cottage cheese" appearance; may leave red base when rubbed off	189
▪••	**Morsicatio**	Surface may appear to be peeling off	253
	Thermal burn	Example: pizza burn	258
▪▪	Sloughing traumatic lesion	Example: cotton roll "burn"	260
••	Toothpaste or mouthwash **reaction**	Filmy whiteness; leaves normal appearing mucosa when rubbed off	303
	Chemical burn	Example: aspirin burn secondary 10 direct application for toothache	259
	Secondary syphilis	Mucous patch; may be only partially scraped off	168
	Diphtheria	Gray-white pseudomembrane of oropharynx	166
	B. *White Lesions: Cannot Be Scraped Off*		
▪••	linea alba	Buccal mucosa along occlusal plane	253
	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**	337
▪••	Tobacco pouch keratosis	Usually in mandibular vestibule; associated with use of snuff or chewing tobacco	346
•••	Actinic cheilosis	Pale. gray-white. scaly alteration of lower lip; usually in older men with history of chronic sun **exposure; precancerous**	353
•••	lichen planus	Wickham's striae; typically bilateral on buccal mucosa	680
▪••	**Morsicatio**	**Most common on anterior buccal mucosa, labial mucosa,** and lateral border of tongue; exhibits ragged surface	253

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
		B. White Lesions: Cannot Be Scraped Off-continued	
•••	White coated tongue	Diffuse involvement of dorsal tongue	
••	**Nicotine stomatitis**	**Usually associated with pipe smoking; occurs on** hard palate	350
	Hairy leukoplakia	Usually lateral border of tongue; rough surface with vertical fissures; usually associated with HIV infection	241
	Hyperplastic candidiasis	Most commonly affects anterior buccal mucosa	194
	Lupus erythematosus	**Most common on buccal mucosa; may mimic lichen planus** or leukoplakia; associated skin lesions usually present	689
	Skin graft	**History of previous surgery**	
	Submucous fibrosis	More common in South Asia; associated with betel quid chewing	349
	White sponge nevus	Hereditary; onset in childhood; generalized lesions, **especially buccal mucosa**	645
	Hereditary benign intraepithelial dyskeratosis	Hereditary; onset in childhood; generalized lesions, especially buccal mucosa; ocular involvement possible	646
	Pachyonychia congenita	Hereditary; onset in childhood; most common on **dorsal tongue and areas of trauma; nail, palmar,** and plantar changes also present	647
	Dyskeratosis congenita	Hereditary; onset in childhood; dystrophic nail changes	648
	Tertiary syphilis	Syphilitic glossitis	169
	Uremic stomatitis	Renal failure	735
		C. White and Red Lesions	
•••	Erythema migrans	Geographic tongue; continually changing pattern; rarely **involves other oral mucosal sites**	677
•••	Candidiasis	White component may be rubbed off	189
•••	Lichen planus	Atrophic or erosive forms; Wickham's striae; typically **bilateral on buccal mucosa**	680
	Burns	Examples: pizza burn, aspirin burn, other chemical burns; white component may be rubbed off	258
••	**Actinic cheilosis**	Pale, gray-white and red alteration to lower lip; usually **in older men with history of chronic sun exposure**	353

Continued

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
		C. White and Red Lesions-continued	
	Nicotine stomatitis	Usually associated with pipe smoking; occurs on hard palate	350
••	Erythroleukoplakia	Usually shows epithelial dysplasia or carcinoma	34t
••	**Cinnamon reaction**	Related to cinnamon-flavored gum; typically on buccal mucosa and lateral tongue	305
	LUpus erythematosus	**Most common on buccal mucosa; may mimic lichen** planus or leukoplakia; associated skin lesions usually present	689
	Scarlet fever	Secondary to II-hemolytic streptococcal infection; strawberry/raspberry tongue	165
	Verruciform xanthoma	Most common on gingiva and hard palate; surface may be papillary	324
		D. Red Lesions	
•••	Pharyngitis	Examples: strep throat. viral pharyngitis	164
•••	Traumatic erythema	Caused by local irritation	
	Denture stomatitis	Denture-bearing palatal mucosa	t92
	Erythematous candidiasis	Example: central papillary atrophy (median rhomboid glossitis)	191
•••	Erythema migrans	Geographic tongue (cases with absence of white borders); continually changing pattern; rarely involves other **mucosal sites**	677
•••	Angular cheilitis	**Erythema and cracking at labial commissures**	t92
••	Thermal burns	Example: caused by hot liquids	258
''	Erythroplakia	Usually shows epithelial dysplasia or carcinoma	345
	Anemia	Atrophic. red tongue; can be due to pernicious anemia. iron-deficiency **anemia, hypovitaminosis** B	714
	Hemangioma	Develops in younger patients; may blanch; may show bluish hue	467
	LUpus erythematosus	Usually with associated skin lesions	689
	Scarlet fever	Secondary to II-hemolytic streptococcal infection; strawberry/raspberry tongue	165

