Chapter 76: Oral Mucosal Lesions

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This chapter discusses nonneoplastic lesions that involve the oral mucous membranes. Only the more common lesions seen in the oral cavity are considered; there is no attempt to be comprehensive. More complete and detailed information about these and the less common lesions can be found elsewhere (Cawson and Eveson, 1987; Regezi and Sciubba, 1989; Shafer et al, 1983; Wood and Goaz, 1990).

The principal emphasis is on the clinical features of the lesions and their management, when appropriate. Of the several different formats that can be used to classify lesions, we consider the clinical appearance the most appropriate. Thus lesions are grouped into the three classic clinical presentations that have been described: color change, raised, and depressed. Lesions that show a color change and are raised are discussed under the raised category. Vesiculobullous lesions that initially appear as raised lesions but usually are seen as ulcerations also are discussed in the raised category. Lesions occurring on the gingiva are identified as a specific group; because many of the entities are unique to this area, they are recognized largely by both their clinical appearance and their location. We believe this format is the most practical when trying to identify clinical disease.

Lesions Showing a Color Change

Predominantly white mucosal lesions

The term *leukoplakia* has been used in many contexts in the past, ranging from a general description of any white mucosal lesion to a histologic diagnosis implying premalignant change. As defined by the World Health Organization, however, leukoplakia should be used as a clinical diagnosis to indicate a white lesion that cannot be removed by gentle scraping and that cannot be diagnosed clinically as any other lesion. Therefore several oral mucosal lesions may appear as white patches but should not be diagnosed clinically as leukoplakia.

Leukoedema

Leukoedema is a benign condition that most likely represents a variation of normal mucosal appearance, although smoking may accentuate its features. Almost 90% of blacks and 45% of whites exhibit the filmy, opalescent quality of the buccal mucosa that characterizes leukoedema. Fine folds occasionally are observed in the affected mucosa and superficially may resemble other conditions, such as lichen planus (Fig. 76-1). Leukoedema is asymptomatic and has no malignant potential. Histologically the epithelial cells appear edematous adn swollen, with no evidence of epithelial atypia. Stretching or everting the buccal mucosa causes the white, filmy character to disappear. Since this condition is completely benign, no treatment is necessary.

White sponge nevus

Initially described by Cannon in 1935, white sponge nevus is a benign mucosal disorder inherited as an autosomal dominant trait. Usually the lesions appear in childhood and are seen as thick, white, typically corrugated folds involving primarily the buccal mucosa, although other areas of the oral mucosa and the vaginal and rectal mucosa may be affected (Banoczy et al, 1973). The characteristic histologic appearance is not pathognomonic. A ragged surface parakeratin layer is seen along with a remarkable increase in the epithelial thickness. The cells of the spinous layer exhibit marked intracellular edema and small, pyknotic nuclei. Exfoliative cytology reveals keratinized squamous epithelial cells that exhibit an eosinophilic, pernuclear condensation of the cytoplasm. The diagnosis is made on the basis of history, clinical distribution of lesions, and cytologic or histologic findings. Because there is no malignant potential, no treatment is necessary.

Keratosis follicularis (Darier's disease)

Oral lesions may be seen in patients affected by keratosis follicularis, although the skin manifestations of this autosomal dominant genodermatosis are more striking. These patients typically exhibit numerous erythematous, crusted papules distributed primarily over the skin of the face and trunk. Intraorally, ragged white papules are seen on the gingivae, the alveolar mucosa, and the dorsal tongue (Weathers and Driscoll, 1974). Histologic examination shows the characteristic suprabasilar epithelial clefting, acantholysis, corps ronds, and grains. Diagnosis usually can be made on the basis of the skin lesions, although exfoliative cytology or biopsy will support the clinical impression.

Chemical injury

Application of caustic substances to the oral mucosa may produce varying degrees of epithelial necrosis, which clinically appears as a white, sloughing membrane. Perhaps the most commonly seen injury of this type results from the inappropriate use of aspirin as a topical anesthetic for tootache pain (Fig. 76-2). The clinical appearance of such lesions may be dramatic; however, obtaining a good history should confirm the clinical impression.

