Benign Tumors of the Oral Cavity

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This chapter is concerned with the clinical features, diagnosis, and management of localized nonmalignant growths of the oral cavity. A variety of lesions of miscellaneous etiologies are discussed, many of which are not true neoplasms. Tissue enlargements attributable to irritation or injury represent a hyperplastic reaction and are collectively grouped as “reactive proliferations.”

If left untreated, some of the lesions discussed in this chapter will lead to extensive tissue destruction and deformity whereas others will interfere with mastication and will become secondarily infected following masticatory trauma. Regardless, the major clinical consideration in the management of all of these tumors is to identify their benign nature and to distinguish them from potentially life-threatening malignant lesions. Since this decision usually can be made with certainty only by microscopic examination of excised tissue, biopsy is generally an essential step.1

\section*{NORMAL STRUCTURAL VARIANTS}

Structural variations of the jaw bones and overlying oral soft tissues are sometimes mistakenly identified as tumors, but they are usually easily recognized as within the range of normal variation for the oral cavity; biopsy in these cases is rarely indicated. Examples of such structural variants are ectopic lymphoid nodules,2 or “oral tonsils” (small and slightly reddish nodular elevations of a localized area of the oral mucosa as distinct from the pharyngeal mucosa); tori; a pronounced retro-molar pad remaining after the extraction of the last molar teeth; localized nodular connective-tissue thickening of the attached gingiva; the papilla associated with the opening of Stensen’s duct; a circumvallate dorsum of the tongue; and sublingual varicosities in older individuals.

Localized nodular enlargements of the cortical bone of the palate (torus palatinus) and jaws (torus mandibularis) occur frequently3 and are considered to be normal structural variants that are analagous to the spurs encountered on other bones (eg, on the malleoli of the tibia and fibula) (Figure 7-1). The lack of obvious irritants for most tori and the negligible growth of most tori after an initial slow but steady period of development also suggest that they are usually neither inflammatory hyperplasias nor neoplasms. Histologically, tori consist of layers of dense cortical bone-covered periosteum and an overlying layer of thin epithelium, with minimal rete peg development.

Tori may pose a mechanical problem in the construction of dentures; they are frequently traumatized as a result of their prominent position and thin epithelial covering, and the resulting ulcers are slow to heal. Rarely, tori on the palate or lingual mandibular ridge may become sufficiently large to interfere with eating and speaking. Unless a torus is exceptionally large, its surgical removal (when dictated by mechanical concerns or by a patient’s anxiety) is not a major procedure, provided that splints or stents are fabricated beforehand to provide a protective dressing during healing.

Similar nodular growths or exostoses arise on the buccal aspect of the maxillary and mandibular alveolae and must be differentiated from bony hyperplasia secondary to a chronic periapical abscess. Nodular bony enlargements of the alveolus also can occur in fibrous dysplasia and in Paget’s disease, in which they represent superficial evidence of a more generalized bony dysplasia.

The mylohyoid ridge, located just lingual to the third molars, may be traumatized, resulting in ulceration of the overlying mucosa. This focus of ulceration is painful and can be subject to infection, leading to osteomyelitis. Perhaps the most common insult to this area is intubation for general anesthesia.

Biopsy specimens from oral and perioral tissues, like those from any regional tissue, may contain normal structures that are unique to that area, but such structures have occasionally been mistakenly identified as an abnormality or even as a malignancy. For example, the organ of Chievitz (a group of epithelial cell nests typically located adjacent to the temporal fossa and the long buccal nerve) has in a number of cases been incorrectly diagnosed as a perineuronal invasion of cells from an oral carcinoma,4 leading to a second and unnecessarily wider surgical excision. In similar fashion, pseudopituitary hypomatiomatous hyperplasia, an exuberant but common benign proliferation of the oral epithelium, has been overdiagnosed as invasive carcinoma.

\section*{INFLAMMATORY (REACTIVE) HYPERPLASIAS}

The term “inflammatory hyperplasia” is used to describe a large range of commonly occurring nodular growths of the oral mucosa that histologically represent inflamed fibrous and granulation tissue. The size of these reactive hyperplastic masses may be greater or less, depending on the degree to which one or more of the components of the inflammatory reaction and healing response are exaggerated in the particular lesion. Some are predominantly epithelial overgrowths with only scanty connective-tissue stroma; others are fibromatous with a thin epithelial covering and may exhibit either angiomatosus, desmoplastic (collagenous), or fibroblastic features. In many lesions, different sections may reveal examples of each of these histologic patterns. Like scar tissue, some inflammatory hyperplasias appear to mature and become less vascular (paler and less friable) and more collagenous (firmer and smaller) with time. Others appear to have a high proliferative ability for exophytic growth until they are excised.

This variability of histologic appearance is reflected in the wide range of clinical characteristics that inflammatory hyperplasias show and in the clinical names many of them have acquired that suggest a specific etiology or natural history. Names such as “fibroma” and “papilloma” are therefore often used to describe these lesions even though there is no evidence to suggest a neoplastic etiology. The major etiologic factor for these lesions is generally assumed to be chronic trauma (such as that produced by ill-fitting dentures, calculus, overhanging dental restorations, acute or chronic tissue injury from biting, and fractured teeth), and chronic irritants can be convincingly demonstrated in many cases (eg, palatal papillary hyper-
plasia associated with aged maxillary dentures). With some of these lesions, (eg, pregnancy epulis and the central giant cell tumor associated with hyperparathyroidism), the levels of circulating hormones also undoubtedly play a role. The majority of lesions occur on the surface of the oral mucous membrane, where irritants are quite common. Two deeper lesions (pseudosarcomatous fasciitis and giant cell reparative granuloma of bone) are also classified as inflammatory hyperplasias, on the basis of their histologic structure and clinical behavior. As surface outgrowths of the oral mucous membrane, most inflammatory hyperplasias are subject to continual masticatory trauma and frequently are ulcerated and hemorrhagic. Dilated blood vessels, acute and chronic inflammatory exudates, and localized abscesses are additional reasons for the swollen, distended, and red to purple inflamed appearance of some inflammatory hyperplasias. Epithelial hyperplasia frequently produces a lesion with a textured surface or an area of mucosa resembling carpet pile. Erosion of the underlying cortical bone rarely occurs with inflammatory hyperplasia of the oral mucosa; when it is noted, there should be a strong suspicion that an aggressive process or even malignancy is involved, and a section of the affected bone should be included with the biopsy specimen.

Unless otherwise specified in the following description of lesions of this type, excisional biopsy is indicated except when the procedure would produce marked deformity; in such a case, incisional biopsy is mandatory. If the chronic irritant is eliminated when the lesion is excised, the majority of inflammatory hyperplasias will not recur. This confirms the benign nature of these lesions (as would be expected from their histologic structure).

The following are examples of inflammatory hyperplasias: fibrous inflammatory hyperplasias (clinical fibroma, epulis fissuratum, and pulp polyp); palatal papillary hyperplasia; pyogenic granuloma; pregnancy epulis; giant cell granuloma (giant cell epulis and central giant cell tumor of the jaw); pseudosarcomatous fasciitis; proliferative myositis; and pseudoepitheliomatous hyperplasia.

**Fibrous Inflammatory Hyperplasias and Traumatic Fibromas**

**FIBROMA, EPULIS FISSURATUM, AND PULP POLYP**

Fibrous inflammatory hyperplasias may occur as either pedunculated or sessile (broad-based) growths on any surface of the oral mucous membrane (Figure 7-2). They are called fibromas if they are sessile, firm, and covered by thin squamous epithelium. On the gingiva, a similar lesion is often referred to as an epulis5,6 (Figure 7-3). The majority remain small, and lesions that are > 1 cm in diameter are rare. An exception to this rule occurs with a lesion that is associated with the periphery of ill-fitting dentures,7 the so-called epulis fissuratum, in which the...
growth is often split by the edge of the denture, one part of the lesion lying under the denture and the other part lying between the lip or cheek and the outer denture surface. This lesion may extend the full length of one side of the denture. Many such hyperplastic growths will become less edematous and inflamed following the removal of the associated chronic irritant, but they rarely resolve entirely. In the preparation of the mouth to receive dentures, these lesions are excised to prevent further irritation and to ensure a soft-tissue seal for the denture periphery. Pulp polyps represent an analogous condition (chronic hyperplastic pulpitis) involving the pulpal connective tissue, which proliferates through a large pulpal exposure and fills the cavity in the tooth with a mushroom-shaped polyp that is connected by a stalk to the pulp chamber. Masticatory

**FIGURE 7-2**  
A, Pedunculated fibrous inflammatory hyperplasia of the cheek, possibly associated with dental trauma. B and C, On biopsy, a comparable soft nodular swelling of the lip proved to be a small benign growth made up of mature fat cells (lipoma). (B and C courtesy of Gary Cohen, DMD, Philadelphia, Pa.)

**FIGURE 7-3**  
Three examples of inflammatory hyperplasia affecting the gingiva. A, A fibrous epulis associated with calculus. B, Generalized hyperplasia of the gingivae as a result of local irritants in a brain-damaged child maintained on phenytoin (Dilantin). C, A pregnancy epulis in an otherwise healthy dental arch; oral hygiene was excellent and the epulis was associated with a “food pack” area that developed after loss of the mandibular first molar. The lesion resolved after delivery.
pressure usually leads to keratinization of the epithelial covering of these lesions. Characteristically, pulp polyps (like granulation tissue) contain few sensory nerve fibers and are remarkably insensitive. The crowns of teeth affected by pulp polyps are usually so badly destroyed by caries that endodontic treatment is not considered; however, when restorative considerations do not preclude it, root canal therapy can be satisfactorily completed on these teeth after the extirpation of the polyp and remaining pulp tissue.

The differential diagnosis of fibrous inflammatory hyperplasia should include consideration of the possibility that the lesion is a true papilloma (a cauliflower-like mass made up of multiple fingerlike projections of stratified squamous epithelium with a central core of vascular connective tissue) or a small verrucous carcinoma. Multiple oral papillomatous lesions also may be virus-induced warts (see “Benign ‘Virus-Induced Tumors”) or one feature of a syndrome with more serious manifestations in other organs (eg, acanthosis nigricans or ichthyosis hystrix). On the dorsal surface of the tongue, nodular lesions may represent scars, neurofibroma, and granular cell tumor as well as fibrous inflammatory hyperplasia. Both pedunculated and broad-based nodules on the pharyngeal surface of the tongue are usually lymphoid nodules or cystic dilations of mucous gland ducts (see Figure 7-3, C). Condyloma latum, one of the characteristic oral lesions of secondary syphilis, has been reported to involve the intraoral mucosa.

Fibrous inflammatory hyperplasias have no malignant potential, and recurrences following excision are almost always a result of the failure to eliminate the particular form of chronic irritation involved. The occasional report of squamous cell carcinoma arising in an area of chronic denture irritation, however, underlines the fact that no oral growth, even those associated with an obvious chronic irritant, can be assumed to be benign until proven so by histologic study. Thus, whenever possible, all fibrous inflammatory hyperplasias of the oral cavity should be treated by local excision, with microscopic examination of the excised tissue.

**PALATAL PAPILLARY HYPERPLASIA**

Palatal papillary hyperplasia (denture papillomatosis) is a common lesion with a characteristic clinical appearance that develops on the hard palate in response to chronic denture irritation in approximately 3 to 4% of denture wearers. Full dentures in which relief areas or “suction chambers” are cut in the palatal seating surface appear to be the strongest stimuli, but the lesion is also seen under partial dentures, and occasional case reports have described the lesion in patients who have never worn dentures.

The palatal lesion is usually associated with some degree of denture sore mouth (stomatitis) due to chronic candidal infection, which influences the appearance of the palatal hyperplasia. When complicated by candidal infection, the lesion may be red to scarlet, and the swollen and tightly packed projections resemble the surface of an overripe berry. Such lesions are friable, often bleed with minimal trauma, and may be covered with a thin whitish exudate. When the candidal infection is eliminated, either by removing the denture or by topical administration of an antifungal agent, the papillary lesion becomes little different in color from the rest of the palate and consists of more or less tightly packed nodular projections. If tiny, the nodular projections simply give a feltlike texture to that portion of the palate, and the lesion may even pass unnoticed unless it is stroked with an instrument or disturbed by a jet of air.

The microscopic appearance of these lesions is little different from that of “papillomas” elsewhere in the mouth although the degree of branching and polypoid proliferation that develop on the epithelial surface occluded by the denture is often quite surprising. Low-power examination of these lesions demonstrates their exophytic nature, and neither epithelial invasion of the submucosa nor resorption of the palatine bone occurs, even under large or long-standing lesions. Despite their sometimes bizarre clinical appearance, these lesions have almost no neoplastic potential, a finding that is borne out by the absence of atypia and cellular dysplasia in biopsy specimens.

If the alveolar ridges are surgically prepared for new dentures, papillary hyperplasia lesions are usually excised or removed (by electrocautery, cryosurgery, or laser surgery), and the old denture or a palatal splint is used to maintain a postoperative surgical dressing over the denuded area.

If florid papillomatosis of the palate occurs or persists in the absence of dentures, the differential diagnosis should also consider several granulomatous diseases that may manifest intraorally in this fashion (eg, infectious granulomas, Cowden disease, and verrucous carcinoma), particularly when the papillary lesions are white and extend beyond the palatal vault and onto the alveolar mucosa.

**Pyogenic Granuloma, Pregnancy Epulis, and Peripheral Ossifying Fibroma**

Pyogenic granuloma is a pedunculated hemorrhagic nodule that occurs most frequently on the gingiva and that has a strong tendency to recur after simple excision (Figure 7-4). Chronic irritation as a causative factor for these lesions may sometimes be hard to identify, but the fact that they are usually located close to the gingival margin suggests that calculus,

![](image-url)
food materials, and overhanging margins of dental restorations are important irritants that should be eliminated when the lesion is excised. Their friable, hemorrhagic, and frequently ulcerated appearance correlates with their histologic structure. They are comprised of proliferating endothelial tissue, much of which is canalized into a rich vascular network with minimal collagenous support. Polymorphs, as well as chronic inflammatory cells, are consistently present throughout the edematous stroma, with microabscess formation. Despite the common name for the lesion, a frank discharge of pus is not present; when such a discharge occurs, one is probably dealing with a fistula from an underlying periodontal or periapical abscess, the opening of which is often marked by a nodule of granulation tissue.

Identical lesions with the same histologic structure occur in association with the florid gingivitis and periodontitis that may complicate pregnancy. Under these circumstances, the lesions are referred to as pregnancy epulis or pregnancy tumor (see Figure 7-3, C). The increased prevalence of pregnancy epulides toward the end of pregnancy (when levels of circulating estrogens are highest) and the tendency for these lesions to shrink after delivery (when there is a precipitous drop in circulating estrogens) indicate a definite role for these hormones in the etiology of the lesion. Like pregnancy gingivitis, these lesions do not occur in mouths that are kept scrupulously free of even minor gingival irritation, and local irritation is clearly also an important etiologic factor. The relatively minor degree of chronic irritation that may be necessary to produce a pregnancy epulis is noteworthy.

Both pyogenic granulomas and pregnancy epulides may mature and become less vascular and more collagenous, gradually converting to fibrous epulides. Similar lesions also occur intraorally in extragingival locations. Histologically, differentiation from hemangioma is important.

A lesion that is closely related to pyogenic granulomas and peripheral giant cell granulomas (see below) is the peripheral ossifying fibroma. This lesion is found exclusively on the gingiva; it does not arise in other oral mucosal locations. Clinically, it varies from pale pink to cherry red and is typically located in the interdental papilla region. This reactive proliferation is so named because of the histologic evidence of calcifications and ossifications that are seen in the context of a hypercellular fibroblastic stroma. Like pyogenic granulomas, peripheral ossifying fibromas are commonly encountered among pregnant women.

The existence of these lesions indicates the need for a periodontal consultation, and treatment should include the elimination of subgingival irritants and gingival “pockets” throughout the mouth, as well as excision of the gingival growth. Small isolated pregnancy tumors occurring in a mouth that is otherwise in excellent gingival health may sometimes be observed for resolution following delivery, but the size of the lesion, episodes of hemorrhage or superimposed acute necrotizing ulcerative gingivitis, and the presence of a generalized pregnancy gingivitis usually dictate treatment during pregnancy. When possible, surgical and periodontal treatment should be completed during the second trimester, with continued surveillance of home care until after delivery.

**Giant Cell Granuloma (Peripheral and Central)**

Giant cell granuloma occurs either as a peripheral exophytic lesion on the gingiva (giant cell epulis, osteoclastoma, peripheral giant cell reparative granuloma) or as a centrally located lesion within the jaw, skull, or facial bones (Figures 7-5, A, and 7-6). It was first described (by Jaffe) as central giant cell reparative granuloma. Both peripheral and central lesions are histologically similar and are considered to be examples of benign inflammatory hyperplasia in which cells with fibroblastic, osteoblastic, and osteoclastic potentials predominate. The
lesions are highly vascular; hemorrhage is a prominent clinical and histologic feature and also contributes a brown stain to the less common central lesions (Figure 7-7; see also Figure 7-5, B and C). True giant cell neoplasms, such as the giant cell tumor that occurs in the humerus and femur, rarely occur in the jaw and usually occur only as a complication of Paget’s disease (see “Paget’s Disease of Bone,” later in this chapter).

Peripheral giant cell granulomas are five times as common as the central lesions. Central lesions occur preferentially in the mandible, anterior to the first molar, and often cross the midline. Several large series of both peripheral and central giant cell granulomas have been reported in the literature. The histologic structure of these lesions has been studied in detail, as have their radiographic and computed tomo-

An important consideration in the management of these lesions is the necessity to search for evidence of hyperparathyroidism in all patients with histologically confirmed giant cell lesions of the jaw. There are documented examples of parathyroid lesions having been discovered as a result of blood and urine chemistry studies requested by a dentist following diagnosis of a giant cell lesion. The frequency with which this is likely to happen is probably quite low since in most series of hyperparathyroidism, lesions of the jaw have been among the last clinical manifestations of the disease to appear. Fewer than 10% of patients with hyperparathyroidism have radiographically visible cystic jaw lesions (see Figure 7-8) or even “loss of the lamina dura” (another effect of hyperparathyroidism, often used clinically to screen for the disease). Serum calcium, phosphorus, and alkaline phosphatase determinations should be requested prior to surgical removal of a jaw bone lesion that is radiographically compatible with a giant cell granuloma and immediately following the histologic diagnosis of central giant cell granuloma. Hyperparathyroidism may be primary, in which case there is a functional adenoma of the parathyroid glands, or secondary to renal disease, in which case renal osteodystrophy evolves as a consequence of tubular electrolyte retention abnormalities. In both cases, serum calcium is elevated, and phosphate is decreased. Parathormone levels are elevated.

In large lesions of the jaw bone, the chance that a biopsy specimen is not representative of the entire lesion is high, particularly since the pathologist is usually supplied with multiple small fragments curetted from the bony cavity rather than a solid specimen. In the interpretation of the results of the biopsy specimen analysis, consideration should always be given to the possibility that granulomatous giant cell-containing tissue may represent either a normal reparative response to some other bone lesion or an inflammatory hyperplasia.

The recurrence rate of central giant cell granulomas after initial conservative surgical therapy (curettage) is reported as 12 to 37%; repeat curettage usually prevents further recurrence. On rare occasions, some giant cell lesions of the jaws behave more aggressively and may eventually require segmental jaw resection with a margin of normal tissue. Debate continues as to the validity of the histologic criteria that have been proposed to distinguish these more aggressive tumors and curettage with cryosurgery of the walls of the bony cavity is advised by some authors for any recurrent giant cell lesion. There is some evidence that the intralesional injection of steroids will cause the resolution of giant cell lesions of the jaws; however, a large controlled clinical series has yet to be reported.

**Pseudosarcomatous Fasciitis (Nodular Fasciitis) and Proliferative Myositis**

Pseudosarcomatous fasciitis, a non-neoplastic connective-tissue proliferation, usually occurs on the trunk or extremities of young adults; it appears as a rapidly growing nodule that histologically imitates a malignant mesenchymal neoplasm but that clinically behaves benignly. Many cases have been origi-
nally mistaken as sarcomas due to the spindle cell nature and cellularity. Nodular fasciitis has distinctive microscopic features that allow for the diagnosis, and the predominant cell type is the myofibroblast. Similar lesions have been described intraorally and in the head and neck regions.\(^{30,31}\)

Proliferative myositis\(^ {32}\) and focal myositis\(^ {33,34}\) are lesions of skeletal muscle that have similar clinical features that are identified on the basis of the histologic picture. Rare cases have been described in the tongue and in other neck and jaw muscles. Biologically, proliferative myositis is a reactive fibroblastic lesion that infiltrates around individual muscle fibers. Despite the nomenclature, these lesions are not inflamed histologically.