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
		D. Red Lesions-continued	
	Plasma cell gingivitis	Allergic reaction usually related to flavoring agents	141
	Radiation mucositis	Patient currently undergoing radiotherapy	261
		E. *Petechial, Ecchymotic, and Telangiectatic Lesions*	
	Nonspecific *trauma*	History of injury to lesional site	
••	Upper respiratory **infections**	Soft palate petechiae	268
	Infectious mononucleosis	Soft palate petechiae; tonsillitis and/or pharyngitis may be present	224
	Idiopathic thrombocytopenic purpura	Areas of trauma; gingival bleeding possibly present	508
	Trauma from fellatio	Posterior **palatal petechiae or ecchymosis**	268
	Hemophilia	Hereditary; childhood onset; gingival bleeding may be present	499
	Leukemia	Caused by secondary thrombocytopenia; gingival bleeding may be present	510
	Hereditary hemorrhagic **telangiectasia**	Multiple, pinhead-sized telangiectasias; possible history of nosebleeds or gastrointestinal bleeding	654
	CREST syndrome	Multiple, pinhead-sized telangiectasias; Calcinosis cutis, Raynaud's phenomenon, Esophageal motility defect, Sclerodactyly, Telangiectasias	695
		F. *Blle and/or Purple Lesions*	
▪▪ ▪	**Varicosities**	Especially after 45 years of age; most common on ventral tongue and lips	14
•••	Submucosal hemorrhage	Also see Appendix List, Part I, E. (previous topic) Petechial, Ecchymotic, and Telangiectatic Lesions	267
•••	Amalgam tattoo	**Most common on gingiva; blue-gray; radiopaque amalgam particles sometimes discovered on radiographs**	269
	Mucocele	Especially on lower labial mucosa; typically pale blue; cyclic swelling and rupturing often exhibited	389
••	Eruption cyst	overlying an erupting tooth	593
••	Salivary duct cyst	Usually pale blue	392

Continued

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
		F. Blue and/or Purple Lesions-continued	
▪▪	Hemangioma	Usually reddish-purple; may blanch under pressure; onset in younger patients	467
▪▪	Ranula	Pale blue. fluctuant swelling of lateral floor of mouth	391
••	**Kaposi's sarcoma**	Especially in AIDS patients; usually purple; most common on palate and maxillary gingiva	242
•	Nasopalatine duct cyst	Midline of anterior palate	27
	Salivary gland tumors	Especially mucoepidermoid carcinoma and pleomorphic adenoma; usually pale blue; most **common on posterior lateral palate**	Ch. II
	Gingival cyst of the adult	Most common in mandibular bicuspid-cuspid region	601
	Blue nevus	**Most common on hard palate**	336
	Malignant melanoma	Most common on hard palate and maxillary gingiva; may show mixture of deep blue. brown. black. and other colors	376
		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	269
	Black/brown hairy tongue	Discoloration and elongation of filiform papillae	13
	Melanotic macule	**Brown; most common on lower lip**	330
	Smoker's melanosis	**Most common on anterior facial gingiva**	274
••	**Non-amalgam tattoos**	Example: graphite from pencil	269
	Melanocytic nevus	Most common on hard palate; can be flat or raised	332
	Malignant melanoma	Most common on hard palate and maxillary gingiva; may show mixture of deep blue. brown. black. and other colors	376
	Oral melanoacanthoma	Rapidly enlarging pigmented lesion; usually occurs in blacks	331
	Drug ingestion	Examples: chloroquine. chlorpromazide. minocycline; especially on hard palate	275

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CIIARACTERISTICS	PAGE
		G. Brown. Gray. and/or Black **Lesions—continued**	
	Peutz-leghers syndrome	Freckle-like lesions of vermilion and perioral skin; intestinal polyps; hereditary	653
	Addison's disease	Chronic adrenal insufficiency; associated with bronzing of skin	727
	Neurofibromatosis	*Café au fait* pigmentation; cutaneous neurofibromas	458
	McCune-Albright syndrome	*Café au fait* pigmentation; polyostotic fibrous dysplasia; endocrine disorders	555
	Heavy metal poisoning	Typically along marginal gingiva; e.g.• lead. bismuth. **silver**	272
	Melanotic neuroectodermal tumor of infancy	Anterior maxilla; destroys underlying bone	462
		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	121
	Accessory lymphoid aggregate	Most common in oropharynx and floor of mouth; may exhibit orange hue	497
	Lymphoepithelial cyst	Most common on lingual and palatine tonsils, and floor of mouth; may be yellowish-white	35
	Lipoma	Most common on buccal mucosa; soft to palpation	452
	Jaundice	Generalized discoloration, especially involving soft palate and floor of mouth; sclera usually affected also	709
	***Verruciform* xanthoma**	Most common on gingiva and hard palate; surface may be rough or papillary	324
	Pyostomatitis vegetans	"Snail-track" pustules; associated with inflammatory bowel disease	734

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	255
	Aphthous stomatitis	Extremely painful; may be single or multiple; **nonkeratinized movable mucosa; often recurs**	285
•••	Recurrent herpes labialis	Vermilion and labial skin; begins as multiple vesicles; **often** recurs	213
••	**Primary herpetic gingivostomatitis**	Fever and malaise; children and young adults: multiple vesicles; gingiva consistently affected	213
••	**Necrotizing ulcerative** gingivitis (NUG)	Painful destruction of gingival papillae; fetid odor; mostly in teenagers and young adults	140
••	Mucosal burns	Chemical or thermal	258
	Recurrent intraoral herpes simplex	**Gingiva or hard palate (except in immunocompromised);** focal cluster of vesicles and shallow ulcers	213
••	**Allergic reactions**	Example: Caused by topical medications or dental materials; erythema and vesicles	303
••	Erythema multiforme	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 (Stevens-**Johnson syndrome)	674
••	**Herpangina**	Especially in children; multiple small ulcers on soft palate and tonsillar pillars	228
	Varicella (chickenpox)	**Associated with skin eruption; few oral vesicles and** ulcers; usually in children	220
	Herpes zoster	**Unilateral involvement along nerve distribution;** usually middle-aged and older adults; painful vesicles **and ulcers**	222
	Hand-foot-and-mouth **disease**	Especially in children; multiple vesicles and ulcers; associated vesicles on hands and feet	228