Nicotine stomatitis

Nicotine stomatitis is seen frequently among patients who smoke, particularly those who smoke pipes. Although the name implies that nicotine is responsible for the lesion, a more likely etiologic factor is the heat, which is associated with resulting tissue injury. These patients are primarily middle-aged men with a long history of smoking. The lesion is seen clinically as a diffuse, whitened palatal mucosa, which serves as a background for a variable number of 1- to 2-mm papules with erythematous centers (Fig. 76-3). These papular structures represent the inlamed orifices of minor salivary glands distributed in this area. Usually these changes are restricted to the hard palate and anterior soft palate, and occasionally keratinization may extend to involve the entire soft palate and buccal mucosa. Although the appearance of this condition is so typical that a clinical diagnosis is usually sufficient, at times one of the papules will enlarge to such an extent that a biopsy may be needed to rule out a salivary gland lesion. Nicotine stomatitis is considered a benign mucosal reaction, but these patients should be encouraged to reduce their tobacco use.

Candidiasis

Inection of the oral mucosa by the yeast *Candida albicans* is quite common and frequently is overlooked because of the range of clinical appearances. The classic description of candidiasis mentions white, curdlike flecks of material that can be wiped of, leaving a raw, bleeding surface. This definition is limited, however, because it describes only the pseudomembranous form of the disease, also termed *thrush.* In addition, the description is not accurate because a "bleeding" surface rarely is encountered, although the mucosa may appear erythematous (Fig. 76-4). The patients afected are usually very young or very old - age groups whose immune systems are not functioning optimally. Patients infected with the human immunodeficiency virus (HIV) often exhibit pseudomembranous oral cadidiasis because of their immunologic deficits. Patients who recently have taken steroids or broad-spectrum antibiotics also are affected. Immune suppression and elimination of competing bacteria are believed to cause the overgrowth of the yeast.

Diagnosis can be made by examining a potassium hydroxide preparation of the lesion's scrapings. The characteristic ovoid yeasts mixed with the hyphal forms of this dimorphic organism are seen. A routine cytologic smear may be stained using the periodic acid-Schiff method. These studies can be confirmed by culturing the organism on a mycologic medium such as Sabouraud's, Pagano-Levin, or BIGGY agar; however, a culture alone should not be used for diagnosing candidiasis because some patients who are simply carriers of the yeast will have a positive culture.

Treatment of oral candidiasis consists of 7 to 14 days of topical antifungal agent therapy, such as with nystatin or clotrimazole, or systemic drug therapy, such as with ketoconazole or fluconazole. Signs and symptoms typically abate in 1 to 3 days, and recurrence is not uncommon.

A less frequently encountered form of oral candidiasis that appears as a white lesion is *chronic hyperplastic candidiasis.* Because these lesions manifest as a white patch that will not rubb off, they have been termed *candidal leukoplakia* (Cawson and Lehner, 1968). The anterior buccal mucosa, just posterior to the angle of the mouth, is a typically affected site (Fig. 76-5). Unless such a lesion is mentioned in the clinical impression, the pathologist may overlook the candidal hyphae in the parakeratin later and simply diagnose the lesion as hyperkeratosis and chronic inflammation. Some degree of atypia may be seen microscopically within the lesion's epithelium, and some investigators have suggested that chronic hyperplastic candidiasis may represent a premalignant lesion (Field et al, 1989). Although a significant percentage of these lesions are removed completely with biopsy, those treated with antifungal agents frequently do not regress fully and need to be excised.

Lichen planus

Erasmus Wilson initially described lichen planus as a dermatologic condition in 1869. Since then little information has been added to our understanding of its etiology. The skin lesions appear as pruritic, violaceous papules distributed over the forearms and medial thigh. Oral lesions may be seen, with or without skin lesions. Patients affected by oral lichen planus are typically middle-aged adults, and most series have reported a female predilection (Scully and El-Kom, 1985). Several clinical forms of the disease have been described, although the

reticular and erosive types are seen most frequently.