**Pseudoepitheliomatous Hyperplasia**

Pseudoepitheliomatous hyperplasia is a rather common exuberant oral epithelial response in which the rete pegs are extended deeply into the underlying connective tissue in an irregular fashion. Keratin pearl formation may be prominent, but other signs of cellular atypia characteristic of carcinoma are absent. Neutrophilic infiltration about the elongated rete pegs is also prominent, in contrast to carcinoma. Sections may show isolated clumps of epithelial cells in the depth of the lesion, where the plane of sectioning cuts across long narrow rete pegs. However, true neoplastic invasion does not occur.

Clinically, lesions exhibiting pseudoepitheliomatous hyperplasia may be indistinguishable from epidermoid carcinoma, and if unnecessary surgery and radiation are to be avoided, the pathologist diagnosing the biopsy specimen must be familiar with the existence of this bizarre type of epithelial hyperplasia that is relatively common in the oral cavity. On occasion, experienced oral pathologists may be hesitant in deciding whether a particular lesion features this change or whether it is actually a carcinoma, despite the fact that morphometric analysis of the two lesions clearly differentiates them on the basis of size and shape of the squamous epithelial nuclei.\(^ {35}\)

Two oral lesions—granular cell tumor of the tongue and keratoacanthoma of the lip (both of which are described later in this chapter)—may exhibit pseudoepitheliomatous hyperplasia along the periphery of the lesion, and errors of diagnosis in which these lesions are wrongly identified as carcinoma are unfortunately not uncommon. The submission of a biopsy specimen that includes the entire lesion and the accurate documentation of the history and clinical appearance of the lesion can significantly help the pathologist recognize pseudoepitheliomatous hyperplasia. This change is also commonly seen in epulis fissuratum, in granulomatous inflammatory lesions attributable to tuberculosis or deep invasive fungi, in the gingival sulcus in cases of periodontitis (to a lesser degree), and (occasionally) in association with tumors such as malignant lymphoma. The pathogenesis of pseudoepitheliomatous hyperplasia has not been elucidated; the change may be related to the production of cellular growth factors by adjacent cells.\(^ {36}\)

Like other inflammatory hyperplasias, pseudoepitheliomatous hyperplasia is cured by local excision, provided that the chronic initiating irritant is also eliminated.

**Benign Lymphoid Hyperplasia**

Unencapsulated lymphoid aggregates that are normally present in the oral cavity (primarily on the soft palate, the foliate
papillae on the posterolateral aspects of the tongue dorsum, and the anterior tonsillar pillar) can increase in size as a result of benign (reactive) processes as well as lymphoid neoplasms. In the absence of other evidence of lymphoid disease, diagnosis of intraoral swellings of this type may be difficult even when adequate biopsy specimens are obtained. The differential diagnosis of such swellings includes benign (follicular) lymphoid hyperplasia of the palate;37,38 reactive hyperplasia of a buccal, facial, or submandibular lymph node, possibly associated with a chronic periapical or periodontal infection; viral infection (eg, Epstein-Barr virus) or a specific bacterial infection (eg, mycobacteria, Rochemela); and lymphoproliferative disease or lymphoma. Histologic criteria based on architectural, cytologic, and immunologic (leukocyte monoclonal antigen-antibody reactions) features of the lymphoid aggregate have been described in recent years.38,39

▼ HAMARTOMAS

Hamartomas are tumorlike malformations characterized by the presence of a cellular proliferation that is native to the part but that manifests growth cessation without potential for further growth.40 On the one hand, hamartomas are to be distinguished from malformations such as extra digits, supernumerary teeth, and ectopic salivary gland tissue, in which excessive tissue is present in its usual histologic relationship. On the other hand, hamartomas are to be distinguished from true benign tumors that have a relatively unlimited capacity for expansive growth (which may continue after the exciting agent has ceased to operate).

Hamartomas are usually congenital and have their major period of growth when the rest of the body is growing. Once they have achieved their adult dimensions, they do not extend to involve more tissue and rarely increase in size unless trauma, thrombosis, or infection cause edema, inflammatory infiltration, and filling of new vascular channels. They are also to be distinguished from the excessive proliferation of reparative tissue described earlier in this chapter (see “Inflammatory [Reactive] Hyperplasias”) and are usually easily separated histologically from such lesions. Hamartomas are found in many tissues of the body, and a tendency to such malformations is often hereditary. Individual oral hamartomas, therefore, often occur in association with other gross and microscopic developmental abnormalities that assist considerably in their diagnosis.

Hemangioma (both solitary and when found in association with other developmental anomalies in the various angiomatosis syndromes), lymphangioma, glomus tumor, nevi, granular cell tumor of the tongue and granular cell epulis, neuromas of the type III multiple endocrine neoplasia (MEN III) syndrome, fibrous dysplasia of bone, cherubism, various odontomas, some odontogenic tumors, and (possibly) the melanotic neuroectodermal tumor of infancy are all examples of hamartomatous development in the oral region. To a greater or lesser extent, these lesions all possess the characteristics of hamartomas. These variants aside, the treatment of hamartomas is essentially a cosmetic problem, and the complete removal of these lesions is often neither desirable nor possible. Neoplastic and malignant transformation are unusual in hamartomas although some have a greater tendency in this regard (eg, neurofibromas; see “Nerve Sheath Tumors and Traumatic Neuroma,” below).

Teratomas (which are often thought of as malformations but which are actually neoplasms of developing tissues) are mentioned at the end of this section, in comparison with hamartomas (see “Teratomas and Dermoid Cysts,” below).

Hemangioma and Angiomatous Syndromes

Hemangiomas are tumorlike malformations composed of seemingly disorganized masses of endothelium-lined vessels that are filled with blood and connected to the main blood vascular system.41 They have been described in almost all locations in and about the oral cavity and face and may involve deep structures such as the jaw and facial bones, salivary glands, muscles,32 and the temporomandibular joint, as well as the surface mucosa and skin. They may occur as isolated lesions in the oral cavity (Figure 7-10), as multiple lesions affecting different parts of the body, and in association with other developmental anomalies in the various angiomatous syndromes described below. They range from simple red patches (nevus flammeus, port-wine stain)43 (Figure 7-11, A) or birthmarks (nongeneti-
cally transmitted embryologic mishaps), which do not raise the mucosal or skin surface, to large fungating masses, which bury teeth and cause serious deformity and disfiguration. Small lesions may be clinically indistinguishable from pyogenic granulomas and superficial venous varicosities. Both cavernous and capillary types have been described; the former consists of relatively large blood-filled lakes, and the latter consists of masses of proliferating vessels of capillary dimension. In both cases, there is a simple endothelial lining to the vascular channels and little connective-tissue stroma. Such lesions characteristically bleed profusely when traumatized.

Many hemangiomas are evident at birth, and they frequently increase in size with general bodily growth. The filling of previously empty vascular channels also accounts for an increase in the size of these lesions, and such changes sometimes occur very rapidly following trauma. While such growth is to be distinguished from neoplasia, this distinction may not be easy to make clinically, and the clinician will quite reasonably sometimes be concerned that what is assumed to be a hamartomatous lesion may be developing a neoplastic tendency. Diascopy is the technique of applying pressure to a suspected vascular lesion to visualize the evacuation of coloration, a finding that supports the fact that patent blood-filled spaces constitute the lesion. If compression fails to evacuate the pigmentation, the lesion could be extravasated blood or some other type of intrinsic or extrinsic pigment that has been deposited in the tissues (see Chapter 6, “Pigmented Lesions of the Oral Mucosa”).

When located on the surface of the skin or oral mucous membrane, hemangiomas are usually readily identified. Large lesions are warm and may even be pulsatile if associated with a large vessel. Hemangiomas of the tongue (see Figure 7-10) and gingiva are often covered by unusually rugose epithelium. Differentiation should be made from vascular inflammatory hyperplasias, sublingual varicosities (varicosities of the superficial veins on the ventral surface of the tongue that are common after 50 years of age), pigmented nevi, telangiectasias of various etiologies, and hematomas. Centrally located hemangiomas must be distinguished from the many osteolytic tumors and cystlike lesions that affect the jaws, as well as from both congenital and acquired arteriovenous aneurysms of the jaw. Care should be taken in excising or performing biopsies on hemangiomas, partly because of their tendency to uncontrolled hemorrhage and partly because of the difficulty of knowing the extent of the lesion, only a small part of which may be evident in the mouth.

Gingival hemangiomas may connect with similar lesions in the jawbone, and radiographic examination of the bone may not always reveal an abnormality of the trabecular architecture. Most such lesions are observed clinically as multilocular radiolucencies; therefore, when this radiographic pattern is observed, the lesion should be aspirated. Some central hemangiomas of bone represent arteriovenous malformations, and the blood coursing through them is under arterial pressure. A bright red aspirate is highly suggestive of central hemangioma and requires that imaging studies be instituted to confirm the clinical impression. Computed tomography, Doppler and conventional ultrasonography, radionuclide-labeled red cell scintigraphic scanning, and superselective microangiography are used to define the extent of bony hemangiomas, and radiographic examination of the affected tissues may reveal not only bony defects but also phleboliths in the cheek that mark the location of abnormal vessels. Hemorrhage from centrally located hemangiomas of the jaw is especially difficult to control, and surgery on hemangiomas should be attempted only when provision has been made beforehand to control any untoward hemorrhage that may occur (typed and cross-matched blood, splints, and means of tying off branches of the external carotid artery). In general, electrocoagulation and cryosurgery cause less postoperative hemorrhage than incision with a scalpel causes.

The treatment of hemangiomas continues to be a difficult problem fraught with the danger of uncontrollable hemorrhage. Conventional surgical techniques have been largely replaced by cryosurgery and laser surgery, often preceded by the injection of sclerosing solutions. Also,
intravascular embolization with plastic spheres\textsuperscript{55,56} is now a commonly used and successful approach. Although radiation can be used to sclerose these lesions,\textsuperscript{37} the risk of inducing neoplastic and other degenerative changes\textsuperscript{58} later in life is very high, and its use is now generally contraindicated, particularly in children. Many of the reported cases of malignant change in hemangiomas undoubtedly are the results of radiation treatment. IntraleSIONal injection of corticosteroids is sometimes a successful alternative to surgery for hemangiomas in infants.\textsuperscript{39}

Hemangiomas of the skin and oral mucous membrane often coexist with similar lesions of the central nervous system and the meninges.\textsuperscript{60,61} A variety of such angiomatosyn dromes have been described, with eponyms applied to both complete and incomplete variants of each syndrome. Although the skin and oral lesions are the most deforming and disfiguring lesions, the central nervous system lesions are often associated with serious problems of epilepsy, hemiplegia, mental retardation, and retinal changes.

Sturge-Weber syndrome\textsuperscript{59} (encephalofacial or encephalotrigeminal angiomatisis) is probably the most common of these malformations (see Figure 7-11). It is characterized by angiomatosis of the face (nevus flammeus), with a variable distribution sometimes matching the dermatomes of one or more trigeminal nerve divisions; leptomeningeal angiomatis, particularly of the parietal and occipital lobes of the brain, with associated characteristic intracranial calcifications; contralateral hemiplegia; and one or more of the neurologic symptoms just mentioned. Oral changes occur in 40% of cases of this syndrome and may include massive growths of the gingiva and asymmetric jaw growth and tooth eruption sequence (due to differential blood flow to the affected area). Since many patients with this syndrome are treated for many years with phenytoin (Dilantin) as an anticonvulsant, a distinction needs to be made in these patients between gingival hypertrophy due to phenytoin and that due to angiomatous changes, particularly if gingivectomy is planned.\textsuperscript{62,63} The intraoral lesions in this syndrome classically occur on the same side of the body as other angiomas in the patient, but the classic pattern is not always found in either the distribution or the expression of the various components of the syndrome. Fortunately, this serious malformation is not of hereditary origin (compare with Rendu-Osler-Weber syndrome\textsuperscript{64} or hereditary hemorrhagic telangiectasia).

Other (rarer) angiomatosyndromes are Maffucci’s syndrome\textsuperscript{65,66} (multiple angioma of the skin and enchondromas of bone) and von Hippel-Lindau disease\textsuperscript{67} (a familial syndrome involving hemangioblastomas in the retina and cerebellum, pancreatic and renal cysts, renal adenomas, hepatic hemangiomas, and multiple endocrine neoplasia)\textsuperscript{68} (see pertinent section). Conditions such as Sturge-Weber syndrome and von Hippel-Lindau disease, which involve a visible congenitally acquired external lesion (ie, a birthmark or “phakos”) and other systemic anomalies, are sometimes referred to as phakomatoses.

Many reviews and case reports\textsuperscript{60,69,70} of both isolated oral hemangiomas and the various angiomatosyndromes are available and attest to the problems associated with treating these non-neoplastic lesions.

**Lymphangioma**

Lymphangioma is histologically and etiologically similar to hemangioma, except that the abnormal vessels are filled with a clear protein-rich fluid containing a few cells (lymph) rather than blood.\textsuperscript{60,70–72} Lymphangiomas may occur alone or (more frequently) in association with hemangiomas or other anomalous blood vessels with which the lymphangiomaticus vessels are anastomosed. The tongue is the most common oral location for this lesion. Together with hemangioma, lymphangioma is an important cause of congenital macroglossia.\textsuperscript{73}

Lymphangiomas are frequently without a clear anatomic outline and present on clinical examination as soft masses that dissect tissue planes and turn out to be more extensive than anticipated. Large lymphangiomas spreading into and distending the neck are referred to as cystic hygromas.\textsuperscript{74} Differential diagnoses of lymphangiomas of the tongue include hemangioma, congenital hypothyroidism, mongolism, amyloidosis, neurofibromatosis, various storage diseases (eg, Hurler’s syndrome and glycogen storage disease), and primary muscular hypertrophy of the tongue, all of which may cause macroglossia. The differential diagnosis should also consider certain anomalies in the neck, including various inclusion cysts, cellulitis, and plunging ranula, which large angiomas of the neck may simulate. Abnormalities of the mucosa overlying a lymphangioma may give the appearance of a localized glositis and may draw attention to the presence of a small lesion buried in the tongue. The typical clinical appearance of oral lymphangioma is that of a racemose surface. The problems of managing lymphangiomas are similar to those of managing hemangiomas.

In neonates, localized superficial cysts of the alveolar mucosa with a lymphangiomaticus histologic picture are described as alveolar lymphangiomas.\textsuperscript{71} Such lesions, which are more common in black neonates than in white neonates and which are probably often misidentified as eruption cysts or mucoceles, disappear spontaneously with chewing and with tooth eruption.

**Glomus Tumor and Other Vascular Endothelial Growths**

An unusual abnormality, glomus tumor\textsuperscript{75} (glomangioma) develops as a small painful unencapsulated nodule as a result of hamartomatous proliferation of the modified smooth-muscle pericytic cells\textsuperscript{76} found in the characteristic type of peripheral arteriovenous anastomosis known as the glomus. In addition to having a characteristic histology, these lesions also may secrete various catecholamines. The glomus tumor is rare in the mouth\textsuperscript{76,77} but can occur in the pterygoplatospotympanic region,\textsuperscript{78,79} glomus jugulare, and skull base. Glomus tumors arising in the carotid and aortic bodies may produce neck masses; they are of a different cell derivation (ie, chemosensory) and are more appropriately referred to as chemodec tomas or paragangliomas. Differentiation of the glomus tumor from other masses of proliferating vascular endothelial cells (hemangioendothelioma and hemangiopericytoma) requires special stains and considerable histopathologic diagnostic skills. Another important diagnostic feature that characterizes
at least some glomus tumors is an autosomal dominant inheritance pattern. Because of the associated pain, glomus tumors tend to be removed while still quite small.

**Granular Cell Tumor and Granular Cell Epulis**

The granular cell tumor is an important oral hamartomatous lesion (1) because of its frequent occurrence as a nodule on the tongue and as its variant form on the gingiva (congenital epulis) (Figure 7-12) or other mucosal site; (2) because of the controversy as to its nature and cytologic structure; and (3) because of the overlying pseudoepitheliomatous hyperplasia that often leads to a misdiagnosis of squamous cell carcinoma and to unnecessary radical surgery. Histologically, these lesions are composed of masses of large eosinophilic granular cells interspersed with a collagenous stroma and covered with hyperplastic epithelium.

About one-third of oral granular cell tumors occur on the tongue; those occurring elsewhere in the mouth (ie, on the palate, gum, floor of mouth, buccal mucosa, and lips) and on the skin are similar in most of their clinical features and in their appearances on light and electron microscopy. Important distinctions between lingual and extralingual granular cell tumors are (in the latter) the absence of overlying pseudoepitheliomatous hyperplasia and a female sex predilection. The large granular cells have been variously identified as of muscle cell (Abrikosov’s myocytes), histiocytic, Schwann cell, and mesenchymal origin. Immunocytochemical staining reveals that nongingival lesions of this type are.

**FIGURE 7-12** A, Congenital epulis arising from the upper and lower jaw of a 2-day-old infant. B, Section of one of these tumors; both showed identical histologic structure despite different clinical appearances. The lesions are composed of masses of granular eosinophilic cells characteristic of the granular cell–type of congenital epulis. (Reproduced with permission from Blair A, Edwards DM. Congenital epulis of the newborn. Oral Surg Oral Med Oral Pathol 1977;43:687) C, Similar cells from a granular cell myoblastoma presenting as a painless indurated mass in the anterior third of the tongue of a 49-year-old man. (Courtesy of E.P. Rossi, DDS, MS, Cleveland, Ohio)
immunologically reactive for S-100 protein and myelin but negative for myogenous and histiocytic markers and that they are probably derived from Schwann cells or their mesenchymal precursors.

Quite innocent-looking and often long-standing tongue nodules in biopsy specimens from adults may turn out to be granular cell tumors. Treatment of these oral lesions, both on the tongue and in extralingual locations, is by local excision. The differential diagnosis for congenital epulis includes other hamartomatous and hyperplastic oral mucosal lesions, odontogenic tumors, and ectopic tooth germs. Multiple and familial occurring oral granular cell tumors have been reported on several occasions. In contrast to the prevalence of the granular cell tumor, true neoplasms of the muscle of the body of the tongue (rhabdomyoma) are exceedingly rare and are positive for myogenous markers.80

Nerve Sheath Tumors and Traumatic Neuroma

The nerve sheath includes the Schwann cells, which surround individual axis cylinders; perineural fibroblasts, which form collagen networks between individual nerve fibers with their surrounding Schwann cells; and the epineurium, a sheath that envelops entire nerve trunks and that is composed of fibroblastic-type cells and collagen.60,69,83,84 Most nerve sheath tumors are true neoplasms. The developmental abnormalities (ie, hamartomas and not neoplasms) of neurofibromatosis and traumatic neuroma arise from nerve sheath cells. Neurofibromas of the oral cavity are usually solitary;85 a significant feature of neurofibroma is its tendency to be multiple and to be associated with a variety of other familial abnormalities in the syndrome of von Recklinghausen’s neurofibromatosis, an inherited autosomal dominant condition in which there is also a tendency to develop sarcoma (see the later section, “ Syndromes with Benign Oral Neoplastic or Hamartomatous Components”). Neurofibromatosis evolves as a consequence of a mutation in the NFI gene. Since 5% of patients with neurofibromatosis develop sarcoma,86 recognition of an otherwise innocent-appearing nodule in the oral cavity as a neurofibroma can be an important diagnosis.

Histologically, neurofibromas are to be distinguished from neurilemomas (tumors of the nerve sheath, or schwannomas). Neurilemomas are encapsulated S-100 protein–positive tumors that show patterns of whorled connective-tissue elements interspersed with readily recognizable axons with or without a myelin sheath. Neurilemomas also exhibit a characteristic palisading of nuclei and other suggestions of a histologic organization referred to as an organoid structure; both features are usually absent from neurofibromas and neurilemomas.87 Rarely, neurilemomas may occur in patients with neurofibromatosis. Oral lesions are usually asymptomatic and do not recur after local excision (Figure 7-13).