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	A. *Vesiculoerosive and Ulcerative Lesions: Acute (Short Duration and Sudden Onset)*—*continued*		
	Necrotizing sialometaplasia	Usually posterior lateral hard palate; prior swelling may be present; deep crater-like ulcer; may be only minimal pain	405
	Anesthetic necrosis	Usually at site of palatal injection	265
	Primary syphilis	Chancre at site of inoculation; usually painless with clean ulcer bed	168
	Behcet's syndrome	Aphthous-like ulcers; genital ulcers and ocular inflammation	290
	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")	680
	Squamous cell carcinoma	Usually in middle-aged and older adults; usually indurated and may have rolled border; may be painless	356
	Cicatricial (mucous membrane) pemphigoid	Most common in middle-aged and older women; **most commonly presents as a "desquamative gingivitis"; may involve ocular and genital mucosa**	669
••	**Traumatic granuloma**	Solitary. non-healing ulcer	255
	LUpus erythematosus	May have associated red and white change; usually with skin involvement	689
	Pemphigus vulgaris	Usually in middle-aged and older patients; multiple oral blisters and ulcers usually precede skin lesions	664
	Deep fungal infections	Examples; histoplasmosis. blastomycosis; may be painless	Ch. 6
	Tuberculosis	Associated mass may be present; may be painless	173
	Sarcoidosis	May be associated with erythematous macules or plaques; may be painless	292
	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**	660
	Pyostomatitis vegetans	Yellowish "snail-track" pustules; associated with **inflammatory bowel disease**	734

continued

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	B. *vesiculoerosive and Ulcerative Lesions: Chronic (Long Duralion)-continued*		
	Wegener's granulomatosis	Usually palatal ulceration and destruction; associated lung and kidney involvement may be present; may **show "strawberry gingivitis"**	297
	Midline lethal granuloma	Palatal lymphoma with ulceration and destruction of underlying bone; may be painless	524
	Noma	**Gangrenous necrosis secondary to necrotizing** ulcerative gingivitis; usually in malnourished children or immunocompromised individuals	**178**
	Tertiary syphilis	Gumma; associated mass may be present; may be painless; may perforate palate	169
	C. *Papillary Growths: Focal or Diffuse*		
•••	Hairy tongue	Usually brown or black discoloration; hyperkeratotic elongation of filiform papillae on posterior dorsal tongue	13
•••	Papilloma	Can be white or pink; most common on soft palate and tongue; usually pedunculated	316
•••	Inflammatory papillary hyperplasia	Usually involves midportion of hard palate beneath **denture**	442
••	Verruca vulgaris	**Common wart; especially in younger patients; most common on labial mucosa**	317
	Leukoplakia (some variants)	Examples: proliferative verrucous leukoplakia. granular or nodular leukoplakia	337
••	Squamous cell carcinoma	Examples with papillary surface changes	356
	Hairy leukoplakia	Usually lateral border of tongue; rough surface with vertical fissures; usually associated with HIV infection	241
	Giant cell fibroma	Usually in children and young adults; most common on gingiva	439
	Verruciform xanthoma	Most common on gingiva and hard palate	324
	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	367
	Condyloma acuminatum	Venereal wart; broad-based lesions with blunted projections; frequently multiple	318

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CIIARACTERISTICS	PAGE
		C. *Papillary Growths: Focal or Diffuse- continued*	
	Focal epithelial hyperplasia	Usually multiple, flat-topped papular lesions; usually in children; *most* common in native Americans and Inuits (Eskimos); color may vary from normal to white	320
	Darter's disease	Most commonly appears as pebbly appearance of hard palate; associated crusty. greasy skin lesions; hereditary	65t
	Acanthosis nigricans (malignant type)	Most commonly appears as generalized pebbly alteration of upper lip; pigmented. pebbly skin changes in flexural areas; associated gastro-intestinal malignancy	697

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	389
•••	Irritation fibroma	Usually normal in color	438
••	**Squamous cell carcinoma**	**Tumor with rough, granular, irregular surface; usually on vermilion border**	356
	Other mesenchymal **tumors**	Examples; hemangioma, neurofibroma, lipoma	Ch. 12
	Salivary duct cyst	May be bluish; labial mucosa only	392
	Salivary gland tumor	**Usually** mucoepidermoid carcinoma	Ch. II
	Keratoacanthoma	Volcano-shaped mass with central keratin plug; rapid **development; vermilion border only**	354
	B. Soft Tissue Masses (Lumps and Bumps): Upper Lip		
••	Irritation fibroma	Usually normal in color	438
••	Salivary gland tumor	Usually canalicular adenoma (older than age 40) or pleomorphic adenoma (younger than age 40)	Ch. II
••	Salivary duct cyst	May be bluish	392
	Minor gland sialolith	Small, hard submucosal mass; may be tender	393
	Other mesenchymal **tumors**	Examples: hemangioma, neurofibroma, neurilemoma	Ch. 12
	Nasolabial cyst	Fluctuant swelling of lateral labial vestibule	25
	C. *Soft Tissue Masses (Lumps and Bumps): Buccal Mucosa*		
	Irritation fibroma	Usually normal in color; along occlusal plane	438
	Lipoma	May be yellow; soft to palpation	452
••	Mucocele	Typically pale blue; often exhibits cyclic swelling and **rupturing**	389