Reticular lichen planus generally exhibits such a characteristic clinical pattern that biopsy is seldom necessary to establish the diagnosis. The lesions typically are seen on the buccal mucosa, often bilaterally, and consist of an interlacing network of white, slightly raised striae (Fig. 76-6). Gingival involvement also may be observed; however, the floor of the mouth and palatal mucosa usually are not affected. Lichen planus may occur on the dorsum of the tongue, but these lesions do not usually exhibit the characteristic linear pattern. Instead a flattened, well-delineated area of mucosal involvement is seen, characterized by a patchy, streaked pattern of atrophic, erythematous, and keratotic areas (Plate 13, A).

Erosive lichen planus is typically painful, unlike the reticular form. The most commonly affected areas include the buccal mucosa, the gingivae, and the lateral tongue. Clinically these lesions exhibit an erythematous or ulcerated central area surrounded by a keratotic periphery (Plates 13 and 14). Close inspection shows the peripheral keratosis forming fine, delicate striae radiating away from the center of the lesion. Occasionally these lesions may mimic those of chronic discoid lupus erythematosus. If biopsy is necessary to differentiate between the two, the specimen should be taken from the periphery of the lesion to obtain diagnostic tissue. The ulcerated center will not provide the necessary histologic information. The clinician should also be aware that 25% to 30% of lichen planus lesions will have a superimposed candidal infection.

Microscopically, oral lichen planus exhibits varying degrees of hyperorthokeratosis and/or hyperparakeratosis, irregular acanthosis and atrophy, degeneration of the basal cell layer, and a bandlike infiltrate of predominantly T lymphocytes. Immunofluorescence shows a coarsely granular deposition of fibrinogen at the basement membrane zone (Daniels and Quadra-White, 1981).

The reticular form of the condition requires no treatment because the lesions are asymptomatic. Erosive lichen planus is best managed by steroid therapy. With smaller, focal ulcerations topical application of triamcinolone or fluocinonide may be used to control symptoms. More diffuse lesions may require a steroid syrup, such as betamethasone, which can be applied topically or can be swallowed to provide systemic effect. Once the lesions are controlled, the dosage can be tapered, although the condition rarely is eliminated.

Chronic discoid lupus erythematosus

Approximately 25% of patients with chronic discoid lupus erythematosus (CDLE), a dermatologic condition, exhibit oral manifestations; oral lesions rarely are observed without skin lesions. Both the etiology of CDLE and its relationship to systemic lupus erythematosus remain unclear. The oral lesions clinically and histologically resemble erosive lichen planus. Clinically the presence of skin lesions should assist in the diagnosis. Histologically a perivascular lymphocytic iniltrate in the deeper submucosal tissue should suggest CDLE.

Leukoplakia

As stated earlier, the term *leukoplakia* should represent a clinical diagnosis only and should apply to white lesions that cannot be scraped off or recognized as any other disease process. Leukoplakic lesions tend to occur in an older age group, and males are affected more than females (Waldron and Shafer, 1975). Approximately 80% of these lesions microscopically show a benign histology consisting of either hyperorthokeratosis, hyperparakeratosis, acanthosis, or a combination of these. The remaining 20%, however, represent premalignant epithelial dysplasia, carcinoma in situ, or frank invasive squamous cell carcinoma. Obviously these lesions should be biopsied to establish a diagnosis. Biopsy is particularly indicated for a leukoplakic lesion that has no apparent cause, such as a source of irritation, or a lesion that does not resolve once the irritating factor is removed. Lesions that are found on the lower lip, the lateral tongue, and the floor of the mouth also should be viewed with suspicion.

Chapter 73 discusses further the premalignant aspects of leukoplakia.

Hairy leukoplakia

In 1984 Deborah Greenspan and her colleagues described an oral lesion that appeared to be strongly associated with patients who were infected with HIV. Because the lesion often exhibited a shaggy white surface and could not be wiped off, it was termed *hairy leukoplakia.* Initially hairy leukoplakia was thought to be caused by a chronic candidal infection because the organism frequently colonized the lesion; however, current research indicates that hairy leukoplakia is caused by infection of the epithelium by Epstein-Barr virus (Greenspan and Greenspan, 1989).