The term “traumatic neuroma” describes a localized exuberant growth of nerve and nerve sheath elements that develop after section or other local damage to a peripheral nerve.88

Melanotic Neuroectodermal Tumor of Infancy

Melanotic neuroectodermal tumor of infancy has been classified both as a hamartoma and as a benign neoplasm, with recent authors favoring the latter etiology.89,90 It is a rare tumor, occurring both orally and extraorally (usually in children under 6 months of age) and showing a characteristic biphasic histologic picture of melanin-containing epithelial cells lining slitlike spaces and small round cells resembling neuroblasts. Its origin is probably the neuroectoderm (the embryonic layer that contributes greatly to cranial and oral development) although its gnathic location has led some authors in the older literature to consider it to be of odontogenic origin and to use such synonyms as “melanotic ameloblastoma” and “pigmented epulis.” Theories that assign its origin to ectopic retinal epithelium have produced the synonyms “retinal anlage tumor” and “melanotic progonoma.” Recent immunohistochemical studies confirm that it is a tumor with “polyphenotypic expression of neural and epithelial markers, melanin production, and glial and rhabdomyoblastic differentiation.”89 The lesion usually protrudes into the mouth and may also involve underlying bone. The lesion does not necessarily appear pigmented clinically. It is rarely an aggressive lesion although aggressive behavior with recurrences after local excision have been described.91 Findings on magnetic resonance imaging (MRI) have been recently described.90

Fibrous Dysplasia of Bone and Albright’s Syndrome

Fibrous dysplasia of bone results from an abnormality in the development of bone-forming mesenchyme.92–94 This is manifested by the replacement of spongy bone by a peculiar fibrous tissue, within which trabeculae or spherules of poorly calcified nonlamellar bone are formed by osseous metaplasia. Histologically, a given lesion may show a great variability of pattern, with some fields that are predominantly collagenous, some that are osteoid, and others that are fully ossified and calcified.
Radiographically, the lesion will usually present varying degrees of radiopacity and lucency; some areas will resemble compact bone, and others will be cystic areas. Surgical exploration of such cystic areas usually reveals either a soft fibrous tissue or (more characteristically) a tissue that is gritty on section or curettage. Because these lesions often develop to quite a large size with few symptoms other than a slowly developing asymmetry of the bone, they may exhibit a quite dramatic deformity and apparent bony destruction upon radiographic examination. Patients may have a small solitary focus (monostotic form) or may have many bones affected with multiple lesions (polyostotic form). Rare cases exist in which the lesions of fibrous dysplasia coexist with other developmental bony defects or with extraskeletal changes, notably a blotchy cutaneous hyperpigmentation and precocious puberty. The term “McCune-Albright syndrome” (or simply “Albright’s syndrome”) has been used to describe these more dramatic cases occurring in children (see “Syndromes with Benign Oral Neoplastic or Hamartomatous Components,” below). Recently, the lesional tissues taken from patients with Albright’s syndrome have revealed a mutation in the G protein of the internal signaling pathways. Solitary foci are far more common than multiple lesions, particularly in the jaw bone. Other than the greater variety of histologic patterns and sizes of lesions seen in the polyostotic form, there is no essential difference between the two lesions.

The hamartomatous nature of the condition is exemplified by (1) the existence of congenital forms of the disease, (2) the association of fibrous dysplasia with other developmental bone problems in the same patient, (3) the frequency with which increasing size of the lesion correlates with periods of increased skeletal growth rate, (4) the association of endocrine abnormalities with bony lesions in patients with Albright’s syndrome, and (5) the rarity of malignant transformation of these lesions (considering the frequency with which fibrous dysplasia is seen). Recent reviews have stressed that malignant transformation of these lesions probably occurs more frequently than is usually believed because small foci of fibrous dysplasia are often overlooked in the examination of a patient with a malignant bone lesion. In most cases, fibrous dysplasia can be safely handled as a benign developmental anomaly, and superficial recontouring of the lesion or curettage of a large cystic lesion remains appropriate management, provided that an adequate and representative bone biopsy specimen has been obtained.96 Radiotherapy is contraindicated in the treatment of fibrous dysplasia. Radiotherapy administered in earlier decades of the twentieth century may have played a role in the rare cases of malignant transformation to fibrosarcoma or osteogenic sarcoma.

The extensive size and the nonuniform radiographic appearance of some lesions of fibrous dysplasia pose a problem to the surgeon who needs to obtain representative biopsy specimens with minimal disturbance of the lesion. Biopsy specimens of these lesions, as do other bone biopsy specimens, frequently reveal nothing more than superficial layers of reactive normal bone formation. Curettage of one of the cystic cavities usually provides material of more diagnostic value. At times, the hypercellularity, pleomorphism, and aggressiveness of the fibrous tissue in these lesions will lead the pathologist to suspect a fibrosarcoma or an osteogenic sarcoma; consideration of both the clinical behavior and the histologic appearance of the lesion is needed to arrive at a diagnosis. Fibrous dysplasia has been described in association with giant cell reparative granuloma of bone, aneurysmal bone cyst, and a number of other fibro-osseous lesions, and the coexistence of different histologic pictures in one lesion or in one patient can provide added diagnostic difficulties.

The clinical problems associated with fibrous dysplasia of bone are related to the site and extent of involvement. Many small foci probably remain unrecognized throughout life. In the long bones, deformity and fractures are common complications that often lead to the initial diagnosis of the lesion. In the jaws and other parts of the craniofacial skeleton, involvement of adjacent structures such as the cranial sinuses, cranial nerves, and ocular contents can lead to serious complications in addition to cosmetic and functional problems. Intracranial lesions arising from the cranial bones may produce seizures and electroencephalographic changes. Extension into and occlusion of the maxillary and ethmoid sinuses and mastoid air spaces is common.97 Proptosis, diplopia, and interference with jaw function also often prompt surgical intervention.

Computed tomography and technetium (Tc)-99m bone scans have proved to be of great help in the diagnosis of lesions of fibrous dysplasia.98 99 Trimming and surface contouring of the affected bone, curettage of bony cavities, and packing with bone chips remain the recommended treatments. Surgical interventions before the patient has reached puberty may actually activate these fibro-osseous lesions and should be avoided except in cases of the more disfiguring lesions. Attempts at treating advanced cases of the polyostotic form with calcitonin100 have not been greatly successful. There is laboratory evidence of increased bone turnover, increased alkaline phosphatase, and high urinary hydroxyproline levels with normal serum calcium and phosphate levels in large monostotic lesions of fibrous dysplasia and in the polyostotic form.

Opinions differ as to whether pain is a common feature of fibrous dysplasia. In the general skeleton, small lesions are undoubtedly often asymptomatic. Larger lesions associated with cortical fractures are painful and incapacitating and lead to extreme degrees of deformity in many cases. Pain is not a feature of craniofacial lesions. The extent of the deformity may be as great as that associated with untreated von Recklinghausen’s disease of bone due to hyperparathyroidism, and in the early part of this century, fibrous dysplasia was often confused with this metabolic bone disorder.

Other Benign Fibro-Osseous Lesions

Before 1970, “fibrous dysplasia” was used as an all-inclusive term for both the monostotic and polyostotic forms of fibrous dysplasia described above and for a variety of other fibro-osseous lesions, notably ossifying fibroma, cementifying fibroma, and osteoblastoma94 (Figure 7-14). Histologic studies often failed to establish definitive differences between these lesions, particularly in regard to the problems of the matura-
tion of the connective-tissue elements, the heterogeneity of large lesions, and inadequate biopsy specimens. The problem of separating these different lesions in the jaw bone is further compounded by the occurrence in the jaw of lesions with cemental as well as osseous differentiation (Figure 7-15) and the frequency of giant cell granulomas in this region. A number of papers that were published by oral pathologists during the late 1960s and early 1970s emphasized the variety of histologic appearances in fibro-osseous lesions that were derived from the periodontal membrane and distinguished them from similar lesions arising from medullary bone.101–103

The difficulty of differentiating tumors of periodontal membrane origin from tumors of medullary bone origin has long been recognized. Differentiation between the two is important because tumors of medullary bone origin usually behave in a more aggressive fashion even though they are essentially benign. The absolute proof of medullary bone origin in this group of tumors has not yet been shown, however. Benign fibro-osseous lesions of periodontal membrane origin are much more prevalent in the jaws than are fibro-osseous lesions of medullary bone origin. These latter lesions may be differentiated by clinical, radiographic, hematologic, and

**FIGURE 7-14** A, Low-power and B, high-power views of an aggressive osteoblastoma developing in association with a tooth socket. (Courtesy of D.R. Weathers, S. Muller, Emory University, Atlanta, Ga.)

**FIGURE 7-15** Large cemento-ossifying fibroma of the mandibular molar region in a 21-year-old black female with a 2-year history of localized enlargement of the body of the mandible associated with a dull throbbing pain and loosening of the teeth in this region. A, Radiographic examination revealed a large multilocular lesion extending from the third molar to the premolar area, with expansion of the bone. C, Histologic examination of the excised lesion revealed spherules of bone and cementum in a fibrous matrix. (Courtesy of T. Beckerman, DDS, Baltimore, Md.)
Diagnosis and Management of Oral and Salivary Gland Diseases

OSSIFYING FIBROMA

Differentiation of solitary lesions of ossifying fibroma and fibrous dysplasia can be quite difficult on histologic grounds alone, but the lesions generally can be distinguished if radiographic and clinical criteria are used together with an analysis of a biopsy specimen from the central part of the lesion. Fibrous dysplasia has a diffuse margin radiographically; ossifying fibroma is an expansile process with a clearly defined cortical margin (being a benign tumor). Fibrous dysplasia tends to favor the maxilla whereas ossifying fibroma occurs more often in the mandible. Both are slow growing and originate early in life, but fibrous dysplasia grows endosteally and follows the general structure of the affected bone, usually producing a thickening and irregular deformation of the bone. Ossifying fibroma, by contrast, grows into and fills cavities such as the nasal cavity and accessory sinuses and destroys surrounding bone as it enlarges. Management of the two benign lesions differs considerably. Fibrous dysplasia is treated by surface sculpting whereas ossifying fibromas are managed by surgical enucleation. Juvenile aggressive forms are seen and may require en bloc resection.

ANEURYSMAL BONE CYST, TRAUMATIC BONE CYST, AND STATIC BONE CYST

Aneurysmal bone cyst, unlike ossifying fibroma and fibrous dysplasia, occurs less frequently in the jaw bones than in the long bones and usually involves the mandible rather than the maxilla. Eighty percent of aneurysmal bone cysts occur in patients younger than 30 years of age; both sexes are equally affected. Microscopically, curedt material from the cavity resembles giant cell reparative granuloma but has more prominent vascular spaces, with evidence of old and recent hemorrhages and thrombosis and hyalinization of some of the vascular spaces. Like giant cell granuloma, it has no epithelial lining despite the common use of the word “cyst” to describe it. Aneurysmal bone cyst is to be differentiated from two other pseudocysts of the jaw: the so-called traumatic bone cyst (the name given to solitary and usually asymptomatic cavities that are found in the mandible, that are without any epithelial or other distinguishing lining and that contain only serum or are apparently empty), for which a traumatic etiology seems to be less convincingly established, and the submandibular salivary gland depression (static or latent bone cyst, or Stafne’s cyst), located below the inferior mandibular canal just anterior to the angle of the mandible, where it presents as a well-delineated radiolucency that may contain salivary gland tissue. A similar defect can be seen in the anterior mandible apical to the canine, where the sublingual gland resides, and is termed a sublingual salivary gland depression. For both the aneurysmal and traumatic bone cysts, a thorough curettage of the lesion and its walls and packing with bone chips result in the healing of the defect.

CHERUBISM

Cherubism is a rare disease of children that is characterized by bilateral painless mandibular (and often corresponding maxillary) swellings that cause fullness of the cheeks, firm protuberant intraoral alveolar masses, and missing or displaced teeth (Figure 7-16). Submaxillary lymphadenopathy is an early and fairly constant feature that tends to subside after the age of 5 years and that usually has regressed by the age of 12 years. Maxillary involvement can often produce a slightly upward turning of the child’s eyes, revealing an abnormal amount of sclera beneath them. It was the upward “looking toward heaven” cast of the eyes, combined with the characteristic facial chubbiness of these children, that prompted the term “cherubism.” Cherubism is inherited as a dominant gene, with a penetrance of nearly 100% in males and 50 to 75% in females; however, the exact cause of cherubism remains unknown, and other patterns of inheritance as well as the occurrence of cherubism in association with other syndromes have been described. The clinical appearance may vary from barely discernible posterior swellings of a single jaw to a grotesque anterior and posterior expansion of both jaws, with concomitant difficulties in mastication, speech, swallowing, and respiration. Disease activity declines with advancing age.

Radiographically, the lesions are multiple well-defined multilocular radiolucencies in the mandible and maxilla. These rarefactions begin in the posterior alveolar region and ramus and can spread anteriorly. They are irregular in size and usually cause marked destruction of the alveolar bone. Numerous displaced and unerupted teeth appear to be floating in radiolucent spaces. Serum calcium and phosphorus are within normal limits, but the serum alkaline phosphatase level may be elevated.

Histologically, the jaw lesion can bear a close resemblance to benign giant cell granuloma. Other specimens have been described as being more mature, with a greater amount of fibrous tissue and collagen and fewer giant cells. The prominent eosinophilic perivascular cuffing material noted around capillaries in these lesions has been proved to be collagen; this finding is a distinctive histologic diagnostic feature (Figure 7-17).

The reported treatment of cherubism has varied considerably, and there are advocates for each of the following methods: no active treatment, extraction of teeth in the involved areas, surgical contouring of expanded lesions, and complete curettage. Long-term longitudinal clinical studies have disclosed that the childhood lesions give way to partial or complete resolution in the adult.

Teratomas and Dermoid Cysts

Teratomas are neoplasms that are composed of a mixture of tissues, more than one of which exhibits neoplastic proliferation. They are congenitally acquired and are usually found in the ovary. Rare examples, either arising from the oral cavity or protruding into the oral cavity from the base of the skull, have been described in children. The finding of various organlike structures (ie, teeth, tissue, hair, and skin) in these tumors and their common location in the ovary may give the
Benign Tumors of the Oral Cavity

misleading impression that they are fetal malformations rather than neoplastic growths of developing tissue; the latter is the currently accepted understanding and clearly provides a more convincing explanation for oral teratomas than does the former. Teratomas that arise from the base of the skull often extend into the cranial cavity as well as the oral cavity, and newborn infants with such lesions rarely survive. No single histologic picture is characteristic although the usual appearance of disorganized neoplastic tissues of various types readily identifies the lesion to the pathologist.

Some teratomas of the ovary are primarily cystic; these are often referred to as dermoid cysts because they may include epidermal tissue and even hair follicles. Dermoid cysts of the oral cavity are most commonly encountered in the floor of the mouth although they may arise in other soft-tissue locations (Figures 7-18 and 7-19). These cysts also feature epidermal tissues and (even) hair follicles, sweat and sebaceous glands in the cyst wall, and keratin and sebum in the cyst cavity. Cysts that harbor tissues from all three germ layers are more correctly referred to as teratoid cysts.

▼ CYSTS OF THE JAWS AND BENIGN ODONTOGENIC TUMORS

Cysts of the Jaw

Cysts (ie, fluid-filled epithelial-lined cavities in the jaw bones and soft tissues of the face, floor of the mouth, and neck) may cause either intraoral or extraoral swellings that may clinically
resemble a benign tumor. Unilocular and multilocular radiolucencies discovered in the jaw bones by radiographic examination must also be differentiated from solid growths in the jaw, a distinction that cannot always be made by inspecting the radiograph. However, the majority of cysts are small, do not distend surface tissues, and are often first recognized in routine dental radiographic examinations. Others are discovered during investigation of a nonvital tooth or an acute dental abscess due to secondary infection of the cyst or by loosening of the teeth and by jaw fracture. Small isolated radiolucencies in the jaw bone that are not associated with a loss of pulp vitality are usually observed over several months for increase in size before surgical exploration. Radiolucencies that are suspected of being cysts or tumors and that are not associated with a necrotic tooth require biopsy.

Radiographic examination rarely provides a conclusive diagnosis as to the nature of a radiolucency in the jaw although it may be used to gauge the rate of growth of such lesions and to detect erosion of tooth roots and cortical destruction. These features are characteristic of aggressive benign lesions as well as malignant lesions. Contrary to traditional lore, there is no size range that separates periapical cysts from dental granulomas, and microscopic examination of periapical lesions frequently reveals tiny cystic areas and areas of epithelial proliferation in what is clinically thought to be a granuloma. Similarly, caution must be used in diagnosing even large radiolucent jaw lesions as cysts simply because they appear “spherical” on the radiograph. The differential diagnosis of multiple radiolucencies in the jaw should include consideration of multiple myeloma, Langerhans cell histiocytosis, metastatic carcinoma, giant cell granuloma and hyperparathyroidism, multiple dental granulomas, periapical cysts, cemental dysplasia, ossifying fibroma, and fibrous dysplasia. Microscopic examination of the cyst wall provides the clear diagnosis that is important to the management of the lesion, and submission of all excised tissue (including fragments scraped from the wall of the jaw cyst and periapical tissues curetted at the time of dental extraction or apicoectomy) for histopathologic examination is strongly urged.

The treatment of choice for a cyst is local excision with complete removal of the cyst lining. With larger lesions, the surgeon may decide to curet the lining through a relatively small window; removal of the lining can be expected to be incomplete, with recurrence a possibility. Alternatively, the lining of larger cysts may be sutured to the oral mucosa adjacent to the surgically created window, and the cyst may be “marsupialized.” If such a lesion is kept patent by repeated irrigation, it will cease to expand, it will not become secondarily infected, and the defect in the jaw will gradually even out.

It is beyond the scope of this chapter to include detailed discussion of the clinical, radiographic, and histologic features of each of the different types of cysts that affect the jaws and adjacent oral tissues. The reader is referred to the more extensive coverage provided in most textbooks of oral pathology and oral radiology, as well as to articles that review particular classes of cysts.

The radiographic appearance of some odontogenic and non-odontogenic cysts is illustrated in Figures 7-20, 7-21, and 7-22. The 1971 World Health Organization (WHO) classification (also the 1992 revision) of epithelial jaw cysts, which distinguishes cysts arising from the tooth germ tissues (odontogenic cysts) from those of non-odontogenic origin and also distinguishes cysts that represent an inflammatory process from those that arise “autonomously,” remains the generally accepted classification. Minor revisions of this classification were pro-
FIGURE 7-20  
A, Pseudocyst ("Stafne's bone cyst") caused by developmental inclusion of salivary gland tissue within the body of the mandible.  
B, Multiple jaw cysts in a patient with nevoid basal cell carcinoma syndrome (see "Syndromes with Benign Oral Neoplastic or Hamartomatous Components," in this chapter). (Courtesy of Robert Beideman, Philadelphia, Pa.)

FIGURE 7-21  
Radiographic appearance of several jaw cysts.  
A and B, Radicular (periapical) cysts, a result of pulp necrosis and infection.  
C, Mucous cyst of the maxillary sinus.  
D, Non-odontogenic fissural cyst in the midline of the anterior maxilla (note intact nasopalatine canal). (Courtesy of Robert Beideman, DMD, Philadelphia, Pa.)
posed by Main\textsuperscript{123} and Shear\textsuperscript{120,124} in 1985. Main’s revision of the WHO classification is presented in Table 7-1. Four types of cyst (follicular or dentigerous, nasopalatine, radicular, and kerato-cyst) constitute 95% of all epithelial jaw cysts and are frequently those that attain considerable size before they are recognized.

The follicular (or dentigerous) cyst arises from the reduced enamel epithelium of the dental follicle of an unerupted tooth, which may be part of the regular dentition or a supernumerary, and remains attached to the neck of the tooth, enclosing the crown within the cyst. Some unerupted teeth appear to be more susceptible than others to the development of such cysts (eg, third molars and canines). Studies with tooth germ isografts in the hamster cheek pouch and clinical observations suggest a correlation between cystic degeneration of the tooth follicle and enamel hypoplasia.\textsuperscript{132} In addition to their potential for attaining large size, follicular cysts are noteworthy for their tendency to resorb the roots of adjacent teeth,\textsuperscript{133} and for the occasional development of neoplastic changes such as plexiform ameloblastoma\textsuperscript{134} and carcinoma\textsuperscript{131,135} within an isolated segment of the cyst wall. This potential for neoplastic change and infiltration beyond the cyst wall and the occasional finding of other odontogenic tumors in association with a follicular cyst fully justify the need for histopathologic examination of all material derived from jaw cysts.

The eruption cyst is the soft-tissue analogue of the follicular cyst; it presents clinically as a bluish gray swelling of the mucosa over an erupting tooth and has been characterized as a “cyst arising within the oral mucosa by the separation of the follicle from around the anatomical crown of an erupting tooth.”\textsuperscript{123} Excision of a wedge of the mucosa to expose the tooth crown is usually adequate.