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	C. Soft Tissue Masses (Lumps and Bumps): Buccal Mucosa-continued		
	Hyperplastic lymph node	Usually buccinator node; movable submucosal mass	497
	Other mesenchymal tumors	Examples: hemangioma. neurofibroma	Ch. 12
•	**Squamous cell carcinoma**	Tumor with rough. granular. irregular surface	356
	Salivary gland tumor	**Pleomorphic adenoma and mucoepidermoid carcinoma most common**	Ch. II
	D. Soft Tissue Masses (Lumps and Bumps): Gingival Alveolar Mucosa		
•••	Parulis	Fistula from nonvitaltooth	121
•••	Epulis fissuratum	III-fining denture	440
•••	PyogeniC granuloma	Usually red. ulcerated, easily bleeding: increased frequency in pregnant women	447
•••	Peripheral ossifying fibroma	May be red or normal in color; may be ulcerated	45t
••	Peripheral giant cell granuloma	Reddish-purple; frequently ulcerated	449
▪	Irritation fibroma	Usually normal in color	438
	Squamous cell carcinoma	Tumor with rough. granular. irregular surface	356
	Metastatic tumors	May be painful and destroy bone	489
	Gingival cyst of the adult	Most common in mandibular bicuspid-cuspid region; may be blue	601
	Traumatic neuroma	Edentulous mandible in mental foramen area; often painful to palpation	454
	Kaposi's sarcoma	Especially in AIDS patients: usually purple	242
	Peripheral odontogenic **tumors**	Example: peripheral ameloblastoma	618
	Congenital epulis	Usually in females; especially anterior maxilla	466
	Melanotic neuroectodermal tumor of infancy	Anterior maxilla: destroys underlying bone: may be pigmented	462
	Other mesenchymal **tumors**	Examples: hemangioma. neurofibroma	Ch. 12

Continued

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	E. Soft Tissue Masses (Lumps and Bumps}: Floor of Mouth		
''	Ranula/ mucocele	Typically a pale blue. fluctuant swelling	391
••	Sialolith	Usually hard mass in submandibular duct; may be associated with tender swelling of affected gland; **radiopaque mass**	393
••	Squamous cell carcinoma	Tumor with rough. granular. irregular surface	356
	Lymphoepithelial cyst	Small. yellow-white submucosal lesion	35
	Epidermoid or dermoid cyst	Midline yellow-white submucosal lesion	32
	Salivary gland tumors	Especially mucoepidermoid carcinoma	Ch. II
	Mesenchymal tumors	Examples: lipoma. neurofibroma. hemangioma	Ch.12
	F. *Soft Tissue Masses (Lumps and Bumps): Tongue*		
•• •	Irritation fibroma	Usually normal in color; most common on margins of tongue	438
••	Squamous cell carcinoma	Tumor with rough. granular, irregular surface	356
••	Mucocele	Usually anterior ventral surface; usually bluish or dear color	389
	Granular cell tumor	Dome-shaped; usually on dorsum of tongue	465
	Other mesenchymal **tumors**	Examples: lymphangioma, hemangioma, neurofibroma. **osseous choristoma**	Ch.12
	Pyogenic granuloma	Usually red. ulcerated, easily bleeding	447
	Salivary gland tumors	Especially mucoepidermoid carcinoma and adenoid **cystic carcinoma**	Ch. II
	Lingual thyroid	Usually posterior midline of dorsal surface; usually **in women**	II
	G. *Soft Tissue Masses (Lumps and Bumps): Hard or Soft Palate*		
•••	Palatal abscess	Associated with nonvital tooth	121
•• •	Leaf-like denture fibroma	Pedunculated hyperplastic growth beneath ill-fitting denture	441
••	Salivary gland tumors	Especially pleomorphic adenoma, mucoepidermoid **carcinoma. adenoid cystic carcinoma, polymorphous** low-grade adenocarcinoma; may have bluish hue	Ch. II

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	G. Soft Tissue Masses (Lumps and Bumps): Hard or soft Palate- continued		
••	**Kaposi's sarcoma**	Usually purple; may be multiple; usually associated with AIDS	242
▪	Nasopalatine duct cyst	Fluctuant swelling of anterior midline palate	27
	Other mesenchymal tumors	**Examples: irritation fibroma. hemangioma, neurofibroma**	Ch. 12
	Squamous cell carcinoma	Tumor with rough, granular, irregular surface; **occasionally arises from maxillary sinus**	356
	Mucocele/salivary duct cyst	Usually has bluish hue	389
•	Lymphoma	Often boggy and edematous; may have bluish hue; may be bilateral	517
	Melanocytic nevus/ **melanoma**	Usually pigmented	332
	Necrotizing sialometaplasia	Early-stage lesion; often associated with pain or paresthesia	405
•	Adenornatoid hyperplasia of minor salivary glands		405
	H. Soft Tissue Masses (Lumps and Bumps): Multiple Lesions		
••	**Kaposi's sarcoma**	Usually purple lesions of palate and maxillary gingiva; usually associated with AIDS	242
••	Neurofibromatosis	Oral and skin neurofibromas; *café au lait* skin pigmentation	458
	Focal epithelial hyperplasia	Usually flat-topped papular lesions; usually in children; **most common in Native Americans and Inuits (Eskimos);** color may vary from normal to white	320
	Amyloidosis	Pale, firm deposits, especially in tongue; periocular cutaneous lesions frequently present; most often associated with multiple myeloma	710
	Granulomatous diseases	Examples: sarcoidosis, Crohn's disease, leprosy	292
	Multiple endocrine neoplasia, type 2B	Mucosal neuromas of lips and tongue; adrenal pheochromocytomas; medullary thyroid carcinoma; marfanoid body build	461
	Tuberous sclerosis	Small fibroma-like growths on gingiva; angiofibromas of face; epilepsy; mental retardation	657
	Multiple hamartoma syndrome	Cowden syndrome; small fibroma-like growths on gingiva; **multiple hamartomas of various tissues; breast cancer** in affected women	659