Clinically, hairy leukoplakia occurs on the lateral/ventral tongue of HIV-infected patients (Fig. 76-7). The lesions may be unilateral or bilateral, and uncommonly extend onto the dorsal surface of the tongue, the buccal mucosa, or the soft palate. Incipient lesions often do not exhibit the ragged, hairlike projections of more fully developed hairy leukoplakia. The microscopic features of hairy leukoplakia are characteristic, but not pathognomonic. Ideally, demonstration of Epstein-Barr virus by DNA hybridization studies would confirm the diagnosis.

Unlike classic leukoplakia, hairy leukoplakia shows no known tendency for malignant transformation. It is significant because its appearance correlates well with the rapid development of acquired immunodeficiency syndrome in HIV-infected patients. A majority of these patients will proceed to the end-stage of their disease within a 3-year period following the onset of hairy leukoplakia. Treatment of hairy leukoplakia is generally not necessary; however, it will regress with anti-herpesvirus therapy.

Predominanly red mucosal lesions

As with the white oral mucosal lesions, the etiologic agents associated with red lesions are numerous, representing a broad spectrum of disease. Most of these lesions are inflammatory and frequently nonspecific; however, these must be distinguished from specific microbial infections and preneoplastic conditions.

Benign migratory glossitis (geographic tongue)

Benign migratory glossitis is relatively common, affecting approximately 1% of the population. The etiology is unknown, although histologically the lesion resembles psoriasis of the skin. No particular age, race, or sex predilection is observed. Clinically the lesions are asymptomatic, or much less frequently, associated with a mild burning sensation from hot or spicy foods. A spectrum of clinical appearances exists because the lesions tend to appear and then regress, only to appear in another site and repeat the pattern. At their peak the lesions consists of an erythematous central area of atrophic mucosa. The tongue papillae are commonly lost in this area, resulting in a flat but nonulcerated mucosal surface. The erythematous area usually is surrounded by a serpiginous keratotic border, although this can vary in degree (Fig. 76-8. Frequently the tongues of these patients also show evidence of fissuring, an asymptomatic developmental condition seen on the dorsum. An infrequent finding is the appearance of similar lesions on other oral mucosal surfaces.

Benign migratory glossitis may occur on mucosal sites other than the tongue, such as the buccal and labial mucosa. These lesions have been reported under a variety of names, including *erythema migrans, stomatitis areata migrans,* and *ectopic geographic tongue.* Because these lesions are benign and usually asymptomatic, no treatment is recommended. In the occasional patient whose lesions are symptomatic, topical corticosteroid therapy is sometimes beneficial.

Vascular proliferations

The hemangioma is a fairly common lesion composed of a benign aggregation or proliferation of blood vessels. Whether these lesions represent true neoplasms or simply hamartomatous structures is open to debate. Frequently hemangiomas are present at birth, although at times they may appear later. Both the clinical size of the lesion and the histologic size of the vascular components may vary considerably. Usually these lesions blanch when pressure is applied, a phenomenon most easily observed by diascopy.

Treatment of hemangiomas varies according to their size and site and the patient's age. Many congenital lesions regress dramatically during childhood. Smaller lesions can be remove surgically. With larger, cosmetically deforming lesions, treatment is more difficult, although sclerosing agents, cryotherapy, and laser therapy all have been used with varying degrees of success.

Encephalotrigeminal angiomatosis, or *Sturge-Weber syndrome,* is a developmental disorder characterized by hemangiomas affecting the leptomeninges and/or the skin and mucosal surfaces innervated by the trigeminal nerve. The condition does not seem to be inherited but rather occurs sporadically, probably because the cephalic vascular plexus fails to regress during the ninth week of gestation.