Radicular cysts (see Figure 7-21, A and B) derive from inflammatory proliferation and cystic degeneration of epithelial cell Malassez rests contained in periapical granulomatous tissue, usually secondary to pulp necrosis. When this change occurs in a granuloma that has not been eliminated by tooth extraction, the cyst is no longer associated with the apex of a tooth and is customarily referred to as a residual cyst. Radicular cysts are the most frequent type of jaw cyst and make up as much as 55% of jaw cysts in some series (once again, the difficulties of determining if a given radiolucency is a cyst, a granuloma, or some other lesion influence the validity of the estimates given for different series). There is a large body of literature devoted to elucidating the mechanism and cause of the epithelial proliferation, fluid accumulation, bone resorption, and expansion that underlie the development of radicular cysts.\textsuperscript{123}

The odontogenic keratocyst (formerly, primordial cyst)\textsuperscript{136,137} (Figures 7-23 and 7-24; see also Figure 7-20, B, and

\textbf{FIGURE 7-22} A, Asymptomatic odontogenic keratocyst in the mandibular third molar region, noted as an incidental finding in a periapical radiograph. B and C, Histologically, the cyst has a well-keratinized epithelial lining, with nests of cells of presumed odontogenic origin located in the surrounding connective tissue.
Benign Tumors of the Oral Cavity

Figure 7-22), which arises from reduced enamel epithelium, dental lamina rests, and Malassez rests, are of considerable interest because of their tendency for recurrence after initial surgical intervention. Keratocysts are characterized by keratinization and budding cyst lining. This cyst occurs as an isolated finding and in association with other basal cell cancers and various other lesions in nevoid basal cell carcinoma syndrome (see “Neviod Basal Cell Carcinoma Syndrome,” below).

Cysts of the maxillary sinus (see Figure 7-21, C) were thought to arise from pseudostratified columnar respiratory-type epithelium rather than from the oral mucosa, but they are of interest because of the frequency (as high as 2.6% in one series) with which they are recognized in panoramic dental radiographs, which demonstrate them more efficiently than the traditional Waters’ projection. In reality, most of these dome-shaped radiopacities of the sinus floor are nothing more than inflammatory polyps and are not true “retention” cysts.

The nasopalatine (incisive canal) cyst (see Figure 7-21, D) is derived from remnants of epithelium-lined vestigial oronasal duct tissue and possibly also from Jacobson’s (vomeronasal) organ, which is said to account for the occasional finding of pigmented cells in the wall of these cysts. On the basis of radiographic surveys of dried skulls, the frequency of this cyst has been described as being as high as 1.8% although differences of opinion as to the maximum size the image of the incisive canal may attain without being considered cystic raise doubt as to the validity of this figure. The surgical removal of a nasopalatine cyst commonly produces loss of sensation and paresthesia of the anterior palate supplied by the nasopalatine nerve; thus, unequivocal signs of cystic swelling in the canal are required before exploration of the area or excision of a suspected cyst is undertaken.

Cysts of the maxillary sinus (see Figure 7-21, C) were thought to arise from pseudostratified columnar respiratory-type epithelium rather than from the oral mucosa, but they are of interest because of the frequency (as high as 2.6% in one series) with which they are recognized in panoramic dental radiographs, which demonstrate them more efficiently than the traditional Waters’ projection. In reality, most of these dome-shaped radiopacities of the sinus floor are nothing more than inflammatory polyps and are not true “retention” cysts.

Cysts and odontogenic tumors arising in the maxilla, especially

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**TABLE 7-1 Proposed Revision of World Health Organization Jaw Cyst Classification**

<table>
<thead>
<tr>
<th>Developmental</th>
<th>Odontogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odontogenic keratocyst (formerly, primordial cyst)</td>
<td></td>
</tr>
<tr>
<td>Follicular cyst; eruption cyst</td>
<td></td>
</tr>
<tr>
<td>Alveolar cyst of infants; gingival cyst of adults*</td>
<td></td>
</tr>
<tr>
<td>Developmental lateral periodontal cyst†</td>
<td></td>
</tr>
<tr>
<td>Nonodontogenic</td>
<td></td>
</tr>
<tr>
<td>Midpalatal cyst of infants*</td>
<td></td>
</tr>
<tr>
<td>Nasopalatine duct cyst</td>
<td></td>
</tr>
<tr>
<td>Nasolabial cyst‡</td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td></td>
</tr>
<tr>
<td>Inflammatory follicular cyst§</td>
<td></td>
</tr>
<tr>
<td>Radicular cyst</td>
<td></td>
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<tr>
<td>Inflammatory lateral periodontal cyst</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Main DMG; Kramer et al. Minor cysts (< 5% of all jaw cysts) that develop from epithelial rests in gingival, alveolar, or midpalatal mucosa.

Lateral follicular cysts that develop between vital maxillary lateral and cuspid teeth. Formerly referred to as globulomaxillary cysts, these are no longer believed to have a fissural origin (see Christ TF. The globulomaxillary cyst: an embryological misconception. Oral Surg Oral Med Oral Pathol 1970;30:515).

Rare cysts of uncertain origin developing in the nasolabial region.

Arousing from the spread of periapical inflammation from a nonvital deciduous tooth to the follicle of an underlying successor (see Shaw W, Smith M, Hill F. Inflammatory follicular cysts. ASDC J Dent Child 1980;47:97).

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**FIGURE 7-23** Radiograph of an odontogenic keratocyst located between the upper lateral incisor and cuspid teeth. (Courtesy of D. Lovas, DDS, Halifax, N.S., Canada)
molar and premolar radicular cysts, may extend into the maxillary sinus but usually do so by expanding the floor of the sinus ahead of them.\textsuperscript{141}

Cystic degeneration may also occur in benign odontogenic tumors, but the hamartomatous or neoplastic nature of odontogenic tumors requires that they be given special consideration (see following section). The misleading so-called cystic radiographic appearance of many odontogenic tumors (reflected in the synonym “multilocular cyst” for ameloblastoma), the majority of which develop within and expand the jaw, has also led to clinical confusion between the two classes of lesions.\textsuperscript{124} Cystic degeneration is a common change in odontogenic tissue, and it is not surprising that odontogenic tumors frequently contain cystic areas. The importance of a thorough histopathologic examination of all curetted material is once again underlined by the fact that tumor tissue may be recognized in only a small section of a lesion, the bulk of which is represented by a relatively nonspecific odontogenic cyst.

**Benign Odontogenic Tumors**

With the exception of odontomas, odontogenic tumors are quite rare, probably constituting fewer than 1% of all jaw cysts and tumors.\textsuperscript{75,123,142} Some, such as the ameloblastoma and the calcifying epithelial odontogenic (Pindborg) tumor, are undoubtedly neoplastic; others, such as the compound odontoma and periapical cemental dysplasia, are most likely hamartomas. Malignant variants of several odontogenic tumors also attest to the neoplastic nature of at least some odontogenic growths.\textsuperscript{143} Although there have been many attempts at classifying odontogenic tumors, uncertainty concerning the cells of origin of many of these lesions, the bewildering array of histologic types of odontogenic tumors that result from inductive changes in the mesodermal component of these lesions, and their relative rarity all cause difficulty in the histopathologic diagnosis of some of these lesions.

For the majority of these lesions, the descriptions and illustrations included in the 1971 WHO classification of neoplasms and other tumors related to the odontogenic apparatus\textsuperscript{121} remain unchanged although the categories of squamous odontogenic tumor and clear cell odontogenic carcinoma are generally included in more recent classifications. Subclassifications of epithelial, mesenchymal, and mixed epithelial and mesenchymal origin (Table 7-2) and subclassification of noninductive versus inductive\textsuperscript{144} have also become common practice.

Of most significance to the clinician is the basis for the typing and classification of odontogenic tumors because the various designations are cause for bewilderment. These tumors are classified according to their emulation of the process of odontogenesis, their differentiation, and the tissues from which they are derived. Recall that the epithelial portion of the tooth germ arises as an invagination of the primitive oral ectoderm into a linear strand of cells, the dental lamina. The tip of the lamina undergoes bulbous expansion to form the cap and bell stages of odontogenesis, with differentiation into the ameloblastic layer and the inner zone of stellate reticulum. During the differentiation of the odontogenic epithelium, the underlying connective tissues condense with cells recruited from the neural crest. This ectomesoderm transforms into the pulp, and those cells that lie in juxtaposition to the epithelium differentiate into odontoblasts. Once the crown morphology is outlined, dentinogenesis proceeds initially and is a requisite for subsequent amelogenesis. The cervical epithelial tissues then invaginate once again to outline the morphology of the roots as Hertwig’s sheath. Surrounding periodontal connective tissues then form bone on the alveolus side of the process and form cementum on the tooth side.

These developmental stages are emulated in various odontogenic tumors. Those that derive strictly from epithelium do not show dentin formation since no ectomesoderm is a component of the neoplasm. Indeed, no enamel formation can be seen because dentin (the prerequisite for amelogenesis) is lacking. Conversely, the mixed odontogenic tumors.

**CALCIFYING EPITHELIAL ODONTOGENIC CYST**

Calcifying epithelial odontogenic cyst (CEOC) or Gorlin’s cyst, occurs both as a cyst and (less commonly) as a solid tumor, the common characteristics being derivation from odontogenic epithelium, calcification, and so-called ghost

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**TABLE 7-2 Histopathologic Classification of Odontogenic Tumors**

<table>
<thead>
<tr>
<th>Ectodermal Origin</th>
<th>Mesodermal Origin</th>
<th>Mixed Ectodermal and Mesodermal Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ameloblastoma</td>
<td>Odontogenic myxoma</td>
<td>Ameloblastic fibroma</td>
</tr>
<tr>
<td>Adenomatoid odontogenic tumor*</td>
<td>Central odontogenic fibroma</td>
<td>Ameloblastic fibro-odontoma</td>
</tr>
<tr>
<td>Calcifying epithelial odontogenic tumor (Pindborg tumor)</td>
<td>Cementomas</td>
<td>Odontomas</td>
</tr>
<tr>
<td>Squamous odontogenic tumor</td>
<td>Periapical cemental dysplasia</td>
<td>Complex</td>
</tr>
<tr>
<td>Clear cell odontogenic tumor</td>
<td>Familial multiple gigantiform cementoma</td>
<td>Compound</td>
</tr>
<tr>
<td>Calcifying odontogenic cyst (Gorlin’s cyst)†</td>
<td>Cementifying fibroma</td>
<td>Cementoblastoma</td>
</tr>
</tbody>
</table>

*Formerly called adenoameloblastoma.
†May occur as either a cyst or tumor.
cell keratinization (recently identified as coagulative necrosis of proliferated odontogenic epithelium)\textsuperscript{145} (Figure 7-25). Both central and peripherally located lesions are described.\textsuperscript{146} Calcifying odontogenic cysts or areas exhibiting these characteristic histologic changes are sometimes found in association with ameloblastomas or other odontogenic tumors, partially accounting for the variety of names under which this lesion has been described in the literature (Figure 7-26, F). Benign and malignant varieties are described, and the lesion mostly occurs in adolescents, appearing as a uni- or multilocular radiopacity enclosing calcified structures of variable size (“pepper-and-salt” appearance). Enucleation usually eliminates the lesion unless it is a component of another odontogenic tumor with a tendency to recur.

**AMELOBLASTOMA**

Without doubt, the best-known odontogenic tumor, the ameloblastoma, is often used as the norm by which other odontogenic tumors are judged.* Most tumor registries also list it as the most prevalent odontogenic tumor; but because these data are based on biopsy specimens of lesions and because well-differentiated and calcified lesions such as compound odontomas are often never removed, the data may not reflect the true frequency. However, the prevalence of ameloblastomas ensures that all pathologists have encountered them, and there is agreement among surgeons that ameloblastomas should be treated by block excision because of their tendency for local invasion. Thus, to describe a given odontogenic tumor as “more aggressive” or “less aggressive” than an ameloblastoma can be a useful means of communication in this rather uncertain field.\textsuperscript{147–150}

In defining the ameloblastoma as the norm for odontogenic tumors, care must be given to the range of lesions accepted as ameloblastoma since several lesions of a quite different nature have been included under this diagnosis in past years. In particular, it is important that the melanotic neuroectodermal tumor of infancy (sometimes referred to as a melanotic ameloblastoma [see previous discussion]), the adenomatoid odontogenic tumor (formerly called adenoameloblastoma), and ameloblastic odontoma (odontoameloblastoma) are excluded from the category of ameloblastoma. Used in this restricted sense, ameloblastoma is a slow-growing benign neoplasm that has a strong tendency to local invasion and that can grow to be quite large without metastasizing (Figure 7-27). Rare examples of distant metastasis of an ameloblastoma in lungs or regional lymph nodes do exist.\textsuperscript{143,151–153}

Ameloblastomas are rare in children; the greatest period of prevalence is in the age range of 20 to 50 years. The majority occur in the mandible, and over two-thirds occur in the molar-ramus area. Curettage of the unilocular or multilocular lesions (both radiographic appearances are characteristic) is often followed by local recurrence, and block excision of the lesion with a good margin of unaffected bone (or hemisection of the mandible, for a large lesion) is the treatment of choice and is rarely followed by recurrence.

Microscopically, all ameloblastomas show a fibrous stroma, with islands or masses of proliferating epithelium that always resembles the odontogenic epithelium of the enamel organ to some degree (ie, palisading of cells around proliferating nests of odontogenic epithelium in a pattern similar to ameloblasts). Follicular, plexiform, and acanthomatous histologic variants in which the appearances of basal cells, stellate reticulum (with varying degrees of cystic degeneration), and squamous metaplasia are reproduced

*Discussion of ameloblastoma under the heading of “Benign Odontogenic Tumors” may be questioned because the capacity for local invasion that this tumor can show certainly belies a “benign” character. Distant metastasis,\textsuperscript{143} however, is quite rare, and the local invasion shown by this tumor probably differs biologically from that shown by squamous cell carcinoma, for example. Provided that the student fully recognizes the locally destructive tendency of this tumor and the need for block excision in its treatment, it is conveniently discussed at this point, because it provides a useful comparison with other rarer odontogenic tumors.
have been described. These histologic variants show no correlation with either the clinical appearance of the lesion or its behavior, and different sections of the same tumor may show one or the other histologic variation (see Figure 7-26, A to E). There are only two significant subcategories of ameloblastoma; those that arise from the lining of an odontogenic cyst are called unicystic ameloblastomas, and those that are solid tumors are called solid or invasive ameloblastomas. The former tend to occur during teenage years; the latter tend to occur in midlife. The primary reason for distinguishing between these two variations of ameloblastoma is the difference in natural history and behavior. Fewer than 20% of unicystic ameloblastomas recur after curettage whereas over 75% of solid ameloblastomas will recur unless treated by resection. Attempts have been made to marsupialize unicystic tumors, yet this treatment eventuates in failure, with persistent and even progressive disease.

The distinction between an area of proliferating odontogenic epithelium in the wall of a dentigerous cyst and early ameloblastoma may be difficult to make (Figure 7-28), and studies of lectins and other cell markers on the proliferating epithelial cells have so far failed to identify those lesions that are most likely to develop into an ameloblastoma.154 There is no clear origin for the ameloblastoma; the dentigerous cyst is only one possibility, but remnants of the dental lamina and the basal layer of the oral mucosal epithelium also are strong contenders.
However, there does seem to be good reason for repeated curetage or excision of the bony wall of a cyst in which such a change has been noted, especially in young patients.

There is no justification for the use of radiation therapy in the treatment of ameloblastomas; its use in past years has been associated with a considerable occurrence of radiation-induced sarcoma.\textsuperscript{155}

**FIGURE 7-27**

*A*, Gross appearance of a very large multilocular ameloblastoma that occupied and distended the entire mandible. *B*, Histologic appearance of the same lesion. *C*, Radiograph of an ameloblastoma of similar dimension.

**ADENOMATOID ODONTOGENIC TUMOR**

Adenomatoid odontogenic tumor (AOT) is a tumor of odontogenic epithelium with ductlike structures and with varying degrees of inductive change in the stroma.\textsuperscript{156} It differs considerably from the ameloblastic norm and is usually now excluded from that category. By contrast with ameloblastoma, it reflects all of the characteristics of a hamartoma as a well-encapsulated lesion that rarely recurs even with conservative
curettage. Recognition of its characteristic histology should prevent the need for block excision of the lesion. Clinically, it may be suspected because of its preference for the maxilla rather than the mandible and for anterior rather than posterior segments of the jaws. Often it presents as a cystic lesion that is not associated with a missing tooth and that is found (by biopsy specimen examination) to have several masses of tumor tissue in its wall. These mural nodules are composed of characteristic masses of ductlike structures lined with basal or columnar cells with peripherally placed nuclei. The “lumen” of some of these “ducts” is nonexistent, and that of others is dilated with an eosinophilic or fibrillar material, giving some suggestion of poorly formed stellate reticulum. Amorphous calcification may be apparent both microscopically and radiographically (Figure 7-29).

PINDBORG TUMOR (CALCIFYING EPITHELIAL ODONTOGENIC TUMOR)

The Pindborg tumor (Figure 7-30) resembles an ameloblastoma in that it is locally invasive and is commonly identified as a uni- or multilocular swelling in the molar-ramus region. Histologically, it differs from ameloblastoma in being composed of masses of polyhedral epithelial cells with little stroma. The cells may be eosinophilic, exhibit intercellular bridges, and be quite pleomorphic, with multiple giant nuclei. In many ways, it appears microscopically like a potentially aggressive squamous cell carcinoma, with a predominance of cells resembling those of the stratum spinosum of oral epithelium, and many cases have undoubtedly been wrongly diagnosed as squamous cell carcinoma. The central location of the tumor in the jaw, often with expansion of the cortex (in contrast to the destructive lesion of carcinoma), and the areas of spotty calcification seen radiographically should alert the clinician to the possibility of a Pindborg tumor, but peripheral lesions are also occasionally reported. Sections of such a tumor should be examined for the characteristic hyaline concentrically calcified globules of amyloid within the masses of epithelioid cells that confirm the lesion as odontogenic in origin. Larger areas of calcification and dentin formation may also be found.

Treatment is by enucleation or local block excision; the recurrence rate is reported to be 20%. Exploration of regional nodes and follow-up radiation therapy (as might be used for squamous cell carcinoma) are quite unjustified for this odontogenic lesion.

OTHER EPITHELIAL ODONTOGENIC TUMORS

Two other relatively rare epithelial odontogenic tumors that have been recognized as separate entities in recent years are the squamous and clear cell odontogenic tumors. The squamous odontogenic tumor is a lesion composed of multiple islands of squamous epithelium (often with central cystic degeneration) that arises in the alveolar process from proliferation of Malassez rests or gingival pseudoepitheliomatous hyperplasia. It occurs equally frequently in the maxilla or the mandible, and
it may recur following enucleation; multiple lesions have been described. The clear cell odontogenic tumor,\textsuperscript{161} previously considered a variant of ameloblastoma, is now considered to represent a malignant tumor. Histologic differentiation of this tumor from other oral and metastatic tumors (such as renal cell carcinoma) is important.

**ODONTOGENIC TUMORS OF MESENCHYMAL ORIGIN**

**Odontogenic Myxoma and Central Odontogenic Fibroma.** Myxomas (tumors composed of very loose cellular connective tissue containing little collagen and large amounts of an intercellular substance that is rich in acid mucopolysaccharide) occur with some frequency in the jaw bones. Since similar lesions are rare in other bones and since some oral myxomas contain tiny epithelial remnants that resemble inactive odontogenic epithelium, tumors with this histologic appearance that occur in the jaw bone are referred to as odontogenic myxomas.\textsuperscript{162} This lesion usually consists of rounded and angular cells lying in an abundant mucoid stroma that is reminiscent of dental pulp, with very scanty epithelial elements. It is a slow-growing but invasive tumor that sometimes reaches quite large dimensions and distends the jaw. Characteristically, it appears radiographically as a uni- or multilocular lesion (“soap bubble” effect) that may be indistinguishable from ameloblastoma, fibrous dysplasia, giant cell reparative granuloma, cherubism, and the jaw lesion of hyperparathyroidism (osteitis fibrosa cystica). Treatment is similar to that recommended for ameloblastoma although tooth root resorption in an area affected by a myxoma and recurrence after simple curettage may give the impression of a more aggressive lesion.

Central odontogenic fibroma\textsuperscript{163,164} (a tumor composed of mature fibroblastic tissue with rare nests and strands of odontogenic epithelium) is an uncommon, slow-growing, and nonaggressive lesion. These tumors are generally small, yet they may cause root resorption, and many will underlie a distinct region of dimpling of the oral mucosa.