Continued

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	I. Soft Tissue Masses (Lumps and Bumps): MidUne Neck Lesions		
••	Thyroid gland enlargement	Examples: goiter, thyroid tumor	
	Thyroglossal duct cyst	May move up and down with tongue motion	33
	Dermoid cyst	Soft and fluctuant	32
	Plunging ranula	Soft and compressible	391
	}. Soft Tissue Masses (Lumps and Bumps): Lateral Neck Lesions		
•••	Reactive lymphadenopathy	Secondary to oral and maxillofacial infection; often tender to palpation	497
▪▪	Epidermoid cyst	Soft and movable	31
••	Lipoma	Soft mass	452
••	**Infectious mononucleosis**	Fatigue; sore throat; tender lymph nodes	224
••	**Metastatic carcinoma**	Deposits from oral and pharyngeal carcinomas; usually indurated and painless; may be fixed	363
	Lymphoma	May be unilateral or bilateral; usually painless; Hodgkin's and non-Hodgkin's types	515
	Salivary gland tumors	Arising from submandibular gland or tail of parotid gland	Ch. II
	Submandibular slaladcnitls	Example: secondary to sialolithiasis	395
	Cervical lymphoepithelial cyst	Soft and fluctuant; most common in young adults	34
	Granulomatous diseases	**Examples: sarcoidosis. tuberculosis**	292
	Cat-scratch disease	**History of exposure to cat**	182
	Cystic hygroma	Infants: soft and fluctuant	475
	Plunging ranula	Soft and compressible	391
	Other mesenchymal tumors	Examples: neurofibroma, carotid body tumor	Ch. 12
	K. Generalized Gingival Enlargement		
•••	Hyperplastic gingivitis	Examples: associated with puberty, pregnancy. diabetes	137
••	Drug-related gingival hyperplasia	Examples: phenytoin. calcium-channel blockers, cyclosponnc: may be fibrotic	145
	Gingival fibromatosis	May be hereditary; onset in childhood	148

FREQU ENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CIIARACTERISTICS	PAGE
	K. *Generalized Gingival Enlargement—continued*		
	leukemic infiltrate	Usually boggy and hemorrhagic	510
	Wegener's granulomatosis	**"Strawberry" gingivitis; may have palatal ulceration** and destruction: lung and kidney involvement	297
	Scurvy	Vitamin C deficiency	713

PART 4
Radiographic Pathology

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
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•••	Hyperplastic dental follicle	< 5 mm in thickness	592
▪..	**Dentigerous cyst**	**> 5 mm in thickness**	590
••	Eruption cyst	Bluish swelling overlying erupting tooth	593
••	Odontogenic keratocyst		594
	Orthokeratinized odontogenic cyst		597
	Ameloblastoma	Especially unicystic type	611
	Ameloblastic fibroma	Usually in younger patients	626
	Adenomatoid odontogenic **tumor**	Usually in anterior region of jaws; most often with **maxillary canine; usually in teenagers**	621
	Calcifying odontogenic cyst	Gorlin cyst	604
	Carcinoma arising in dentigerous cyst	Mostly in older adults	609
	Intraosseous **muco-epidermoid carcinoma**	Mostly in posterior mandible	422
	Other odontogenic lesions	Examples: calcifying epithelial odontogenic tumor. odontogenic myxoma, central odontogenic fibroma	Ch.15
	B. Unilocular Radiolucencies: Periapical Location		
•••	Periapical granuloma	Nonvital tooth	113
•••	Periapical cyst	**Nonvital tooth**	116
••	**Periapical** cemento-osseous dysplasia (early)	Especially in black females; usually apical to **mandibular anteriors; teeth are vital**	557
•	**Periapical scar**	Usually endodontically treated tooth with destruction of cortical plate	115
•	Dentin dysplasia type I	Multiple periapical granulomas or cysts; shortened, **malformed roots**	96

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
		C. *Unilocular Radiolucencies: Other Locations*	
•••	Developing tooth bud	Within alveolar bone	
	Lateral radicular cyst	Nonvital tooth; lateral canal	116
••	Nasopalatine duct cyst	Between and apical to rnaxillary central incisors; palatal swelling may occur	27
	Lateral periodontal cyst	Especially in mandibular bicuspid-cuspid region	602
••	Residual (periapical) cyst	Edentulous area	116
	Odontogenic keratocyst		594
••	Central giant eel) granuloma	Especially in anterior mandible	544
••	Stafne bone defect	Angle of mandible below mandibular canal	23
	Cemento-osseous dysplasia	Early stage; usually in young adult and middle-aged black women; usually in mandible	557
•	Central ossifying fibroma	Early-stage lesion	563
	Ameloblastoma	Especially unicystic type	611
	Other odontogenic cysts and tumors	Examples; ameloblastic fibroma, central odontogenic fibroma. calcifying odontogenic cyst	Ch. 15
	Langerhans cell disease	"Histiocytosis X"; usually in children or young adults	513
	Melanotic neuroecto-dermal tumor of infancy	Anterior maxilla; may be pigmented	462
•	Median palatal cyst	Clinical midline swelling of hard palate	30
	Neurilemoma/ neurofibroma	Usually associated with mandibular nerve	456
		D. *Multilocular Radiolucencies*	
•••	Odontogenic keratocyst		594
•••	Ameloblastoma	Especially in posterior mandible; often associated with impacted tooth	611
••	Central giant cell granuloma	Especially in anterior mandible	544
	Ameloblastic fibroma	Especially in younger patients	626