Hereditary hemorrhagic telangiectasia is inherited as an autosomal dominant trait and is characterized by the appearance of multiple, 1- to 2-mm vascular dilatations. These surface lesions are traumatized easily and can be a source of bothersome hemorrhage. Although such blood loss occasionally has resulted in death, this is uncommon. Epistaxis is frequently the patient's initial complaint. Condition one must consider in the differential diagnosis include

Ehlers-Danlos syndrome and CRST (calcinosis, Raynaud's phenomenon, sclerodactyly, telangiectasia) syndrome. Treatment has included cryosurgery, skin grafting, and steroid therapy.

Candidiasis

Although candidiasis is regarded more frequently as a white lesion, it also may manifest as an erythematous one. This generally is associated with broad-spectrum antibiotic therapy, such as with tetracycline. The patient frequently reports a burning sensation on the tongue, and clinically the tongue may show a diffuse redness over the entire dorsum. A culture and exfoliative cytology should establish the diagnosis.

Another commonly observed red lesion associated with *Candida albicans* is *denture stomatitis.* This conditition involves only the denture-bearing mucosa of a patient who wears a complete or partial upper denture. In contrast to what the name implies, most patients are completely asymptomatic. Certain authors also have suggested the term *chronic atrophic candidiasis.* Even though *C. albicans* may be cultured from either the denture or the mucosa, this is not a consistent finding. Marked improvement of the mucosa may occur if the patient removes the denture while sleeping. Otherwise oral nystatin rinses and weak sodium hypochlorite solution soaks for the denture usually restore the mucosa's normal appearance.

Median rhomboid glossitis (central papillary atrophy)

Median rhomboid glossitis (MRG) appears as an asymptomatic, well-defined erythematous area involving the midline posterior dorsum of the tongue (Fig. 76-9). Loss of the lingual papillae is a prominent feature in this area of the lesion, which has prompted some investigators to suggest the term *central papillary atrophy* (Farman et al, 1977). The lesion's surface is usually smooth but may appear somewhat uneven or mammillated.

The etiology of MRG is controversial. For many years MRG was thought to be a developmental lesion resulting from a failure of the lateral processes of the tongue to cover the midline tuberculum impar during embryologic formation. MRG, however, is seen almost exclusively in adults, which would not be expected if the lesion were truly developmental.

Perhaps the most widely accepted etiologic hypothesis is that MRG results from a chronic candidal infection (Cooke, 1975). *C. albicans* often can be cultured from these lesions and identified in cytologic smears; also, antifungal therapy may result in regression of the lesion with regeneration of the lingual papillae. Such findings unfortunately are not consistent, and further study is necessary to better define the pathogenesis of MRG.

The management of MRG consists of establishing the presence of *C. albicans* and treating the patient accordingly. If the lesion shows a tendency to recur following antifungal therapy, then immunologic evaluation may be indicated because such lesions are common in HIV-infected patients. The dorsal tongue mucosa is a rare location for malignancy, and the patient can be reassured that the lesion has no precancerous potential.

Histoplasmosis

Although uncommon, oral lesions of histoplasmosis should be included in the differential diagnosis of erythematous lesions. Infection by the fungal organism *Histoplasma capsulatum* is confined primarily to the lower respiratory tract. In areas where the disease is endemic, such as the Ohio and Mississippi River valleys, as many as 80% to 100% of the population show evidence of past infection, usually identified as calcified perihilar lymph nodes on chest radiographs. Oral lesions usually occur in debilitated patients with disseminated disease. The lesion may appear as an ill-defined erythematous patch with an irregular, granulomatous surface, or it may exhibit ulceration, simulating malignancy (Fig. 76-10) (Miller et al, 1982). Biopsy and a culture are necessary to establish a diagnosis. Treatment for disseminated disease pregiously was limited to administration of amphotericin B; however, good results have been reported with ketoconazole (Toth and Frame, 1983).