**Cementomas.** “Cementoma” is a nonspecific term often used to describe localized masses of radiopaque condensed areas of the alveolus adjacent to the roots of the teeth (see Figure 7-15).\textsuperscript{102–104,121,165,166} Periapical cementomas are often multiple and are distinguished from chronic periapical abscesses by their association with vital teeth.\textsuperscript{167} There is good evidence that periapical cementomas are reactive lesions that pass through an osteolytic phase (in which they can be distinguished from periapical cysts and granulomas only by the retention of vitality in the tooth), through a stage in which one or more radiopaque zones appear within the radiolucent area, to a final stage of uniform radiopacity. “Periapical cemental dysplasia” (PACD)\textsuperscript{168} is the accepted term for such lesions and emphasizes their benign hamartomatous nature (Figure 7-31). Provided that such lesions do not increase in size or otherwise exhibit atypical behavior, there seems to be no reason to remove them. Should caries or other pulpal disease warrant endodontic treatment of a tooth with associated PACD, apicoectomy with removal of the dense periapical lesion is desirable, if only to prevent complication of the postoperative evaluation of the success of the endodontic therapy.\textsuperscript{169}

In addition to PACD, the WHO classification of odontogenic tumors distinguishes three other lesions with prominent and excessive cementum formation: familial multiple gigantiform cementoma,\textsuperscript{170} cementifying fibroma,\textsuperscript{171} and cementoblastoma.\textsuperscript{172}
In regard to familial multiple gigantiform cementoma, females appear to be preferentially susceptible to both localized and widespread cementoma formation, in which both maxilla and mandible may be occupied by large globular and lobulated masses of dense acellular cementum. The differentiation of this condition from chronic sclerosing osteomyelitis, florid osseous dysplasia, and ossifying fibroma is usually unproblematic since these tumors are huge, beginning in childhood years and progressively increasing in size into adult life (Figure 7-32). There is usually (but not invariably) a familial history, with variable penetrance in expressivity. Treatment is wide excision, followed by grafting and facial plastic surgery interventions.

Cementifying fibroma is merely a variant of ossifying fibroma and occurs in the mandible of older individuals. Radiographically, it passes through the stages that were described for periapical cemental dysplasia in younger patients. Histologically, it consists of cellular fibroblastic tissue containing rounded, heavily calcified, and basophilic masses of cementum, as opposed to ossifying fibroma, in which the hard tissue is represented by osseous trabeculae. Nevertheless, there are many tumors of this nature that elaborate both osseous and cementicle trabeculae, and similar lesions are found in facial bones that do not bear teeth. Those lesions that are treated enucleate readily, and recurrence is uncommon.

Cementoblastoma (true cementoma) is a radiographically and histologically distinctive benign tumor that usually occurs around the root of a mandibular premolar or molar tooth. It is composed of layers of cemental tissue with prominent accretion lines; the inner layers are acellular, and the formative peripheral layers are uncalcified, allowing ready enucleation. Radiologically, the prominent linear calcifications provide a distinctive and unusual picture that may even suggest an osteosarcoma.

Focal osseous dysplasia and florid osseous dysplasia are benign fibro-osseous lesions that histologically resemble other “cementifying” lesions yet are self-limited non-neoplastic jaw lesions localized to tooth-bearing regions. Radiologically, focal osseous dysplasia appears (usually in the mandible) as a localized small radiolucency with central calcifications. It is nonexpansile, and its etiology is unknown. Many such lesions are located in edentulous sites, and some may represent the residua of condensing osteitis, left behind after tooth extraction. Florid osseous dysplasia is typically seen in middle-aged black women but can occur in individuals of any race. This condition is characterized by multiple confluent “cotton wool” radiopacities with surrounding lucent regions that resemble traumatic bone cysts (vacant cavities in bone). Biopsy of these lesions may result in osteomyelitis, probably owing to the lack of vascularity in the dense bony regions. Both focal and florid osseous dysplasias show similar histologic features. There is a benign fibro-osseous lesion with foci of dense cortical bony structures.

**ODONTOGENIC TUMORS OF MIXED EPITHELIAL AND MES-ENCHYMAL ORIGIN**

**Ameloblastic Fibroma and Fibro-odontoma.** Odontogenic jaw tumors in which varying degrees of both dentin and enamel matrix (with or without calcification) occur are of two types. The ameloblastic fibroma is a child tumor that resembles an ameloblastoma radiologically and histologically (except that the stroma consists of pulp tissue rather than undifferentiated connective tissue) and that behaves less aggressively than an ameloblastoma (Figure 7-33). The other type comprises various odontomas such as ameloblastic fibro-odontoma and complex and compound odontomas. Calcification within an ameloblastoma does not occur unless there is reactive osteogenesis, as may occur in desmoplastic variants (Figure 7-34), and this feature can serve to distinguish ameloblastoma from both adenomatoid odontogenic tumor and ameloblastic fibro-odontoma or odontoameloblastoma. This latter lesion consists of ameloblastic tissue found in association with an abnormal mass of partially calcified dental tissues that histologically may contain enamel, dentin, osteodentin, bone, cementum, and pulp tissue as well as various developing stages of these tissues. This rare tumor should be treated the same way that a solid ameloblastoma is treated (generally by resection). In essence, it is an ameloblastoma arising in an odontoma.

**FIGURE 7-32** Radiographic appearance of chronic sclerosing osteomyelitis affecting the major portion of the body of the mandible. Clinical and histologic differentiation of this lesion from ossifying fibroma may be difficult, particularly if teeth have been extracted or surgery has been carried out adjacent to the area. (Reproduced with permission from Nichols C, Brightman VJ. Parotid calcifications and cementoma in a patient with Sjögren's syndrome and idiopathic thrombocytopenia. J Oral Pathol 1977;6:52)
Benign Tumors of the Oral Cavity

Complex and Compound Odontomas. Complex and compound odontomas\(^\text{177–179}\) are nonaggressive lesions that are more likely to be hamartomatous than neoplastic. They are often small and may remain undiscovered for many years until they are revealed by routine panoramic radiography or by a search for a missing permanent tooth. Their radiographic appearance is often characteristic, and if their presence does not interfere with orderly tooth eruption, they may safely be left undisturbed. Dentigerous cysts may form in association with these lesions, and this possibility may justify their removal and certainly justifies repeated radiographic examination for new cyst development every 2 to 3 years.

The term “complex odontoma” is used for lesions that contain mature calcified dental tissue that is poorly differentiated as to its exact identity as enamel, dentin, or cementum. Such lesions characteristically appear as dense radiopaque objects sometimes lying in a clear space or associated with a “cyst,” but more often enclosed by a well-defined “lamina dura.” Compound odontomas contain calcified structures that grossly and radiographically resemble poorly formed and often small teeth in which enamel, dentin, and cementum can be distinguished. Remembering the common meanings of “complex” (complicated, hard to separate or analyze) and “compound” (a joining together of parts so as to form a whole) may help the student to distinguish these two types of odontoma, which are quite aptly described by these terms.

\section*{Benign “Virus-Induced” Tumors (Oral Squamous Papillomas and Warts)}

For many years, several benign oral epithelial growths that contain virus particles or viral antigens (warts, squamous papillomas and condyloma acuminata, focal epithelial hyperplasia, molluscum contagiosum, and keratoacanthoma) have been considered to be virus-induced neoplasms; leukoplakia, lichen planus, hairy leukoplakia, and squamous carcinoma have also been placed in this category by some authors.\(^\text{180–183}\) More recently, molecular biologic techniques (eg, deoxyribonucleic acid [DNA] hybridization, restriction endonuclease analysis, the polymerase chain reaction,\(^\text{184}\) which have proven to be more sensitive probes than electron microscopy or immunologic staining techniques that detect only virus or viral antigen) have revealed that viral DNA can be found in a number of oral mucosal lesions and that even normal oral mucosa may also harbor a limited number of viral strains, notably one that is related to human papillomavirus (HPV) subtype 16.\(^\text{185}\) Although an extensive literature has documented the association of many of the 80 known strains of papillomavirus, herpes simplex virus, and Epstein-Barr virus with these lesions, the role of many of these viral strains remains unproven, and additional evidence is needed before particular viruses can be considered as etiologic agents.\(^\text{180,183}\) For example, normal oral mucosa from as many as 40% of individuals, as well as 80% of leukoplakias and lichenoid lesions, contains the strain related to the HPV subtype 16. This HPV subtype is usually found only in genital carcinomas, and its presence in normal mucosa and in leukoplakia and lichenoid lesions suggests that some HPV subtypes at least may replicate in these tissues and are not necessarily causal. In contrast, HPV subtypes 1, 2, 4, 6, 11, 13, and 18, which are associated with various oral lesions, have not been detected in normal oral mucosa. Herpes simplex and Epstein-Barr viruses likewise have been detected in normal oral mucosa as well as in mucosal lesions.\(^\text{186}\)

Although malignant transformation in these virus-associated lesions is quite unusual, the viral genomic material in oral mucosal cells can replicate, produce intact virus, and transform the host cell. The frequent development of unusual oral malignancies and of oral mucosal lesions that are associated with herpes simplex virus, Epstein-Barr virus, Cytomegalovirus, and papillomavirus in acquired immuno-
deficiency syndrome (AIDS) patients and in intentionally immunosuppressed patients also demonstrates that these oral viruses probably have clinical significance and that immunosuppressive medications (such as cyclosporine, corticosteroids, and azathioprine) should be administered with considerable caution, particularly if they must be used for extended periods of time.

Oral squamous papillomas and warts are proliferative epithelial lesions generally considered to be caused by HPV, with subtypes 6 and 11 being commonly implicated. Isolated reports of an association with subtypes 2 and 16 have not been confirmed. Oral papillomas and warts (verrucae vulgaris) share many similarities. The term “verruca vulgaris” is usually applied when a crop of lesions develops, sometimes in association with similar skin lesions. Squamous papillomas usually occur in the third to the fifth decades, most commonly as isolated palatal lesions. When these lesions occur on the keratinized surface of the lips, alveolar gingivae, or palate, they are well keratinized and wartlike, often with a definite narrow pedicle (Figures 7-35 and 7-36). On the nonkeratinized mucosal surface, they may appear soft and redder and may be hard to differentiate from the lesions of fibrous hyperplasia described earlier. A rugose cauliflower-like exophytic lesion is more likely to be a papilloma than to be fibrous hyperplasia. Local excision of these lesions is desirable; electrocoagulation is the treatment of choice on the lips, where the lesions cause a cosmetic problem. Carbon dioxide laser treatment has also been described.

Although these lesions are probably infectious, a history of direct contact with another infected person is unusual, except in the case of a multiple and often recurrent oral wart associated with sexual contact, referred to as condyloma acuminatum (see Chapter 22). HPV DNA sequences have also been described in condyloma acuminatum.

Intraoral papillomatosis may be inherited in such rare conditions as ichthyosis hystrix, but other manifestations of this syndrome (a congenitally acquired deforming skin papillomatosis) serve to differentiate these lesions from other congenital conditions, such as Down syndrome, in which florid papillomatosis may also occur. The role of genetic predisposition in promoting HPV expression in these conditions has not yet been explored.

Focal epithelial hyperplasia (Heck’s disease), a condition characterized by numerous soft, well-circumscribed, flat, and sessile (ie, nonpapillomatous) papules that are distributed throughout the oral mucosa, is endemic in some Eskimo and Native American communities but is rare in white people. Examples among Puerto Ricans and (more recently) among black people suggest that further searches for this lesion may show it to be more widespread. Histologically, it is characterized by nondyskeratotic nodular acanthosis, which forms the basis of the papules, and a subepithelial lymphocytic infiltration. These lesions have been considered to be of viral origin for many years, initially on the basis of electron microscopic demonstration of Papovavirus particles and (more recently) on the finding of DNA sequences for HPV subtypes 13 and 32.

![Figure 7-35](image-url)
which appear to be specific for this lesion and which are expressed only in those individuals who are genetically pre-
disposed. Once identified, the lesions require no treat-
ment; malignant transformation does not occur.

Molluscum contagiosum, a dermatologic infection acquired by direct skin contact and characterized by clusters of tiny firm nodules that can be curedtted from the skin, is histo-
logically composed of clumps of proliferating epithelial cells with prominent eosinophilic inclusion bodies. It is not a neo-
plasm, but it is included here as one of the spectra of oral epithelial proliferations that result from viral infection. Both intraoral and labial lesions of molluscum contagiosum have been reported.

Molluscum contagiosum is caused by a poxvirus that infects the skin, where the virus replicates in the stratum spin-
osum, producing the characteristic and pathognomonic Cowdry type A inclusion bodies that are commonly associated with poxvirus infections but apparently producing only a small number of complete viruses. Cytotoxic T cells and delayed-
type hypersensitivity are most likely the effective means of recovery from this infection, which explains the increased fre-
quency and persistence of this infection in AIDS patients. Treatment usually involves the shelling out of the epithelial nodules with a curet.

Keratoacanthoma is a localized lesion (usually found on sun-exposed skin, including the upper lip) whose rapid growth may be quite frightening, to the point where it is often mistaken for a squamous or basal cell carcinoma (Figure 7-37). Like some carcinomas, these lesions appear fixed to the surrounding tissue, often grow rapidly, and are usually capped by thick keratin. Occasionally, the lesion matures, exfoliates, and heals spontaneously, but more frequently, block excision is carried out, and the diagnosis becomes apparent when the entire lesion is examined micro-
scopically. Incisional biopsy specimens are almost always diag-
nosed as carcinoma since they lack the panoramic view of the entire lesion, which is of greatest help in differentiating it from carcinoma.

Epithelial tissue adjacent to the lesion is sharply demar-
cated from that of the lesion, which appears to lie in a cup-
shaped depression. The proliferating epithelium constituting this amazing lesion consists of masses of reasonably well-dif-
ferentiated squamous cells that often produce keratin pearls and show little cellular atypia. Viralike inclusions have also been demonstrated in some specimens. Clumps of cells that appear to be separated along the base of the lesion and the accompanying chronic inflammatory exudate in this region presumably are the cause for the mistaken diagnosis of carcino-
ma, a diagnosis that seems, at the time, to be confirmed by the aggressive growth of the lesion. This fact and the lesion’s usual location on the upper lip (where squamous cell carcino-
ma of actinic etiology is rare, compared with the lower lip) should remind the clinician to consider keratoacanthoma in the differential diagnosis. Intraoral lesions are rare.

The emphasis in this chapter has been on the accurate diag-
nosis of benign oral tumors by means of histopathologic examination, so that they may be clearly separated from malig-
nant lesions and treated accordingly. The oral cavity and face can also provide evidence of malignancy elsewhere in the body, and clinicians need to be aware of a variety of oral signs that can serve as an index of internal malignancy, in much the same way that dermatologic conditions such as recurrent herpes zoster and erythema multiforme may occasionally signal the presence of an otherwise undetected lymphoma or carcinoma.

Of particular pertinence to this chapter are a group of con-
ditions in which benign oral growths, which of themselves have no precancerous potential, are associated with a predis-
position to a malignancy in another organ system. Such con-
ditions, which are usually familial (often with autosomal dominant inheritance), are uncommon, but the very frequent association of a particular oral lesion in such families with the internal malignancy makes the recognition of these oral lesions very important.

Several authors have reviewed cancer syndromes that are associated with characteristic skin lesions. Table 7-3 summarizes those syndromes that are associated with benign oral tumors. A brief discussion of these syndromes follows.

**Von Recklinghausen’s Neurofibromatosis**

Two distinct varieties of this classic syndrome (neurofibromatosis 1, which affects approximately 100,000 people in the United States and which is often associated with oral lesions; and neurofibromatosis 2 (bilateral acoustic neurofibromatosis), which (1) is caused by a gene on a different chromosome, (2) is much less common, and (3) is less frequently associated with obvious peripheral neurofibromatosis or oral lesions even though it is often accompanied by other central nervous system tumors. Unidentified hormones or nerve growth factors are thought to contribute to tumor formation in both varieties of this syndrome.

Neurofibromatosis 1 is inherited as an autosomal dominant condition, but only half of the cases exhibit a familial history. The syndrome is characterized by the simultaneous occurrence, usually on the trunk, axilla, and pelvic area, of café au lait spots (light brown macules with a smooth outline “like the coast of Florida”; the finding of six or more macules ≥ 1.5 cm in diameter is diagnostic of neurofibromatosis),† axillary freckling (Crowe’s sign), and a wide variety of nerve and nerve sheath tumors in both the central and peripheral nervous systems. The peripheral lesions are often indistinguishable from those described earlier in this chapter (see “Nerve Sheath Tumors and Traumatic Neuroma,” above). The central lesions, because of their location within a bony cavity, often in association with various nerve roots, lead to neurolologic symptoms, mental retardation, and vertebral anomalies. Large infiltrating lesions that occur both peripherally and centrally and that lead to severe deformity are referred to as plexiform neuromas (Figure 7-38).

Malignant transformation of one or more neurofibromas occurs in about 5% of patients with this syndrome. Pheochromocytomas (tumors of the adrenal medulla and paraganglia) also may occur and produce hypertension by the secretion of excess catecholamines. Approximately 5% of patients with neurofibromatosis have well-developed oral lesions and macroGLOSSIA (the tongue being the most common oral location for neurofibroma, both in this syndrome and in cases of solitary oral neurofibroma) (see Figure 7-13). This condition and the associated oral lesions are said to be more prevalent in patients in mental institutions. The lesions may be asymptomatic; about one-third are recognized on routine physical examination. The neurofibromatosis gene (NF1) has been cloned and is mutated in neurofibromatosis.

**Gardner’s Syndrome**

Although rare, Gardner’s syndrome is of importance because of the high frequency with which carcinomatous transformation occurs in the adenomatous intestinal (colonic and rectal) polyps that are characteristic of this condition. Recognition of the multiple osteomas of the face and jaws and the accompanying skin cysts and tumors as phenotypic indicators of Gardner’s syndrome fully justifies radiographic examination of the bowel and the resection of the polypoid tissue, even in young adults (Figure 7-39). Approximately 15

† Café au lait spots are also found in 10% of the normal population, especially in fair-skinned persons. Similar skin lesions with the same name occur in Albright’s syndrome.
### TABLE 7–3 Syndromes in which Benign Tumors and Other Mucosal Lesions of the Oral Cavity Are Associated with a Predisposition to Internal Malignancy

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Oral Lesions</th>
<th>Other Skin Lesions</th>
<th>Associated Abnormalities</th>
<th>Associated Malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Recklinghausen’s</td>
<td>Intraoral neurofibromas (especially of tongue) leading to macroglossia</td>
<td>Multiple neurofibromas (especially trunk and extremities)</td>
<td>CNS tumors (acoustic neuroma, meningioma, glioma, and pleiomorphic</td>
<td>Malignant neurilemmoma (5% of cases)</td>
</tr>
<tr>
<td>neurofibromatosis</td>
<td>Intradural neurofibromas of jaws (rarely)</td>
<td>Café au lait spots (especially trunk, axilla, pelvic area)</td>
<td>mucosa</td>
<td>Phaeochromocytoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axillary freckles</td>
<td>Bone cysts and hyperplasia associated with neoplasms</td>
<td>Astrocytoma and glioma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Giant nevi</td>
<td>Mental retardation</td>
<td></td>
</tr>
<tr>
<td>Gardner’s syndrome</td>
<td>Multiple osteomas of cranial and facial skeleton (especially frontal bone, mandible, and maxilla)</td>
<td>Epidermoid and sebaceous cysts</td>
<td>Polyps of the colon and rectum</td>
<td>Adenocarcinoma of colon (very high incidence)</td>
</tr>
<tr>
<td></td>
<td>Compound odontomas and hypercementosis</td>
<td>Desmoid tumors, lipomas, fibromas, and leiomyomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>Freckling and pigmentation of lips and oral mucosa</td>
<td>Similar lesions on fingers and toes</td>
<td>Intestinal polyposis (usually small intestine)</td>
<td>Gastric, duodenal, and colonic adenocarcinoma</td>
</tr>
<tr>
<td>Nevoid basal cell carcinoma</td>
<td>Multiple jaw cysts (simple and odontogenic keratocysts)</td>
<td>Epidermoid cysts</td>
<td>Rib and vertebral anomalies</td>
<td>Basal cell carcinoma of skin (often without sunlight exposure)</td>
</tr>
<tr>
<td>syndrome</td>
<td>Dilaceration of teeth adjacent to cysts</td>
<td>Milia and calcium deposits</td>
<td>Short metacarpals</td>
<td>Medulloblastoma</td>
</tr>
<tr>
<td></td>
<td>Facial abnormalities (frontal bossing, sunken eyes, and wide nasal bridge; mild mandibular prognathism)</td>
<td>Calcium deposition</td>
<td>Ovarian fibromas</td>
<td>Anoeblastoma and fibrosarcoma of jaws (low incidence)</td>
</tr>
<tr>
<td>Multiple mucosal nevus</td>
<td>Neomas of lips, tongue and buccal mucosa (oral cavity is most common site)</td>
<td>Neomas of eyelids and nasal laryngeal mucosa</td>
<td>Parathyroid adenomas</td>
<td>Medulillary carcinoma of thyroid</td>
</tr>
<tr>
<td>syndrome (multiple endocrine neoplasia type III)</td>
<td>Thick or “bumpy” lips Prognathism (infrequent)</td>
<td>Abnormal triple response to intradermal histamine injections (no flare)</td>
<td>Hypertension</td>
<td>Phaeochromocytoma</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Adenoma sebaceum, gingival lesions and enamel hypoplasia, and facial defects</td>
<td>Adenoma sebaceum</td>
<td>Epilepsy</td>
<td>Astrocytoma and glioblastoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mental retardation</td>
<td></td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Perioral and oral mucosal papillomatosis with areas of black pigmentation</td>
<td>Similar lesions on neck, axilla, and groin</td>
<td>Absence of endocrine abnormalities, obesity, and family history</td>
<td>Gastric adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albright’s syndrome</td>
<td>Solitary or multiple foci of fibrous dysplasia of jaw bones</td>
<td>Café au lait spots</td>
<td>Polyostotic fibrous dysplasia and bony deformities (1% of cases)</td>
<td>Fibrosarcoma and osteogenic sarcoma developing in areas of fibrous dysplasia</td>
</tr>
<tr>
<td></td>
<td>Oral pigmentation (rarely)</td>
<td></td>
<td>Periconrous sexual development</td>
<td></td>
</tr>
<tr>
<td>Paget’s disease of bone*</td>
<td>Localized or generalized bony jaw growths</td>
<td>—</td>
<td>Large head, curved back, and bowed legs deformity</td>
<td>Osteogenic sarcoma, chondrosarcoma, fibrosarcoma, and giant cell tumor of bone developing in affected areas</td>
</tr>
<tr>
<td>(osteitis deformans)</td>
<td>Hypercementosis</td>
<td></td>
<td>Raised serum alkaline phosphatase, usually with normal calcium and phosphorus levels</td>
<td></td>
</tr>
<tr>
<td>Cowden’s syndrome</td>
<td>Papillomatosis of lips, gingivae, palate, pharynx, and faucaces</td>
<td>Lichenoid and papillomatous lesions of perioral, perinasal, and periorbital areas, ear, and neck</td>
<td>Hamartomas of skin, gastrointestinal tract, breasts, and thyroid</td>
<td>A variety of neoplasms affecting principally the ovaries, colon, ear canal, and various soft and hard tissues</td>
</tr>
</tbody>
</table>