Continued

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	D. Mulukxular Radiolucencies-continued		
	Odontogenic myxoma	' Cobweb" trabeculation	635
	Central odontogenic fibroma		633
	Calcifying epithelial **odontogenic tumor**	Often associated with impacted tooth	623
	Orthokeratinized odontogenic cyst	Often associated with impacted tooth	597
	Lateral periodontal cyst (botryoid type)	Especially in mandibular bicuspid-cuspid region	602
	Calcifying odontogenic cyst	Especially in cases with minimal or no calcifications; often associated with impacted tooth	604
	Central hemangioma! **arteriovenous** malformation	Especially in younger patients: may have honeycombed radiographic appearance: may pulsate	469
	Aneurysmal bone cyst	Especially in younger patients	551
	Cherubism	Hereditary: onset in childhood; multiple quadrants involved	547
	Hyperparathyroidism (brown tumor)	Usually elevated serum calcium levels	724
	Intraosseous muco-epidermoid carcinoma	Usually in posterior mandible	422
	Fibrous dysplasia	Very rarely on panoramic films of mandibular lesions	553
	E. *Radiolucencies: Poorly Defined or Ragged Borders*		
	Periapical granuloma or cyst	Nonvital tooth	113
	Hematopoietic bone marrow defect	Especially edentulous areas in posterior mandible; **more common in females**	539
	Osteomyelitis	Usually painful or tender	126
	Traumatic bone cyst	Mandibular lesion that scallops up between roots of teeth; usually in younger patients	549
	Metastatic tumors	Painful; paresthesia; usually in older adults	582
	Osteoradionecrosis	History of radiation therapy; painful	263
	Multiple myeloma	May be painful: in older adults	526

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	E. ***Radiolucencies:*** *Poorly Defined or Ragged Borders-continued*		
	Primary intraosscous carcinomas	**Odontogenic or salivary origin**	619
	Osteosarcoma	Often painful; usually in young adults	574
	Chondrosarcoma		578
	Ewing's sarcoma	Almost always in children	58\
	Other primary bone **malignancies**	Examples: fibrosarcoma . lymphoma	
	Desmoplastic fibroma of bone	Especially in younger patients	573
	Massive osteolysis .	Phantom (vanishing) bone disease	54\
	NICO (neuralgia-inducing cavitational **osteonecrosis)**	Local or referred pain	746
	F. *Radiolucencies: Multifocal or Generalized*		
	Cernento-osscous dysplasia	Early-stage lesion; usually in black females; usually in mandible	557
••	Nevoid basal cell **carcinoma syndrome**	Odontogenic keratocysts	598
	Multiple myeloma	Painful; in older adults; "punched-out" lesions	526
	Cherubism	Usually multilocular; onset in childhood; hereditary	547
	Hyperparathyroidism	Multiple brown tumors	724
	Langerhans cell disease	"Histiocytosis X"; in children and young adults; teeth "floating in air"	513
	G. *Radiopacities: Well-Demarcated Borders*		
•••	**Torus or exostosis**	**Associated with bony surface mass**	\8
	Retained root tip	Remnants of periodontal ligament usually seen	
•••	**Condensing osteitis**	Usually at apex of nonvital tooth	\31
	Idiopathic osteosclerosis	**Most commonly associated with roots of posterior** teeth; no apparent inflammatory etiology	540
	Pseudocyst of the **maxillary sinus**	Homogeneous. dome-shaped relative opacity rising above bony floor of maxillary sinus	277

Continued

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	G. Radiopacities: Well-Demarcated Borders-continued		
▪▪	Odontoma, compound	Tooth-like structures with thin, radiolucent rim at junction with surrounding bone; may prevent eruption of teeth; more common in anterior segments of jaws	631
••	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	631
	Cementa-osseous dysplasia	Late-stage lesions; especially in middle-aged and older black women; usually in mandible	557
••	Soft tissue radiopacity superimposed on bone	Examples: sialoliths, calcified nodes, phlcbollths, bullet fragments, shotgun pellets, amalgam tattoos (Also see Appendix List, Part 4, Q, p. 811)	
•	Intraosseous foreign body		
	Osteoma	Associated with bony surface mass	566
	Enamel pearl	Furcation area of molar tooth	82
	Osteoblastoma/osteoid osteoma/cementoblastoma	Late-stage lesions	568
	H. *Radiopacities: Poorly Demarcated Borders*		
••	Cementa-osseous dysplasia	Late-stage lesions; especially in middle-aged and older black women; usually in mandible	557
▪▪	Condensing osteitis	Usually at apex of nonvital tooth	131
	Sclerosing osteomyelitis	May be painful	128
▪▪	Fibrous dysplasia	"Ground glass" appearance; onset usually in younger patients	553
	Paget's disease of bone	"Cotton wool" appearance; late-stage lesions; in older patients	542
	Proliferative periostitis	"Onion-skin" cortical change; in younger patients; often associated with nonvital tooth	131
	Osteosarcoma	May have "sunburst" cortical change; frequently painful; usually in young adults	574
	Chondrosarcoma		578