Allergy

Allergy symptoms may be more widespread than generally realized. Patients with allergic reactions are usually adults with a history of a burning or stinging sensation of the oral mucosa. Sometimes the signs are localized, but diffuse involvement of the mucosa may occur. Often the symptoms wax and wane with no readily apparent pattern. The lesions are characterized by an erythematous color and may have a velvety texture. A white, keratotic surface may be superimposed on the erythematous base, clinically suggesting candidiasis (Fig. 76-11). Careful history taking usually reveals that the patient routinely uses a particular brand of chewing gum, mouthwash, breath mint, or other flavored material. Frequently the flavoring agent at fault is cinnamon (Allen and Blozis, 1988). Withdrawal of the offending agent results in complete resolution within 3 to 4 days. Other materials, particularly drugs, may elicit an allergic response from the oral mucosa. Such lesions may appear as a lichenoid mucositis, superficial ulceration, or a vesiculo-bullous process.

Anemia

Erythematous oral lesions have been described in association with various anemias. The most commonly involved site is the dorsal tongue mucosa, which clinically appears atrophic and reddened. Such lesions should not be confused with benign migratory glossitis, which also appears as atrophic dorsal tongue lesions. Benign migratory glossitis is typically sharply demarcated and often exhibits a slightly raised white border. Pernicious anemia (vitamin B12 deficiency) classically has been associated with elderly patients of northern Europe origin, although recent reports suggest that the disorder also may be common in black females (Greenberg, 1981). In these instances the lesions may not be restricted to the tongue mucosa; they also may be found on the buccal and labial mucosa. As with a candidal infection or allergy, the patient may complain of a burning sensation. Blood studies should confirm the diagnosis, and the lesions usually clear following appropriate therapy for the anemia.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) affects multiple organ systems through damage induced by circulating immunce complexes. Kidney involvement usually is seen and represents the most serious aspect of the disease. Skin lesions are also common, typically described as a butterfly-shaped rash distributed over the malar eminences and the bridge of the nose. SLE has a distinct female predilection and generally appears in the third and fourth decades of life. Oral lesions are seen occasionally in SLE and consist of erythematous and hyperemic lesions of the buccal mucosa or palate that may appear macular or somewhat granulomatous. Infrequently the oral lesions may represent the initial signs of the disease. Histologic findings are characteristic but not diagnostic, and the oral lesions usually resolve with systemic therapy.

Erythroplakia

The term *erythroplakia* literally means "red patch" and is used to denote erythematous lesions of the oral mucosa that cannot be diagnosed as any other lesion. Although the term should be used as a clinical diagnosis, microscopically these lesions very likely represent premalignant or malignant disease. Shafer and Waldron (1975) found that 90% of these lesions exhibited severe epithelial dysplasia, carcinoma in situ, or invasive squamous cell carcinoma. Thus even though erythroplakia is seen much less than leukoplakia, its presence is much more ominous. Once inflammatory processes have been ruled out, biopsy of the erythroplakic lesion is mandatory.

Burning tongue (glossopyrosis, burning mouth syndrome)

Burning tongue is a source of frustration to both patients and clinicians. The different terms used to identify the problem, such as *painful tongue (glossodynia), oral dysesthesia,* and *orolingual paresthesia,* reflect the uncertain nature of the problem. Most patients are female and often are post-menopausal; some have denture trauma, oral candidiasis, anemia, diabetes mellitus, psychogenic problems, and folic acid or vitamin B12 deficiencies (Lamey and Lewis, 1989; Main and Basker, 1983). Following appropriate management of these problems, the patient's symptoms often resolve.

Patients usually complain of a burning sensation similar to that caused by drinking extremely hot liquids such as coffee. Occasionally it may be described as a soreness, pain, or stinging sensation that is often constant and may vary in intensity. Some patients indicate that the sensation is not present in the morning but becomes apparent during the course of the day and increases in severity at the end of the day. The problem often is limited to the tongue but may involve the lips, anterior palate, gingiva, or buccal mucosa. Clinical examination typically shows no evidence of mucosal abnormality.

Management of these patients should focus on identifying local factors, systemic disease, or psychogenic causes. When these have been eliminated, patients should be reassured that no apparent evidence of significant disease exists; then they should be managed with supportive measures. Cancer phobia has been associated with burning sensations, and reassurance is extremely important for these patients.