*Continued*
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Oral Lesions</th>
<th>Other Skin Lesions</th>
<th>Associated Abnormalities</th>
<th>Associated Malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanthomatosis</td>
<td>Pale yellow nodular subcutaneous</td>
<td>Similar deposits on skin, eyelids,</td>
<td>Abnormal and elevated serum triglycerides and cholesterol fractions, arterosclerosis, hypertension, diabetes, and heart disease</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td></td>
<td>deposits, especially on lips and cheeks</td>
<td>and tendons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Langerhans cell (eosinophilic) granulomatosis*</td>
<td>Radiolucent jaw bone lesions, gingival swelling, “floating teeth”</td>
<td>Infiltrates on other mucous membrane and skin surfaces</td>
<td>Generalized lymphadenopathy, hepatomegaly, and splenomegaly; focal lesions in lung, thymus, and other organs</td>
<td>Malignant lymphomatous disease</td>
</tr>
<tr>
<td>Amyloidosis* (AL type)</td>
<td>Macroglossia, microscopic and gross waxy deposits in lips and sub-mucosal tissues</td>
<td>Waxy papules or plaques clustered in axillae, anal, inguinal, facial, and neck regions</td>
<td>Similar deposits in heart, kidney, gastrointestinal tract, CNS, PNS, lung, endocrine glands, and joints</td>
<td>Multiple myeloma</td>
</tr>
</tbody>
</table>

AL = amyloid light chain; CNS = central nervous system; PNS =

*Oral lesions are only one part of a generalized neoplastic disease process.
years may elapse between the development of the polyps and adenocarcinomatous change, but since this is a condition with autosomal dominant inheritance with marked penetrance, it is usual to examine (often by elective laparotomy) all family members who are beyond puberty. Several jaw bone and skin lesions have been described in families with genetic susceptibility to these conditions, including solitary and multiple osteomas, impacted teeth, odontomas, desmoid fibroma, and epidermoid cysts.

The adenomatous polyposis carcinoma (APC) gene is mutated, representing a tumor suppressor gene.

**Peutz-Jeghers Syndrome**

True polyps of the gastrointestinal mucosa (ie, adenomatous tumors that frequently demonstrate malignant behavior with both local and lymphatic spread), are relatively rare except in the sigmoid colon and rectum. In addition, a variety of polyloid lesions with very limited tendency to malignant change are found throughout the gastrointestinal tract. Many of these polyloid lesions are thought to be of inflammatory or hamartomatous origin and are also occasionally associated with dermatologic or oral mucosal abnormalities. Peutz-Jeghers syndrome, in which perioral and lip freckling, patchy brown oral mucosal pigmentation, and freckling of the distal aspect of fingers and toes are associated with polyloid lesions that are mainly in the small intestine, is a well-known example of these inherited polyloid syndromes. The polyloid lesions in this autosomal dominant condition generally behave as benign lesions although patients with carcinoma arising from adenomatous polyps have been reported. Bleeding or intussusception are the most likely complications. The perioral freckling often fades as the affected individual matures, leaving oral mucosal pigmentation that may be indistinguishable from racial pigmentation or pigmentation associated with Addison’s disease. Some members of affected families have the oral pigmentation but without any evidence of gastrointestinal polyposis.

**Nevoid Basal Cell Carcinoma Syndrome**

Nevoid basal cell carcinoma syndrome is inherited in a fashion similar to that by which Peutz-Jeghers syndrome is inherited, and thorough examination of all family members is justified when individuals present with characteristic jaw cysts,
facades (enlarged calvarium) and other bony abnormalities (calcification of the meninges and hypoplastic and bifid ribs), and skin lesions (basal cell carcinoma appearing as multiple pink or brown papules on the face, neck, and upper trunk).\textsuperscript{217,218} Despite the syndrome’s name, multiple basal cell carcinomas occur in only 50% of cases. In this condition, however, their multiple nature, appearance at an early age, and tendency to occur anywhere on the skin surface (often on areas covered by clothing) make early recognition and treatment difficult.

Many of the jaw cysts in affected individuals have a keratinized epithelial lining and may be filled with layers of desquamated squame. Such cysts are referred to as primordial or odontogenic keratocysts.\textsuperscript{136–138,219,220} Considerable interest has been shown in cysts of this type in recent years because they frequently “bud” and produce daughter cysts, which may result in a recurrence of the cyst despite its removal and because a keratinizing cyst lining is more common in dentigerous cysts that have undergone carcinomatous change. Such cysts also occur without other evidence of this syndrome (see Figures 7-19, 7-20, and 7-21), and in the older literature, they were often mistakenly referred to as epidermal inclusion cysts of the jaws (ie, epidermoid or dermoid cysts, which also contain various epidermal appendages) or as primordial cysts, indicating an origin from a distal extension of the dental lamina. The finding of multiple odontogenic keratocysts, however, should always suggest the possibility of the syndrome and a search for its other features.

Pitting of the soles and palms (milia, local areas of undermaturation of the epithelial basal cells) is an obvious additional finding in about half of the individuals affected by the syndrome, and facies with occular hypertelorism may be prominent. Continuous monitoring of these patients is advised, and any skin lesions that show signs of aggressiveness should be excised. Recurrences are reported to be rare, however.

There is no evidence that development of squamous cell carcinoma is a hazard associated with the odontogenic keratocysts in this syndrome, but occasional ameloblastoma and fibrosarcoma of the jaws have been reported. Although peripheral osseous curettage or ostectomy is sometimes recommended for odontogenic keratocysts to prevent recurrences,\textsuperscript{221} the literature suggests that simple curettage or marsupialization of the cysts found in this syndrome is adequate treatment.\textsuperscript{138,219,220}

The word “nevus,” sometimes used in the name of this syndrome (eg, “basal cell nevus syndrome”) and in certain other connotations (eg, “nevus flammeus” in Sturge-Weber syndrome, and “nevus unius lateris” for ichthyosis hystrix), refers to a genetically determined hamartoma or birthmark, not to a melanocytic nevus or mole. Nevoid basal cell carcinoma syndrome is inherited as an autosomal dominant condition with complete penetrance, and affected individuals have about a 50% chance of transmitting the condition. The \textit{patched} gene, a component of the sonic hedgehog signaling pathway, is mutated. One mutation is germline; the other is acquired in lesional tissue. \textit{Patched}, therefore, represents a tumor suppressor gene.

\textbf{Multiple Endocrine Neoplasia Type III (Multiple Mucosal Neuroma Syndrome)}

Multiple endocrine neoplasia types I to III (MEN I, II, and III) is a group of familial syndromes in which neoplastic change occurs in several endocrine glands in one individual.\textsuperscript{5} MEN I\textsuperscript{222} involves lesions in some combination of pancreatic islets, adrenal cortex, and parathyroid and pituitary glands; it includes Zollinger-Ellison (or gastrinoma) syndrome, in which multiple primary gastrin-secreting adenomas or adenocarcinomas are located in the pancreas, duodenum, or even extra-abdominal sites such as the parathyroid gland. Stomach ulceration and hyperplasia of the pancreatic islets and parathyroid glands develop secondary to the excess gastrin release and account for the characteristic presenting symptoms. Between one-quarter and one-half of gastrinomas have other features of the MEN I syndrome, which is not associated with any skin or oral phakomatosis.

Likewise, MEN II,\textsuperscript{223} which involves medullary carcinoma of the thyroid gland, pheochromocytoma of the adrenal medulla, and parathyroid hyperplasia or adenoma, is not associated with any phakomatosis. However, a subgroup of these patients exhibits multiple neuromas of the lips, tongue, and buccal, conjunctival, nasal, and pharyngeal mucosae, in association with their endocrine neoplasia (this is referred to as MEN III or multiple mucosal neuroma syndrome).\textsuperscript{224,225} Since these neuromas may occasionally predate any overt endocrine neoplasia, the recognition of these oropharyngeal lesions as possible evidence of MEN III can lead to the early and sometimes successful treatment of the associated malignancies.\textsuperscript{225}

Almost all individuals with MEN III have oral mucosal neuromas (Figure 7-40) that may be extensive enough to thicken the lip and produce a characteristic “bumpy” or “blubbery” lip appearance. In addition, these individuals may exhibit marfanoid habitus, café au lait spots, lentigines, and a history of diverticulosis or lower-bowel surgery.

Although there are complex interactions between the various involved endocrine organs in each of these three variant syndromes, the finding of multiple neoplastic endocrine involvement is thought to be due to a widespread predisposition to cancer in many tissues derived from neuroectoderm, rather than to endocrine interactions. Endocrine interaction is also evident in the occurrence of Cushing’s syndrome, hyperinsulinism, hypertension, and hyperparathyroidism in some affected individuals. Various combinations of abnormalities are found in the relatives of affected individuals. The finding of oral mucosal neuromas in association with a family history of carcinoma of the thyroid or pheochromocytoma clearly indicates a need to search for other evidence of this syndrome.

\textsuperscript{5} Endocrine abnormalities are also sometimes present in patients who have other inherited syndromes with neoplastic associations, such as neurofibromatosis 1, McCune-Albright syndrome, and von Hippel-Lindau syndrome. These conditions are usually excluded from the definition of multiple endocrine neoplasia.\textsuperscript{68}
Multiple oral mucosal neuromas on the posterior third of the tongue of a patient with type III multiple endocrine neoplasia. (Courtesy of C. Dunlap, DDS, Kansas City, Mo.)

**Tuberous Sclerosis**

Tuberous sclerosis is an inherited disorder that is characterized by seizures and mental retardation associated with hamartomatous glial proliferations and neuronal deformity in the central nervous system. Fine wartlike lesions (adenoma sebaceum) occur in a butterfly distribution over the cheeks and forehead, and histologically similar lesions (vascular fibromas) have been described intraorally. Characteristic hypoplastic enamel defects (pitted enamel hypoplasia) occur in 70% of affected individuals and only rarely in unaffected relatives. Rhabdomyoma of the heart and other hamartomas of kidney, liver, adrenal glands, pancreas, and jaw are described. The neoplastic transformation of the glial proliferations constitutes the “internal malignancy” of this syndrome.

**Acanthosis Nigricans**

The term “acanthosis nigricans” describes grayish brown thickened patches of skin, which are usually symmetrically distributed and which have a characteristic velvety papulosquamous texture. The axilla, base of neck, groin, and antecubital fossa are most commonly affected. A similar intraoral papillomatosis has also been described. Acanthosis nigricans is described in association with both benign and malignant systemic disease. Malignant acanthosis nigricans is often of sudden onset, is rapidly progressive, and is most commonly associated with gastric or other intra-abdominal adenocarcinomas (less commonly with lymphoma or squamous cell carcinoma). The skin change may precede the recognition of a malignancy and is considered to be an important diagnostic clue for possible internal malignancy. The skin pigmentation has been ascribed to the release of peptides from the tumor and usually fades following the tumor’s removal. Apart from its rapidity of onset and progression, benign acanthosis nigricans is indistinguishable from the “malignant” variety. Idiopathic (obesity-associated), endocrine (associated with insulin-resistant diabetes, Addison’s disease, or pituitary and pineal tumors), and drug-related (nicotinic acid, glucocorticoids, diethylstilbestrol) types of “benign” acanthosis nigricans are distinguishable.

**Albright’s Syndrome**

Polyostotic fibrous dysplasia with café au lait spots, bony deformities, and precocious sexual development is referred to as McCune-Albright syndrome or Albright’s syndrome (see “Fibrous Dysplasia of Bone and Albright’s Syndrome,” earlier in this chapter) and is an inherited form of fibrous dysplasia, usually with multiple bone involvement. Osteosarcoma develops in about 1% of patients with this syndrome. Since osteosarcoma also occasionally develops in patients with longstanding monostotic fibrous dysplasia (as the result of radiation therapy in some cases but even without such treatment in other cases) and in view of the greater volume of dysplastic bony tissue in which sarcoma can develop in polyostotic fibrous dysplasia, it is not known whether the lesion of Albright’s syndrome is more predisposed to malignant transformation than the lesion of monostotic fibrous dysplasia. Polyostotic fibrous dysplasia may occur in the absence of the other components of the syndrome (ie, café au lait spots and precocious sexual development), and skeletal surveys are indicated for patients with large or multiple lesions of fibrous dysplasia of the jaws, even in the absence of skin pigmentation. The gene that is mutated in Albright’s syndrome is an internal signaling G protein.

**Paget’s Disease of Bone (Osteitis Deformans)**

Paget’s disease of bone is by far the most common disease among those listed in Table 7-3, affecting about 3% of the population older than 45 years of age and about 6 to 7% of hospitalized patients. It is rare in patients younger than 40 years of age. The nature of this bone disease is unknown although evidence to suggest that it is a multicentric benign tumor of osteoclasts has been presented. No endocrine basis for the disease has been found, and the frequency with which malignant transformation occurs (in 1 to 2% of patients, especially those with multiple foci) and the heterogeneity of the osteoclasts in biopsy specimens from patients with Paget’s disease suggest that the disease itself may be a benign (hormone-sensitive) neoplasm of bone cells.

The possibility of an infective viral etiology for Paget’s disease is suggested by the ultrastructural demonstration of intranuclear inclusions in the abnormal osteoclasts found in these patients, as well as in osteosarcoma cells in Paget’s disease lesions that have undergone malignant transformation. Similar inclusions have not been demonstrated in other human sarcomas or in osteoclasts in normal bone, fibrous dysplasia, or metabolic bone disorders such as hyperparathyroidism and ricketts. However, similar inclusions have been reported in a giant cell tumor of bone. These inclusions consisted of bundles of microfilaments with an electron-lucent

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5 These lesions (compare with those of neurofibromatosis) are usually fewer than six in number although they are sometimes quite large and characteristically have an irregular (“coast of Maine”) border. They are usually on the same side as bony lesions and may overlie them.
core and usually showed evidence of paracristalline array. Similar inclusions are seen in cases of measles and in subacute sclerosing panencephalitis virus infections. Measles virus and respiratory syncytial (RS) virus antigens and ribonucleic acid (RNA) have also been reported in osteoclasts from Paget’s disease lesions, and it is possible that various Paramyxovirus infections modified by genetic or environmental factors are involved in the etiology of this multifocal neoplasm.

The bony lesions of Paget’s disease produce characteristic deformities of the skull, jaw, back, pelvis, and legs and are readily recognized both clinically and radiologically. Irregular overgrowth of the jaw bones, especially the maxilla, may occur and may lead to the facial appearance described as “leonias ossea.” A “ground-glass” change in the alveolar bones, which is often associated with loss of the lamina dura and root resorption, is sometimes apparent in dental radiographs made in the early (osteolytic) phase of the disease. Subsequently, the jaw bones and other affected bones are occupied by a dense sclerotic bony deposition that fixes the deformed skeleton in its characteristic shape and creates the diagnostic features of the calvarium (a “cotton wool” appearance between the widened bony tables of the skull), maxilla, maxillary sinuses, and elsewhere. Healing of dental extraction wounds in affected areas is poor, and excessive postsurgical bleeding from the highly vascular bone that is characteristic of this disease is a concern. The narrowing of skull foramina can cause ill-defined neuralgic pains. There is an increased incidence of both salivary and pulpal calculi. Jaw fractures do not usually occur (compare to Paget’s disease of the long bones), but benign giant cell tumors and malignant sarcomatous transformation affect both the jaw bones and the long bones of these patients with some frequency. Multicentric sarcomas are not uncommon.

Although a few patients with Paget’s disease have no symptoms, many suffer considerable pain and deformity. These problems, associated medical problems such as cardiac failure and hypercalcemia, and the high incidence of malignant transformation have encouraged the use of a variety of new treatments of this disease, many of which are still being tested. The majority of these agents are designed to suppress some of the metabolic events by which bone cells remodel the calcified tissue and influence the exchange of mineral ions between bone and the circulating fluids. These agents include antibiotics (ie, intravenous mithramycin, an effective inhibitor of osteoclastic activity), hormones of human and animal origin (high-dose glucocorticoids and porcine, salmon, and human calcitonin administered subcutaneously or by nasal spray or suppository), salts such as the diphosphonate etidronate (which effectively reduces bone resorption), and cytotoxic agents like plicamycin and dactinomycin. A marked reduction in pain and some slowing in the progression of the disease have been attained with many of these agents.

Urinary levels of calcium and hydroxyproline (a measure of collagen metabolism) and serum alkaline phosphatase levels (a measure of osteoblastic activity) are useful for diagnosing Paget’s disease and for monitoring bone resorption and deposition during treatment. Radiologic findings are also often diagnostic, and computed tomography and Tc-99m diphosphonate and gallium-67 bone scanning may be used to define the extent of bone involvement.

Usually not manifest until the patient’s fifth decade, Paget’s disease has a definite familial distribution, and susceptibility to this disease is probably inherited as an autosomal dominant condition, as are the majority of the syndromes listed in Table 7-3. It is clearly not in the same category of disease as the other listed syndromes, in which benign oral lesions may signal the presence of internal malignancy. The oral lesions in Paget’s disease are simply the manifestation, in the jawbone, of a widespread bone disease; however, it is well for the dentist to realize that the patient with Paget’s disease of the jaw bones has an increased chance of developing sarcoma both orally and wherever else the disease is manifested. In view of the rarity of a giant cell tumor in the jaws except as a complication of Paget’s disease, the finding of this lesion in a patient who is older than 40 years of age should raise the possibility of previously undiagnosed Paget’s disease.

**Cowden’s Syndrome**

Cowden’s syndrome (multiple hamartoma and neoplasia syndrome) is characterized by the hamartomatous involvement of many organs, with a potential for neoplastic transformation. It is inherited as an autosomal dominant character. Multiple papules on the lips and gingivae are often present, and papillomatosis (benign fibromatosis) of the buccal, palatal, faucial, and oropharyngeal mucosa often produces a “cobblestone” effect on these mucous membranes. The tongue is also pebbly, fissured, or scrotal. Multiple papillomatous nodules (histologically inverted follicular keratoses or trichilemmomas) are often present on the perioral, peri orbital, and perinasal skin, and oropharyngeal mucosa often manifests a cobblestone effect on these mucous membranes. Multiple papillomatous nodules are often present also on the pinnae of the ears and neck, accompanied by lipomas, hemangiomata, neviomas, vitiligo, café au lait spots, and acromelanosis elsewhere on the skin. A variety of neoplastic changes occur in the organs exhibiting hamartomatous lesions, particularly an increased rate of breast and thyroid carcinoma and gastrointestinal malignancy.