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
		I. Radiopacities: MulIifoca/ or Generalized	
••	Florid cernento-osseous dysplasia	Late-stage lesions; especially in middle-aged and older black women; usually in mandible	558
••	Idiopathic osteosclerosis		540
	Paget's disease of bone	"Cotton wool" appearance; late-stage lesions; **in older patients; more common in maxilla**	542
	Gardner syndrome	Multiple osteomas; epidermoid cysts; gastro-intestinal polyps with high tendency toward **malignant transformation; hereditary**	567
	Polyostotic fibrous dysplasia	**"Ground glass" appearance; onset usually in** younger patients; may be associated with *café au lait* skin pigmentation and endocrine abnormalities (Albright syndrome)	555
	Osteopetrosis	**Hereditary: recessive form may be associated with** secondary osteomyelitis. visual and hearing **impairment**	535
		J Mixed Radiolucent/Radiopaque Lesions: Well-Demarcated Borders	
•••	Developing tooth		
••	**Cementa-osseous** dysplasia	Intermediate-stage lesions; especially in middle-aged black women; usually in mandible	557
••	Odontoma	Compound or complex type; in younger patients; may prevent eruption of teeth	631
	Central ossifying fibroma		563
	Ameloblastic fibro-**odontoma**	Usually in children	628
	Adenomatoid odontogenic **tumor**	**Usually in anterior region of jaws; most often with** maxillary canine; usually in teenagers	621
	Calcifying epithelial **odontogenic tumor**	Pindborg tumor; often associated with impacted tooth; **may show "driven snow" opacities**	623
	Calcifying odontogeniC cyst	Gorlin cyst; may be associated with odontoma	604
	Osteoblastoma/osteoid **osteoma**	Intermediate-stage lesion; usually in younger' patients; often painful	568
	Cementoblastoma	**Intermediate-stage lesion; attached to tooth root**	570

Continued

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
	K. Mixed Radiolucent/Radiopaque Lesions: Poorly Demarcated Borders		
••	Osteomyelitis	With sequestrum formation or with sclerosing type; often painful	126
	Metastatic carcinoma	Especially prostate and breast carcinomas; may be painful	582
	Osteosarcoma/ **chondrosarcoma**	May be painful	574
	L. *Mixed Radiolucent/Radiopaque Lesions: Multifocal or Generalized*		
	Florid cemento- osseous dysplasia	Intermediate-stage lesions; especially in middle-aged black women; usually in mandible	558
	Paget's disease of bone	**In older patients; more common in maxilla**	542
	M. *Unique Radiographic Appearances: "Ground Glass" (Frosted Glass) Radiopacities*		
	Fibrous dysplasia	Onset usually in younger patients	553
	Hyperparathyroidism	May cause loss of lamina dura	724
	N. *Unique Rmliographic Appearances: "Cotton Wool" Radiopacities*		
••	**Cemento-osseous** dysplasia	Especially in middle-aged black women; usually in mandible	557
	Paget's disease of bone	**In older patients: more common in maxilla**	542
	Gardner syndrome	Multiple osteomas; epidermoid cysts; gastro-intestinal polyps with high tendency toward **malignant transformation; hereditary**	567
	Gigantiform cementoma	Hereditary; facial enlargement may be present	561
	O. *Unique Radiographic Appearances: "Sunburst" Radiopacities*		
	Osteosarcoma	Often painful; usually in young adults	574
	Intraosseous hemangioma	Especially in younger patients	469
	P. *Unique Radiographic Appearances: "Onion-Skin" Radiopacities*		
	Proliferative periostitis	In younger patients; often associated with nonvital tooth; best seen with occlusal radiograph	131
	Ewing's sarcoma	In young children	581
	Langerhans cell disease	"Histiocytosis X"; usually in children or young adults	513

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CUARACTERISTICS	PAGE
		Q. *Soft Tissue Radiopacities*	
▪▪▪	Amalgam tattoo	Markedly radiopaque; associated with surface discoloration	269
	Other foreign bodies	Examples; bullet fragments. shotgun pellets	
••	Sialolith	Glandular pain may be present while patient is eating	393
••	Calcified lymph nodes	Example; tuberculosis	173
••	Phlebolith	**May occur in varicosities or hemangiomas**	14
	Tonsillolith		166
	Soft tissue osteoma/ chondroma	**Most common on tongue**	479
	Calcinosis cutis	May be seen with systemic sclerosis (especially CREST syndrome)	695
	Myositis ossificans	**Reactive calcification in muscle**	

PART 5
Pathology of Teeth

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		A. *Hyperdontia (Extra Teeth)*	
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••	Cleft lip and palate	**Extra lateral incisor or canine**	2
•	**Gardner syndrome**	Osteomas and gastrointestinal polyps	567
	Cleidocranial dysplasia	Hypoplastic or missing clavicles; failure of tooth eruption	537
		B. *Hypodontia (Missing Teeth)*	
•••	Idiopathic hypodontia	**Missing third molars. lateral incisors**	69
••	Cleft lip and palate	**Missing lateral incisor or canine**	2
	Hereditary hypohidrotic ectodermal dysplasia	Cone-shaped teeth	644
•	**Incontinentia pigmenti**	Cone-shaped teeth	650
	Radiotherapy during childhood	Stunted tooth development	52
		C. *Macrodontia (Larger Than Normaf Teeth)*	
••	**Fusion**	[olning of two tooth germs	74
••	**Gemination**	Incomplete splitting of a tooth germ	74
•	Idiopathic macrodontia		73
	Facial hemihyperplasia	Affected side only; nondental tissues also enlarged	37
	Gigantism	Abnormally tall stature	718
		D. Microdontia (Smaller Than Normaf Teeth)	
▪▪▪	**Supernumerary teeth**	Mesiodens; fourth molars	69
•••	Peg-shaped lateral incisors	Cone-shaped teeth	73