Mucosal lesions characterized by yellow, brown, blue, or black pigmentation

Hairy tongue

The "coated" tongue is a common condition that has a characteristic white color caused by an accumulation of keratin associated with the filiform papillae. Occasionally, for poorly understood reasons, the keratin is either produced more quickly or desquamated less rapidly, resulting in a marked elongation of the filiform papillae. These elongated keratinaceous papillae resemble hair and frequently assume various colors, ranging from yellow to black, because of colonization with chromogenic bacteria. The condition is harmless, although the patient may complain of a gagging sensation. Treatment consists of having the patient use a tongue scraper to help remove the accumulated keratin.

Melanotic lesions

Melaning pigmentation of the lips and oral mucosa is a relatively common finding. In darker races such pigmentation is considered normal, although its distribution may vary from person to person. The usual sites for normal oral pigmentation include the attached gingival mucosa, the buccal mucosa, and the palate. Occasionally the fungiform papillae of the tongue are also pigmented.

Focal areas of melanin deposition may be seen as brown macular pigmentation that can involve any oral mucosal site but particularly the vermilion zone of the lips, the gingiva, palate, and buccal mucosa. When on the lips, such lesions may represent ephelides (freckles) or lentigines. Ephelides darken with sun exposure, whereas lentigines do not. Such focal pigmentation also may represent posttraumatic melanosis, although often a specific history of trauma cannot be elicited. Some investigators (Weathers et al, 1977) have termed these lesions *melanotic macules* because they do not fit well into any other category: the lack of change with sun exposure rules out ephelis, the lack of melanotyc aggregation at the tips of the rete ridges rules out lentigo, and the absence of a history of trauma rules out posttraumatic melanosis (Fig. 76-12). These lesions should be removed and examined histologically to rule out the possibility of melanoma, particularly if the patient has noticed an increase in the size or density of pigmentation (Buchner and Hansen, 1979).

With more diffuse areas of pigmentation, other conditions must be considered in the differential diagnosis. If the pigmentation has developed recently, a careful history must be taken. Certain drugs may induce melanin pigmentation. Addison's disease (chronid adrenocortical insufficiency) also may show disorders of pigmentation as a prominent feature. A history of weakness, salt craving, diarrhea, and vomiting suggests this diagnosis. The "bronzing" of the skin often is described as the classic sign of Addison's disease; however, the oral pigmentation involving the buccal mucosa, lips, tongue, and gingiva is frequently the initial manifestation of this disorder.

If diffuse melanin pigmentation of the oral mucosa has been present since early childhood, particularly if accompanied by freckling of the perioral, perinasal, and periorbital skin, then Peutz-Jeghers' syndrome should be considered as a diagnostic possibility. Patients with this syndrome frequently have a history of gastrointestinal problems caused by multiple intestinal polyps. Although these polyps are considered benign, with only sporadic reports of

malignant transformation, the problem of intestinal intussusception with its attendant complications may have to be resolved. Other family members should be investigated because this syndrome is inherited as an autosomal dominant trait with a high degree of penetrance.

Exogenous pigmentation

The most common form of exogenous pigmentation of the oral mucosa results from the implantation of silver amalgam during dental restorative procedures. The resulting amalgam "tattoo" may exhibit a range of color (brown, blue, black), depending on the amount of material embedded, the depth, and the duration of implantation (Fig. 76-13, A). These lesions are invariably asymptomatic, although occasionally a patient may notice the pigmentation and, fearing cancer, anxiously seek professional evaluation. Generally the area of discoloration is no more than 5 mm in diameter, and the usual location is the gingiva, although buccal mucosa, palate, tongue, and floor of the mouth are all potential sites (Buchner and Hansen, 1980). A dental radiograph of the lesion area (Fig. 76-13, B) may show fine, radiopaque remnants of the filling material, and histologic examination reveals granular foreign material, usually with little reaction between the host and foreign body. Silver amalgam often can be detected positively in microscopic sections because of the characteristic staining of the connective tissue reticulin fibers by the silver salts.