**Xanthomas**

Xanthomas are localized deposits of lipoprotein that are usually found in the skin, subcutaneous tissue, or tendons. They are of diverse origin; many are associated with vascular disease, and some are associated with internal malignancy. Similar nodules may occur intraorally and on the faces of individuals with a variety of disorders (lipidoses) characterized by an abnormal concentration of lipids in tissues or extracellular fluids. Many of these conditions are inherited, and some are secondary to diseases such as hypothyroidism, diabetes mellitus, obstructive liver diseases, and dysproteinemia (such as multiple myeloma). Isolated xanthomas sometimes occur in...
the absence of recognizable systemic abnormality, but they are almost certain to be a manifestation of a lipodystrophy when multiple lesions are found, and they are associated with similar lipid deposits elsewhere (in the skin, eyelids [xanthelasmas], and cornea, and as nodules on the tendons). It is important that these lesions are recognized and that the patient is referred for plasma triglyceride, cholesterol, and lipoprotein measurement and medical consultation since several of the inherited lipidoses are associated with the early onset of severe coronary atherosclerosis and diabetes mellitus, which are likely to be fatal if not treated. A thorough description of the occurrence of oral and facial xanthomatosis in association with the various lipidoses does not appear to have been published although there are case reports of oral lesions of this type. Many of the lipidoses are characterized in terms of the associated plasma lipoprotein abnormality. Xanthomatosis is manifest in types I to III and V hyperlipoproteinemias, and mucous membrane eruptions are frequent in types I and V (both of which exhibit hyperchylomicronemia). Xanthomas of the tendons, skin, and eyes and atheromatosis of the vascular endothelium are prominent features of types II and III (carbohydrate-induced) hyperlipoproteinemia, both of which carry a high risk of ischemic heart disease.

In Tangier disease, a familial high-density lipoprotein deficiency (a rare autosomal recessive condition) affects children, and adults exhibit startling orange or yellowish gray discolorations and a swelling of the tonsils, pharyngeal mucosa, and gingiva in association with hypocholesterolemia and the enlargement of other organs of the reticuloendothelial system (spleen, liver, and lymph nodes). Xanthomas are also frequently associated with multiple myeloma, leukemia, and some lymphomas, probably as a result of the dysproteinemias accompanying these malignancies.

**Langerhans Cell (Eosinophilic) Histiocytosis**

Osteolytic jaw lesions, xanthomas, and other oral soft-tissue swellings also occur in diseases that were previously referred to by the generic name of histiocytosis X but that have been renamed as Langerhans cell histiocytosis (LCH) with the recognition that the key proliferative component in these lesions is the Langerhans’ cell. This group includes such variants as eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian syndrome (triad of exophthalmos, diabetes insipidus, and destructive bone lesions). Widespread proliferation of tissue macrophages (formerly referred to as histiocytes) and specialized bone marrow–derived Langerhans’ cells characterize these diseases, which are often not benign. These eponyms have been respectively replaced with the following terms: acute disseminated LCH, chronic disseminated LCH, and chronic localized LCH.

Jaw bone lesions are relatively common in patients with Langerhans cell granulomatosis and may be the initial lesion detected. While the diagnosis must be established by examination of biopsy specimens, the presence of each of the following radiologic characteristics increases the likelihood that a given lesion is an example of Langerhans’ cell proliferation: a solitary intraosseous lesion, multiple “scooped-out” and sclerotic bone lesions with a well-defined periphery, periosteal new bone formation, and slight root resorption. Small localized aggregates of Langerhans’ cells that are occasionally noted in inflammatory periapical lesions are often interpreted as chronic localized Langerhans granulomatosis (incipient eosinophilic granuloma). Lesions of this type that have been followed clinically for as long as 10 years have remained localized, suggesting that local curettage may be adequate treatment of these microscopic lesions. Jaw bone lesions that contain lipid-filled macrophages rather than Langerhans’ cells are usually relegated to a category referred to as non-X histiocytosis and include such entities as xanthoma, xanthogranuloma, and benign fibrous histiocytoma. Follow-up studies suggest that these lesions, although locally destructive in some cases, generally are benign, remain localized, and may occasionally heal spontaneously.

**Amyloidosis**

Deposits of the AL type of amyloid (see Chapter 16) frequently occur in the oral cavity, secondary to the proliferation of abnormal clones of plasma cells that characterizes multiple myeloma. These deposits are most common in the tongue and gingiva, and apart from the development of macroGLOSSIA (see Chapter 7), gross enlargement of oral tissues from this cause is unusual although oral amyloidosis is generally included among the oral phakomatoses and has been the initial symptom of multiple myeloma on rare occasions.

**Acute and Granulomatous Inflammations**

Histopathologic examination of a biopsy specimen from a localized swelling of the jaws, tongue, lips, or oral mucosa occasionally reveals a chronic granulomatous inflammatory tissue response. The etiology of such a lesion can be readily identified from the calculus, other foreign body, or specific microorganisms evident on microscopic examination of the tissue. When a foreign body, an infectious agent, or an associated systemic disease cannot be identified, the differential diagnosis can be extensive and includes sarcoidosis, tuberculosis and other mycobacterial infections, fungal infections (histoplasmosis, blastomycosis), actinomycosis, syphilis, leprosy (in endemic areas), Hodgkin’s lymphoma, Crohn’s disease, and Melkerson-Rosenthal and Meischer’s syndromes. Tuberculosis, sarcoidosis, and cat-scratch fever are likely candidates if the swelling arises in a regional lymph node. Soft-tissue granulomas are usually small and are microscopically detectable only as focal collections of modified macrophages (epithelioid cells) and Langhans’ cells or foreign-body-type giant cells with a peripheral rim of lymphocytes; fibroblasts, plasma cells, and neutrophils may also be present. Two classic types of granulomatous response are recognized: (1) in tuberculosis, the granuloma or tubercle characteristically has a central area of amorphous granular debris (caseous necrosis) and usually contains acid-fast bacilli; (2) sarcoid granulo-
mas are noncaseating and may exhibit asteroid bodies in the giant cells as well as concentric calcific concretions (Schaumann's bodies). Variations on either of these two patterns are seen in the other granulomas. Actinomycosis, cat-scratch fever, leprosy, and Melkersson-Rosenthal and Meischer's syndromes are discussed below.

**Cervicofacial Actinomycosis**

Actinomycosis is an infectious disease caused by a slender gram-positive rod-shaped bacterium, *Actinomyces israelii*, that exhibits a number of simple funguslike characteristics, such as a tendency to grow as a mass of rounded bodies (clubs) and filaments in tissue (hence the term "ray fungus"), low virulence, and the property of eliciting suppuration, necrosis, and a chronic granulomatous tissue response. Based on the shared feature of a granulomatous tissue response, actinomycosis, tuberculosis, and syphilis were once grouped as the "specific granulomatous diseases." However, these three infections have little in common as far as their natural histories, clinical features, or treatments are concerned, even though chronic pulmonary infection with *Actinomyces* occasionally can be clinically and radiographically confused with tuberculosis. Since *Actinomyces israelii* is an anaerobic or microaerophilic species, isolation of the organism in pure culture is difficult, and identification is often based on demonstration of the organisms as stained in tissue sections or as microcolonies (sulfur granules) in pus. The organism is included among the normal oral bacterial flora and is especially concentrated in dental plaque, calculus, carious lesions, and tonsillar crypts. Almost all cervicofacial actinomycotic infections are endogenous in origin and occur when dental plaque, calculus, or gingival debris contaminates relatively deep wounds around the mouth. Although the classic lesions of cervicofacial actinomycosis are chronic low-grade persistent infections that may be difficult to eradicate, careful bacteriologic study of acute jaw and soft-tissue abscesses after surgical or other trauma has demonstrated that *Actinomyces israelii* may also be involved in acute and rapidly resolving supplicative lesions. Microscopic examination of periapical lesions of nonvital and endodontically treated teeth may also occasionally reveal an isolated periapical actinomycotic granuloma, suggesting that this otherwise noninvasive organism can also be walled off and tolerated in the oral tissues for long periods of time without evidence of active disease.

It is generally believed that pulmonary actinomycosis results from the aspiration of oral or tonsillar debris and that areas of localized atelectasis secondary to the obstruction of small air passages provide the necessary anaerobic conditions for the growth of *Actinomyces*. It is also possible that pulmonary actinomycosis may arise hematogenously, from an infected oral or cervicofacial focus. Ileocecal (intestinal) actinomycosis is the commonest other form of actinomycosis and usually arises following the rupture of an inflamed appendix, with the development of a mass in the right iliac fossa. Pelvic actinomycosis has been recognized as an important complication of some intrauterine contraceptive devices (IUDs). In immunocompromised individuals, spread via the bloodstream may occur from any of these primary foci of infection.

Approximately 60% of all actinomycotic infections occur in the cervicofacial area, and there is a history of tooth extraction or jaw fracture in about 15 to 20% of cases. It was once believed that the organism was implanted in the oral tissues by chewing wood splinters, blades, or stalks of grass and that the infection was more common in agricultural workers. More recent data fail to support this idea and have also cast doubt on *Actinomyces* as the universal etiologic agent for a cattle disease (referred to as "lumpy jaw") that was believed to be analogous to cervicofacial actinomycosis in man.

The submandibular region is the most frequent site of involvement in classic human cervicofacial actinomycosis, the disease usually having spread by direct tissue extension. There may be associated changes that are detectable at the portal of entry (such as a nonhealing tooth socket), exuberant granulation tissue, or periosteal thickening of the alveolus. On many occasions, however, the chronic infection spreads from the periapical region with minimal clinical signs until it is well established. Then, soft-tissue swelling or the development of a fistula causes the patient to seek treatment. The cheeks, the masseter region, and the parotid gland may also be involved. Extension to the skull and the meninges has occurred on rare occasions.

One of the characteristics of actinomycosis is the lack of immediate tissue reaction after implantation of the organism. It usually requires 6 weeks or longer for an actinomycotic swelling to break down and discharge pus. The multiple discharging sinuses that subsequently develop (Figure 7-41) and the sulfur granules that are often present in the pus are almost pathognomonic of the disease. The adjacent tissues usually have a hard, doughy consistency. The skin surrounding the discharging fistulae is purplish, and there may be small areas of hypertrophic granulation tissue. Acute pain is uncommon.

Primary actinomycosis of the tongue (Figure 7-42) must be differentiated from neoplasms, tuberculous ulceration, syphilitic gumma, and other chronic infectious granulomatous diseases such as histoplasmosis. In actinomycosis of the tongue, there is usually a small deep-seated nodule that is painless at first and causes little discomfort. The lesion gradually increases in size, and the overlying tissues soften and rupture. There may be temporary healing, after which the process is repeated, with the development of a more extensive lesion. Dysphagia is a prominent symptom in cases of extensive involvement.

Actinomycosis of the cervicofacial region may be confused with osteomyelitis. In osteomyelitis, pain is more severe, with greater destruction of bone and more rapidly developing suppuration. Radiologic studies aid in the diagnosis. Tuberculous adenitis and other causes of submandibular and cervical lymphadenopathy, such as cat-scratch disease, lymphogranuloma venereum, and Hodgkin's disease, should be considered. The presence of the boardlike induration found in actinomycosis
Benign Tumors of the Oral Cavity

and the finding of acid-fast organisms on examination of the exudate help in making a diagnosis. A presumptive diagnosis can be made if “sulfur granules” are present and if gram-positive mycelia can be demonstrated. A positive diagnosis can only be made from anaerobic culture and isolation of Actinomyces from infected tissue or pus. As previously discussed, the opportunity for positive diagnosis in this disease is limited and will occur only when the clinician and the microbiologist collaborate to confirm a suspected actinomycotic infection or when the organism is demonstrated in tissue section. Actinomyces spp. have also been isolated from areas of osteomyelitis, and typical actinomycotic colonies are sometimes noted in excised sequestra, suggesting that this infection may play a role in osteoradionecrosis.

Chronic cervicofacial actinomycosis is traditionally considered to be a difficult infection to eradicate, but more recent texts suggest that penicillin and tetracyclines are quite effective, particularly if high doses are used and continued for several weeks of treatment. At least four million units of penicillin should be given daily intramuscularly. Tetracyclines are administered at 500 mg every 6 hours. Preference is usually given to the use of tetracyclines for treatment of this infection to avoid the repeated intramuscular injections of penicillin. Iodides, sulfonamides, and radiation were all used at one time but no longer have any place in the treatment of these infections. Antifungal antibiotics do not affect the growth of actinomyces. Surgical drainage of definable foci of infection may be needed and occasionally may be curative alone. Hyperbaric oxygenation is also used in eradicating chronic jaw bone infections. The major problem associated with the treatment of actinomycosis is the development of allergic reactions to the prolonged high doses of antibiotics.

Asymptomatic periapical actinomycotic foci that are demonstrated in association with necrotic pulp tissue or endodontic treatment rarely result in progressive actinomycotic infection. The apicoectomy procedure by which such foci are demonstrated is adequate treatment alone in most cases. The finding of the ray fungus in a periapical granuloma always raises the question of whether additional antibiotic treatment is needed. If antibiotics are given in this circumstance, a somewhat shorter period of administration (eg, 1 to 2 weeks) is probably adequate.

Acute alveolar abscesses that are shown to be associated with Actinomyces infection have likewise usually resolved with the initial antibiotic treatment prior to recognition of Actinomyces as a possible causative agent. Once again, increased doses of penicillin or tetracyclines may be given for an additional 1 to 2 weeks, but the need for this is not well established. The widespread use of penicillin and other antibiotics prophylactically after dental extractions, jaw fractures, and other orofacial trauma is considered to be responsible for a decreasing prevalence of cervicofacial actinomycosis over recent decades. Localized foci of actinomycotic infection have been reported following the intentional reimplantation of teeth, and it is conceivable that localized actinomycotic lesions may become more frequent as dental implantology expands.

Cat-Scratch Disease

Localized lymphadenopathy of cervical lymph nodes because of an infectious agent that is indigenous to cats (clinically, there is often evidence of a recent infected cat scratch, bite, or other superficial injury on the hand or forearm of the patient) constitutes a specific infection that is referred to as cat-scratch disease or cat-scratch fever. A variety of microorganisms...
Diagnosis and Management of Oral and Salivary Gland Diseases

Cheilitis granulomatosa. A persistent swelling of the lip due to a nonspecific reaction may be self-limiting or require treatment with specific antibiotic therapy (e.g., cephalosporins) or immunologic methods. Most infections are self-limited, and some may require biopsy rather than microbiologic or immunologic methods. Most infections are limited and specific antibiotic treatment (e.g., with cephalosporins) or treatment by incision and drainage is rarely indicated. Disseminated cat-scratch disease, which results in multiple abscesses, pleural effusion, and skin and mucosal lesions in addition to lymphadenopathy, is recognized as an indicator of opportunistic infection. The term “Miescher’s syndrome” may also be used clinically, the latter term usually being restricted to those cases that also exhibit facial paralysis and a folded or plicated tongue dorsum. The differential diagnosis in these circumstances also includes sarcoidosis (particularly if the lip lesions are associated with facial paralysis [Heerfordt’s syndrome]) and Crohn’s disease, as well as the various infections known to be associated with tuberculosis reactions. Occasionally, similar granulomatous enlargements may involve the gingivae.

Hansen’s Disease (Leprosy)

Infection with Mycobacterium leprae remains endemic in many tropical countries. A proportion of infected individuals develop characteristic lesions (primarily on the skin and extremities) that are referred to as tuberculoid, lepromatous, and borderline or reactional, depending on the stage of the infection. Tuberculoid leprosy appears clinically as macular lesions of the skin that on biopsy are found to overlie subepidermal tuberculoid granulomas containing small numbers of acid-fast bacilli. Patients with tuberculoid leprosy give positive delayed hypersensitivity responses (referred to as Fernandez or Mitsuda reactions) to intradermal injections of extracts of the organism (lepromin test) and are not considered infectious. By contrast, the patient with lepromatous leprosy displays little evidence of immunity to the organism and develops multiple granulomatous masses (lepromas) affecting the face, nose, and ears (leontine facies) and the skin over the wrists, elbows, knees, and buttocks. Peripheral nerve tissue is also extensively involved, with both lepromatous nodules and apparently unaffected patches of skin often exhibiting hypoesthesia or anesthesia. Histologically, lepromas consist of aggregates of lipid-rich foamy cells (lepra cells), with large numbers of acid-fast bacilli present and little evidence of the T-cell response that characterizes tuberculoid granulomas. Patients with lepromatous leprosy are infectious and usually have progressive disease requiring antimycobacterial therapy. Borderline or reactional leprosy represents an intermediate stage between the tuberculoid and lepromatous types. The literature contains few descriptions of oral lesions in cases of tuberculoid leprosy. Lepromatous nodules of the tongue, palate, lips, and pharynx are reported more frequently, as reddish yellow or brown sessile or pedunculated mucosal nodules, and destructive lesions of the palate and nasal bones can lead to deformities that are traditionally associated with this disease. Oral lesions have been reported in 20 to 60% of patients with Hansen’s disease, the majority of these being lepromatous nodules.

Orofacial Granulomatosis

Sarcoidlike granulomatous lesions may be encountered anywhere in the oral cavity, head, and neck, and they may be multiple. When there are no other manifestations of systemic sarcoidosis and when the lesions, even though multiple, are confined to the oral mucosa and facial skin, the appellation “orofacial granulomatosis” is applied. A biopsy performed on a persistent and usually painless diffuse swelling of one or both lips that is not associated with any identifiable allergic reaction (angioneurotic edema) or systemic disease occasionally will reveal the presence of noncaseating tuberculoid-type granulomas with Langhans’ giant cells. If serial sectioning and special stains fail to reveal any foreign body or microorganism, the condition is often reported as cheilitis granulomatosa (Figure 7-43).

The terms “Miescher’s syndrome” and “Melkersson-Rosenthal syndrome” may also be used clinically, the latter term usually being restricted to those cases that also exhibit facial paralysis and a folded or plicated tongue dorsum. The differential diagnosis in these circumstances also includes sarcoidosis (particularly if the lip lesions are associated with facial paralysis [Heerfordt’s syndrome]) and Crohn’s disease, as well as the various infections known to be associated with tuberculosis reactions. Occasionally, similar granulomatous enlargements may involve the gingivae.

![FIGURE 7-43 Cheilitis granulomatosa. A persistent swelling of the lip on biopsy revealed noncaseating tuberculoid-type granulomas with no evidence of any foreign body or microorganism. (Courtesy of D. Krutchkoff, DDS, PhD, Farmington, Conn.)](image)
etiology, these lesions are usually treated with topical, intrale-sional, and systemic corticosteroids, with surgical reduc-
tion of the lip when the persistent swelling is a cosmetic or
functional problem.

▼ GINGIVAL ENLARGEMENTS

Gingival enlargement is usually caused by local conditions
such as poor oral hygiene, food impaction, or mouth breath-
ing. Systemic conditions such as hormonal changes, drug
therapy, or tumor infiltrates may complicate the process or
even set the stage for the development of unfavorable local
conditions that lead to food impaction and difficulty with
oral hygiene. Traditionally, a distinction was made between
hypertrophy of the gingiva (an increase in the size of the cel-
lar elements making up the gingiva) and hyperplasia (an
actual increase in the number of the cellular elements). Both
of these elements are usually present in inflammatory disease
of the gingiva. In this section, the word “hyperplasia” is used
simply to describe clinically evident gingival enlargement,
without reference to a particular histologic process underly-
ing the change. When edema, vascular engorgement, and
inflammatory cell infiltration predominate, gingival enlarge-
ment is referred to as inflammatory gingival hyperplasia.
When the enlarged gingivae consist largely of dense fibrous
tissue as a consequence of chronic inflammation or other
causes, the condition is referred to as fibrotic gingival hyper-
plasia. The term “chronic hyperplastic gingivitis” is often
used for either process.

Gingival enlargement may be associated with a wide vari-
ety of local and systemic factors. Enlargement is seen more
consistently with some of these factors. Examples are local
irritants; therapy with anticonvulsants, calcium channel block-
ers, and immunosuppressive medications; pregnancy and
other hyperestrogenic states; monocytic leukemia; and clinical
scurvy. A number of these are discussed elsewhere in this and
other chapters (eg, congenital epulis and pregnancy epulis,
phenytoin-induced hyperplasia, pyogenic granuloma,
leukemic gingival enlargement, diabetic gingivitis, scurvy, and
some of the congenital and inherited gingival enlargements).

Inflammatory Gingival Enlargement

In most instances, inflammatory gingival enlargement
begins at an area of poor oral hygiene, food impaction, or
other local irritation that can be readily controlled. However,
the pseudopockets formed by gingival enlargement make
the maintenance of good oral hygiene difficult, perpetuat-
ing a cycle of inflammation and fibrosis. The involved tissues
are glossy, smooth, and edematous and bleed readily. A fetid
odor may result from the decomposition of food debris and
from the accumulation of bacteria in these inaccessible
areas. Loss of interseptal bone and drifting of the teeth occur
in long-standing cases of inflammatory enlargement. These
changes are commonly referred to as gingivitis, or peri-
odontal disease when the process involves the loss of gingi-
val attachment and the subsequent loss of interproximal
bone.292,293

Gingival inflammation affecting primarily the maxillary
anterior region is observed in mouth breathers.294 In some
patients, abnormal facial development or malocclusion leads to a continued opening of the mouth, which predisposes these patients to this form of gingivitis. Varying degrees of gingival hyperplasia probably due to hormonal changes have been observed in association with the use of contraceptive pills.