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
		D. Microdonlia (Smaller Than Normal Teetht-e-continued	
▪▪	**Dens invaginatus**	Cone-shaped teeth; tendency for pulpal death and periapical pathosis	80
	Cleft lip and palate	**Lateral incisor or canine**	2
•	**Idiopathic microdontia**	Usually generalized	73
	Hereditary hypohidrotic ectodermal dysplasia	Cone-shaped teeth; sparse, blond hair; diminished sweating	644
	Radiotherapy during childhood	Stunted tooth development	52
	Congenital syphilis	**Hutchinson's incisors**	170
	Hypopituitarism	Associated dwarfism	717
		E. *Malformed Crown*	
•••	Mesiodens and other **supernumeraries**	**Cone-shaped teeth or microdont**	69
••	**Environmental enamel** hypoplasia	Examples; high fever during tooth development	50
••	Peg-shaped lateral incisors	Cone-shaped teeth	73
••	**Dens invaginatus**	Cone-shaped teeth; tendency toward pulpal death and periapical pathosis	80
••	Turner's tooth	Infection or trauma to associated primary tooth	51
••	**Fusion or gemination**	"Double" tooth	74
	Talon cusp	Extra cusp on lingual of anterior tooth	78
	Dens evaglnatus	Extra cusp on occlusal of premolar tooth	78
	Amelogenesis imperfecta	**Hereditary defect in enamel formation**	89
	Dentinogenesis irnperfecta	Fracturing away of enamel due to hereditary defect in dentin formation; gray-yellow opalescent teeth; calcified pulp chambers	94
	Regional odontodysplasia	Poor tooth formation in a focal area; "ghost teeth"	99
	Congenital syphilis	Hutchinson's incisors; mulberry molars	170
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	Renal osteodystrophy	Abnormal calcium and phosphate metabolism	725
	Hypoparathyroidism	Possible associated endocrine-candidiasis syndrome	722
•	Pseudohypoparathyroidism		723
	Epidermolysis bullosa	Hereditary blistering skin disease	660
	Radiotherapy during childhood	Stunted tooth development	52
	F. *Enamel Loss After Tooth Formation*		
•••	**Caries**		
	Trauma	Fractured tooth	
•••	Attrition	Physiologic loss of tooth structure	55
•••	Abrasion	Pathologic loss of tooth structure	55
••	**Erosion**	Chemical loss of tooth structure	55
	Dentinogenesis imperfecta	Hereditary defect in dentin formation; poor junction between enamel and dentin	94
	Amelogenesis imperfecta	Hereditary defect in enamel formation; especially hypocalcified types	89
	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
	H. *Intrinsic Discoloration ("Staining") of Teeth*		
•••	Aging	Yellow-brown; less translucency	
	Death of pulp	Gray-black; less translucency	65
••	**Fluorosis**	White; yellow-brown; brown; mottled	53
	Tetracycline	Yellow-brown; yellow fluorescence	65
	Internal resorption	"Pink tooth of Mummery"	59

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CIIARACTERISTICS	PAGE
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	Dentinogenesis imperfecta	Blue-gray; translucent	94
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	Erythroblastosis fetalis	Yellow; green	64
		I. Abnormally Shaped Roots	
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•••	**Dilaceration**	Abnormal curvature	86
	Hypercementosis	**Excessive cementum production**	85
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••	**Concrescence**	Joining of teeth by cementum	74
••	Taurodontism	Enlarged pulp chambers; shortened roots	84
••	Enamel pearl	**Ectopic enamel in furcation**	82
	Benign cementoblastoma	Tumor attached to root	570
	Radiotherapy during childhood	Stunted root development	52
	Dentinogenesis imperfecta	Shortened roots; obliterated pulps	94
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		}. *Enlarged PilIp Chamber or Canal*	
	Internal resorption	**Secondary to caries or trauma**	59
••	Taurodontism	Enlarged pulp *chambers;* shortened roots	84
	Dentinogenesis imperfccta	"Shell teeth"	94
	Regional odontodysplasia	"Ghost teeth"	99
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	Dentinogenesis imperfecta	Pulpal obliteration by excess dentin	94
	Dentin dysplasia type I	Pulpal obiiteration by excess dentin; "chevron"-shaped pulp chambers	96
	Dentin dysplasia type II	Pulpal obiiteration of primary teeth; pulp stones in permanent teeth	98
		L. *Thickened Periodontal Ligament*	
•▪•	Periapical abscess	Focal thickening at apex of nonvital tooth; painful. especially on percussion of involved tooth	121
▪▪▪	Current orthodontic therapy		
	Increased occlusal function		
	Systemic sclerosis (scleroderma)	Generaiized widening	692
	Sarcoma or carcinoma infiltration	Especially osteosarcoma; localized to teeth in area of tumor	576
		M. *Generalized Loss of Lamina Dura*	
	Hyperparathyroidism	Calcium removed from bones; bone may have "ground glass" appearance	724
	Osteomalacia	Vitamin 0 deficiency in adults	713
	Paget's disease of bone	"Cotton wool" change hides lamina dura	542
	Fibrous dysplasia	"Ground glass" change hides lamina dura	553

FREQUENCY OF OCCURRENCE	LESION OR CONDITION	COMMENTS OR SPECIAL CHARACTERISTICS	PAGE
		N. *Premature Exfoliation of Teeth*	
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••	Aggressive periodontitis	Premature alveolar bone loss	154
	Immunocompromised states	AIDS, leukemia, chemotherapy	239
••	Diabetes mellitus	Increased susceptibility to infection and severity of periodontitis	728
	Osteomyelitis	Bone **destruction loosening teeth**	126
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	Langerhans cell disease	"Histiocytosis X": eosinophilic granuloma; premature **alveolar bone loss**	513
	Dentin dysplasia type I	"Rootless teeth"	96
	Regional odontodysplasia	"Ghost teeth"	99
	Papillon-Lefevre syndrome	Palmar and plantar hyperkeratosis: premature periodontitis	156
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