The diagnosis of inflammatory gingival enlargement usually presents no difficulty. The edema of the tissues, their bright red or purplish red color, and their tendency to hemorrhage permits ready differentiation from fibrotic gingival enlargement. Although most gingival enlargements are inflammatory in nature, benign and malignant neoplasms of the gingivae also occur. A biopsy should be performed whenever the cause is unclear or whenever the lesion does not respond to local therapy (Figures 7-47 and 7-48).

Treatment of the inflammatory type of gingival enlargement consists of the establishment of excellent oral hygiene, the elimination of all local predisposing factors if possible, the elimination of any recognized systemic predisposing causes, and proper home care by the patient. In patients with extensive gingival hyperplasia, the affected tissue must be removed surgically, and the remaining tissue must be properly contoured. All local irritative factors such as calculus, the margins of cervical cavities, or areas of food impaction should be corrected. Local treatment is often of value, even when gingival hyperplasia is associated with systemic disease. Although systemic factors should be removed whenever possible, the elimination of local irritative factors may be all that is necessary to obtain a reasonably satisfactory clinical result.

**FIGURE 7-46** Inflammatory gingival enlargement associated with a noncaseating granulomatous tissue response. Such lesions have been described in patients diagnosed with Melkersson-Rosenthal syndrome and Crohn’s disease and are often seen in association with granulomatous cheilitis and nodular enlargements of the tongue and other areas of the oral mucosa. **A,** Red shiny gingivae. **B,** Low-power micrograph of biopsy specimen of gingiva, showing granulomatous infiltrate with Langhans’-type giant cells. **C,** High-power micrograph of the same specimen.

**FIGURE 7-47** **A,** Inflammatory gingival enlargement with secondary ulceronecrotic gingivostomatitis. **B,** Fibrosis of the gingivae, secondary to long-standing periodontitis.
The successful treatment of gingival enlargement in mouth breathers depends mainly on the elimination of the habit. Referral to an otolaryngologist (to determine if there is some obstruction of the upper air passages, such as enlarged adenoids) or orthodontic treatment may be required to permit the normal closure of the lips during sleep. A protective ointment such as Vaseline or Orabase may be applied to the gums at night. The oral changes that are associated with blood dyscrasias are described in the sections devoted to that subject. Generalized gingival enlargement (Figure 7-49, A) is occasionally one of the earlier symptoms of these diseases.

Fibrotic Gingival Enlargement

Gingival lesions of the fibrotic type have a normal pink color, or they may be slightly paler than normal. The tissue is firm, hard, and fibrous in consistency (because of the increase in fibrous tissue) and does not bleed readily or pit on pressure. Typical examples of gingival fibrosis are found in the gingival enlargements associated with the administration of the immunosuppressant cyclosporine, several calcium channel blocking agents, or phenytoin (Dilantin) and its derivatives and in diffuse fibromatosis of the gingiva. A fibrotic gingival enlargement may develop in any patient with long-standing gingival hyperplasia.

Phenytoin-Induced Gingival Hyperplasia

Phenytoin-induced gingival hyperplasia296–298 (see Figure 7-49, B) affects at least 40 to 50% of patients who use the drug for longer than 3 months. More severe effects may not develop until after several years of continued use. Evidence from animal studies, individual case reports, and clinical trials indicates that both the drug and local irritation from plaque and calculus or restorations and appliances are etiologic factors. If gingival irritation can be eliminated completely, gingival hyperplasia will be only minimal at most.299 Continuous and obvious irritation, such as that associated with banded orthodontic appliances, is often associated with very severe hyperplasia. The pathogenesis of the gingival changes caused by phenytoin is still unknown; earlier suggestions that the gingival collagen is modified or that reduced serum and salivary immunoglobulin A (IgA) associated with the chronic use of phenytoin are the cause of the hyperplasia have not been confirmed. In fact, the available data still indicate that the mature fibrous-type phenytoin-induced gingival lesion represents neither hypertrophy, hyperplasia, nor fibrosis but is an example of the uncontrolled growth of a connective tissue of apparently normal cell and fiber composition.

The clinical appearance of phenytoin-induced gingival hyperplasia is characteristic although numerous variants are seen, depending on the location of the lesion, the particular irritant involved, and the extent of secondary inflammatory changes. The diagnosis is made from the history of chronic phenytoin use and the clinical appearance of the lesions; biopsy specimens and measurement of serum levels of phenytoin offer no additional diagnostic information. With very rare exceptions, the hyperplasia is restricted to the gingivae. After extraction of teeth and excision of the hyperplastic tissue, there is no recurrence.
Treatment of phenytoin-induced gingival hyperplasia should emphasize the elimination of local gingival irritants, scrupulous oral hygiene, and interdental massage. Seizures can often be controlled by other nonhydantoin derivatives, and the physician, the patient, and the family may be willing to experiment with supervised alteration of the patient’s anticonvulsive medications in order to reduce the hyperplasia. In general, nonhydantoin derivatives are not associated with gingival hyperplasia although such an association has been described with primidone therapy.

Menarche frequently brings a period of difficult management, partly because of the increased frequency of seizures that may occur at this time, partly because orthodontic treatment is usually begun about this time, and partly because of the patient’s increased awareness of any orofacial cosmetic defects as adolescence progresses. Some authors advocate that phenytoin be routinely avoided in treating female adolescents, to exclude the possibility of both gingival hyperplasia and hirsutism. The epileptic patient’s medication should at least always be reviewed before orthodontic treatment is begun.

Topically applied medications, including antiplaque agents such as chlorhexidine have no effect on the gingival overgrowth although they provide effective plaque control and reduce gingivitis. Hyperplasia of any degree will not be resolved simply by removing local gingival irritants, and excision of hyperplastic gingivae, root planing, and the elimination of rough margins on restorations are usually necessary before adequate gingival hygiene and plaque control can be established. If gingivectomy is not followed by adequate home care and the use of interdental massage, hyperplasia will recur. A customized splint may be constructed to retain the periodontal dressing needed after gingivectomy, ligating it to anterior and posterior teeth to prevent the pack from being dislodged and aspirated during a convulsive seizure. The epileptic patient with brain damage and mental deficits often presents a difficult management problem, particularly if neither parents nor nurses can provide adequate toothbrushing and gingival hygiene. In such cases, the value of gingivectomy must be carefully considered; gingevectomy should be resorted to only when the overgrowth interferes with closure of the teeth or lips or is a source of severe halitosis or hemorrhage.

Other nonsurgical treatments proposed for phenytoin-induced gingival hyperplasia include topical antihistamines and corticosteroids (neither of which has been subjected to a controlled clinical trial) and topical and systemic treatment with folate. Phenytoin resembles folic acid structurally and may serve as a competitive inhibitor of folate metabolism. Folic acid deficiency (subnormal serum folate and macrocytosis) develops in 40 to 90% of patients treated with anticonvulsants, and defects in folic acid utilization have also been described in others who have apparently normal serum folic acid levels. A controlled clinical trial of topical folate rinse (1 mg/mL) versus systemic folate (4 mg daily) in a small group of patients treated with phenytoin for a minimum of 3 months also showed some reduction in hyperplasia and mean periodontal probing depth, without any reduction in plaque or gingival indices. Since the administration of folate supplements to patients who are receiving phenytoin anticonvulsant therapy appears not to increase the risk of seizures, topical folate (which proved to be more effective than systemic folate in this trial) is a safe supplemental therapy for phenytoin-induced gingival hyperplasia. Phenytoin taken during pregnancy, with or without barbiturates, produces a two- to threefold increase in congenital anomalies. Affected offspring exhibit a variety of musculoskeletal growth defects, psychomotor retardation, and facial deformities, including ocular hypertelorism, depressed nasal bridge, hypertrichosis, and wide mouth. Although broad alveolar ridges have been reported in 30% of cases, gingival fibromatosis apparently does not occur with this route of administration.

Gingival Hyperplasia Induced by Cyclosporin A and Calcium Channel Blockers

For more than 40 years, phenytoin and its derivatives were the only drugs that were known to be associated with gingival hyperplasia. In the last 10 years, however, two new classes of drugs, the immunosuppressant cyclosporine and several
calcium channel blockers\textsuperscript{309–315} developed for treatment of hypertension and hypertensive cardiovascular disease, have been shown to have similar effects clinically, in experimental animals and in vitro\textsuperscript{316}. In general, the changes that are produced by these new agents are very similar to changes that are associated with phenytoin therapy although differences in the latent period for the development of gingival changes have been described.\textsuperscript{11} Two of the calcium channel blockers (oxodipine and nifedipine) also appear to cause hyperplasia of the labial mandibular gingiva rather than generalized gingival enlargement\textsuperscript{314} although this phenomenon may reflect species and dose rather than specific drug effects. In comparison with phenytoin-induced gingival hyperplasia, hyperplasia caused by calcium channel blockers (both substituted dihydropyridines and verapamil) is probably of low incidence but is similarly dose dependent (with nifedipine, 48 mg/d produced gingival hyperplasia whereas 35 mg/d did not)\textsuperscript{312} and positively correlated with oral hygiene and with the degree of gingival inflammation.\textsuperscript{298} However, only limited epidemiologic investigations of drug-induced gingival hyperplasia other than those of phenytoin-induced changes have been reported.

Phenytoin, cyclosporin A, and the substituted dihydropyridines are chemically dissimilar compounds, and no common metabolic breakdown product that might serve as a common denominator has been identified. However, all three influence calcium/sodium (Ca\textsuperscript{2+}/Na\textsuperscript{+}) flux, and this effect has been proposed as the common mechanism for development of the gingival hyperplasia associated with the three classes of drugs. Because folic acid is actively taken up at the cellular level by a Na\textsuperscript{+}-dependent transport mechanism, the effect of these three drugs on folic acid metabolism is being investigated. Two other findings associated with the gingival hyperplasia induced by these newer agents may provide new avenues for investigating the long-recognized but poorly understood phenomenon of drug-induced gingival overgrowth; these are

the production of gingival hyperplasia without inflammatory changes in rats treated with the experimental drug oxodipine\textsuperscript{314} and the recognition of ultrastructural myofibroblastic modification of over 20\% of the fibroblasts in human cyclosporine-induced hyperplastic gingiva.\textsuperscript{317}

**Syndromes Associated with Diffuse Gingival Enlargement**

Diffuse or generalized fibromatosis, papillomatosis, or angiomatosis of the gingivae are less common forms of gingival hyperplasia and are congenital or inherited disorders in many cases (Figure 7-50) although diffuse enlargement of the gingivae can also be a response to widespread local irritants, with or without a systemic factor.\textsuperscript{60,318–320} The enlargement may be present at birth or may become apparent only with the eruption of the deciduous or permanent dentitions. The following pathogenetic mechanisms are involved: hemangiomatous enlargement, infiltration of the gingival tissues by macrophages and other cells containing abnormal metabolic products, fibrotic reaction in gingivae overlying multiple impacted or grossly carious or hypoplastic teeth, and idiopathic fibrosis (possibly on a genetic basis). In many cases, the affected individuals have received phenytoin therapy to control the effects of associated central nervous system abnormalities and seizures. In such cases, it may be difficult to separate the basic gingival abnormality from a secondary phenytoin-induced hyperplasia.

If well developed, the dense and firm gingival tissue results in varying spacing of the teeth and in changes in profile and general facial appearance (Figure 7-51). The hyperplasia may be so excessive as to crowd the tongue, interfere with speech, cause difficulty in chewing food, and prevent normal closure of the lips. The surface of the hyperplastic tissue usually has a papillary or nodular appearance. Changes in the underlying alveolar bone are unusual in these patients unless progressive periodontitis develops as a complication of secondary plaque and calculus deposits.

Gingival fibromatosis can occur as a sporadic finding with or without associated physical or mental abnormalities; alter-

\textsuperscript{11}The following calcium channel blockers are associated with fibroblastic proliferation in vitro and gingival hyperplasia in man and experimental animals (specific data on unreferenced drugs are unavailable):\textsuperscript{297}

1. Verapamil\textsuperscript{309} (Calan, G.D. Searle & Co., Chicago, Ill.; Isoptin, Knoll Pharmaceuticals, Division BASF, K&F Corporation, Whippany, N.J.)
2. Substituted dihydropyridines currently marketed in the United States for treatment of hypertension, angina pectoris, cardiac arrhythmias, and other indications: diltiazem\textsuperscript{310} (Cardizem, Marion Merrell Dow Inc., Kansas City, Mo.), nicardipine (Cardene, Syntex Puerto Rico Inc., Humacao, Puerto Rico), nifedipine\textsuperscript{311,312} (Procardia, Pfizer Inc., New York, N.Y.; Adalat, Miles Inc., West Haven, Conn.), nimodipine (Nimorop, Miles Inc.) (used for treatment of cerebrovascular spasm postsubarachnoid hemorrhage), bleomycin (Blenoxane, Bristol-Myers, Evansville, Ind.) (used for chemotherapy for brain tumors, multiple myeloma, and Hodgkin’s and non-Hodgkin’s lymphomas)
3. Other experimental substituted dihydropyridines, some currently marketed overseas: felodipine, isradipine, nisoldipine, nitrendipine (an analogue of nifedipine),\textsuperscript{313} and oxodipine\textsuperscript{314,315}

FIGURE 7-50 Familial gingival hyperplasia.
**FIGURE 7-51** Profile and intraoral appearance of a 49-year-old male before all visible and easily accessible teeth were removed, after which he was able to oppose his lips for the first time in his life. Gingivae had been resected several times before. The father, son, and daughter all suffered from hereditary gingivofibromatosis. (Reproduced with permission from Winstock D. Hereditary gingivofibromatosis. Br J Oral Surg 1964;2:51)

**FIGURE 7-52**

**A**, Pronounced gingival hyperplasia in this 12-month-old child is associated with mucolipidosis II (I-cell disease). (Reproduced with permission from Galili D et al.335) **B**, Hyperplasia, developed during the first year of life and before the eruption of deciduous dentition. This hyperplasia was noted in association with multiple developmental abnormalities, skeletal changes (similar to those of Hurler’s syndrome) in the lower limbs and pelvis, unusual facies, and psychomotor retardation. The enlarged gingival tissue was firm and hard and obstructed mastication and closure of the mouth. (Reproduced with permission from Galili D et al335) **C**, Fibroblasts cultured from the skin biopsy specimen, showing numerous granular inclusions and the complete absence of lysosomal β-galactosidase activity. (Reproduced with permission from Terashima Y et al.336) **D**, Electron microscopic examination of gingival fibroblasts shows numerous membrane-limited empty vacuoles distending these cells. (Courtesy of Daniel Galili, DMD, Jerusalem, Israel) (Reproduced with permission from Mart JJ et al. Acta Neuropathol 1975;33:285)
<table>
<thead>
<tr>
<th>Eponym* or Name of Syndrome</th>
<th>Characteristic Features</th>
<th>Associated Features</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal dominant inheritance</strong></td>
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<tr>
<td>No eponym</td>
<td>Gingival fibromatosis with hypertrichosis, epilepsy, and mental retardation</td>
<td>Skeletal anomalies; commonest gingival fibromatosis syndrome</td>
<td>321, 322</td>
</tr>
<tr>
<td>Rutherford</td>
<td>Congenitally enlarged gingivae, delayed tooth eruption, &quot;curtainlike&quot; superior corneal opacities</td>
<td>Mental retardation, aggressive behavior, dentigerous cysts; only one kindred reported</td>
<td>323</td>
</tr>
<tr>
<td>Zimmerman-Laband</td>
<td>Gingival fibromatosis with defects of ears, nose, bones, nails, and terminal phalanges (&quot;froglike&quot; fingers and toes)</td>
<td>Hyperextensible joints, characteristic facies, hepatosplenomegaly</td>
<td>324, 325, 326</td>
</tr>
<tr>
<td>Cowden</td>
<td>Gingival papillomas as part of widespread oral, facial, and pharyngeal papillomatosis</td>
<td>Multiple hamartomas and neoplasms (see Table 7-3)</td>
<td>239, 240</td>
</tr>
<tr>
<td>No eponym</td>
<td>Familial gingival fibromatosis with progressive neurosensory hearing loss in young adults</td>
<td>Two extensive kindred reported</td>
<td>327</td>
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<tr>
<td>Tuberous sclerosis</td>
<td>Single or multiple fibromas of gingivae, oral mucosa, and skin (adenoma sebaceum), in association with other features of tuberous sclerosis</td>
<td>Epilepsy, mental retardation, and hamartomas of brain, heart, and kidney (see Table 7-3)</td>
<td>228, 229, 230</td>
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<tr>
<td>Gorlin-Goltz (focal dermal hypoplasia)</td>
<td>Gingival and other oral mucosal papillomatosis; lip and tooth defects</td>
<td>Poikiloderma, dermal fat herniation, adactyly and syndactyly; over 90% female</td>
<td>328, 329</td>
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<td><strong>Autosomal recessive inheritance</strong></td>
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<td>Murray-Puretic-Drescher</td>
<td>Gingival fibromatosis with multiple juvenile PAS-positive hyaline fibromas of head (&quot;turban tumors&quot;); trunk, and extremities</td>
<td>Suppurative lesions of skin and mucosa, flexion contractures, mental retardation, elevated urinary hyaluronic acid and dermatan sulfate</td>
<td>330, 331, 332</td>
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<td>Cross</td>
<td>Gingival and alveolar enlargement, microphthalmia, cloudy corneas, hypopigmentation and athetosis</td>
<td>White hair, blond skin; melanocytes decreased with reduced tyrosine activity; mental retardation; very rare</td>
<td>333, 334</td>
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<td>Ramon</td>
<td>Gingival fibromatosis, hypertrichosis, cherubism, mental retardation, and epilepsy; characteristic perivascular fibrosis in gingival biopsy specimens</td>
<td>Juvenile rheumatoid arthritis; gingival fibromatosis precedes cherubism</td>
<td>115</td>
</tr>
<tr>
<td>Lysosomal storage diseases†</td>
<td>Neonatal/childhood gingival enlargement (see Figure 7-46); widened alveolar ridges and/or widely spaced teeth</td>
<td>Specific enzymatic deficiencies; generalized visceromegaly (often with macroGLOSSIA) associated with lysosomal storage of intermediates (see Table 7-1)</td>
<td>60, 335, 336, 337</td>
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<tr>
<td><strong>Sporadic or unknown pattern of inheritance</strong></td>
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<tr>
<td>No eponym</td>
<td>Gingival fibromatosis with or without bony involvement (&quot;diffuse osteofibromatosis&quot;) and with no familial pattern or other associated findings</td>
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<td>333, 339</td>
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<tr>
<td>No eponym</td>
<td>Gingival fibromatosis in a child with a new chromosome translocation</td>
<td>Hypertrichosis, facial anomalies, and sickle cell trait; single case reported</td>
<td>334</td>
</tr>
<tr>
<td>Sturge-Weber</td>
<td>Orofacial and meningeal angiomatosis with secondary mental deficiency, seizures, and hemiplegia; ipsilateral nevus flammeus and mild to severe gingival enlargement</td>
<td>Hyperplastic vascular gingivae blanch with pressure; bony hemangiomomas and delayed tooth eruption</td>
<td>60, 63</td>
</tr>
<tr>
<td>Acanthosis nigricans (malignant variety)</td>
<td>Gingival papillomatosis associated with similar periorificial, mucosal, and skin (pigmented) lesions</td>
<td>Gastric adenocarcinoma (see Table 7-3)</td>
<td>60, 201</td>
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<td>Epidermal nevus (ichthyosis hystrix lateralis)</td>
<td>Cutaneous nevi that can extend to involve oral mucous membrane and gingiva, with localized warty papillomatosis</td>
<td>Mental deficiency, skeletal abnormalities, and hypoplastic teeth</td>
<td>338, 339</td>
</tr>
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PAS = periodic acid–Schiff.

* A number of representative case reports are referenced in this table; see References 60 and 318 to 320 for additional citations.

† Hunter’s (X-linked recessive), Hurler’s, Morquio’s, Maroteaux-Lamy, and Sly’s syndromes; GM1 gangliosidosis type I, aspartylglucosaminuria, mannosidosis, I-cell disease (see Figure 7-52), and sialic acid storage disease (sialuria).
natively, it may occur as part of a well-defined syndrome. Both autosomal dominant and autosomal recessive patterns of inheritance are recognized, as well as sporadic cases with no pedigree history. Genetic heterogeneity and variable expressivity also contribute to the difficulty encountered in assigning a diagnosis to familial gingival fibromatosis in specific clinical situations. The treatment of gingival fibromatosis is often unsatisfactory. Gingivectomy is usually necessary although the tissue may regrow.

A list of the syndromes that are most consistently associated with diffuse gingival enlargement (Figure 7-52) is provided in Table 7-4.321–339

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