If the lesion can be verified by radiography, then no treatment is required because the material is inert. If positive identification cannot be made, excisional biopsy is indicated. Lesions to be considered in the differential diagnosis include other forms of exogenous pigment such as graphite, focal melanosis, the various melanocytic nevi, and malignant melanoma.

Varix

The varix seen on the oral mucosa is essentially the same lesion that affects the subcutaneous tissues of the lower leg, the so-called varicose veins. Varices typically develop in middle-aged or older persons and occur on the lower lip, labial mucosa, buccal mucosa, and ventral tongue. Because the lesions are basically dilated venous structures, they are deep blue or purplish blue. Usually varices are elevated slightly and may appear multilobular. Palpation typically reveals a soft consistency, although some degree of firm nodularity may exist because of thrombi formation within the vascular lumen. Thrombus formations, probably caused by stasis, is relatively common and has little or no adverse influence. Varices are usually characteristic enough to be diagnosed clinically. Excisional biopsy may be performed if the lesion is traumatized periodically or if the patient is concerned. Such a procedure is generally not associated with significant bleeding, since the intravascular pressure is low.

Kaposi's sarcoma

The development of Kaposi's sarcoa in an HIV-infected patient is one manifestation that heralds the onset of acquired immunodeficiency syndrome (AIDS). Although the incidence of AIDS-related Kaposi's sarcoma seems to be decreasing (now affecting 15% to 20% of AIDS patients), 50% of those patients with Kaposi's sarcoma will have oral lesions. Not infrequently the oral lesions are the initial manifestation of AIDS-related Kaposi's sarcoma (Ficarra et al, 1988).

The palate and gingivae are the most common sites of oral involvement of AIDS-related Kaposi's sarcoma. Clinically the lesions will present initially as red or purple macules or plaques that enlarge to form tumor masses (Fig. 76-14). Usually the lesions are asymptomatic; however, they may ulcerate or become so bulky as to interfere with speech or swallowing. Esthetics may also be a consideration in some cases.

Diagnosis is established by means of histologic examination of biopsy material. The purple color seen clinically can be correlated with numerous extravasated erythrocytes that have leaked from incompetent vascular spaces formed by the neoplastic endothelial cell proliferation. Treatment of AIDS-related Kaposi's sarcoma can include surgical excision, radiation therapy, or intralesional vinblastine injections (Epstein et al, 1989).

Lesions with a Raised Surface

Papilloma

Papillomas of the oral cavity are relatively common and easily recognized. Human papillomavirus antigen and DNA have been identified in a significant percentage of these lesions, suggesting an etiologic role for the virus. Papillomas tend to occur more frequently in the third, fourth, and fifth decades of life but may be found at any age without a significant sex predilection. The lesion's surface is usually irregular and is described as warty or cauliflower-like; however, at times it appears smooth. Most are less than 1 cm in size, pedunculated, and white. Papillomas appear most often on the soft and hard palates, uvula, tongue, and lips (Abbey et al, 1980).

Lesions that may have a similar appearance are verruca vulgaris, condyloma accuminatum, verruciform xanthoma, and early verrucous carcinoma. Although the papilloma's appearance is usually sufficiently characteristic to make a diagnosis, a biopsy should be taken to confirm it. An excisional biopsy provides both a diagnostic and a therapeutic service. Recurrences, presumably because of inadequate excision, have been reported infrequently.

Verruca vulgaris

Occasionally warts appear on the oral mucous membranes; these are identical to skin warts caused by the human papillomavirus. Oral verrucae tend to occur most often in children and young adults. Distinct, white, papillary, sessile skin lesions frequently are present and serve as a source of autoinoculation. The lips, labial mucosa, and tongue are affected.

A differential diagnosis should include papilloma, condyloma acuminatum, verruciform xanthoma, and verrucous carcinoma. In typical cases the last two usually can be discounted because of the lesion's location or the patient's age. A biopsy is necessary at times to make a diagnosis. Histologically, elongated rete ridges that are pointed inward and contain large, vacuolated cells with basophilic nuclei help distinguish this papillary lesion from others. Reports indicate that 50% of the lesions disappear spontaneously within 2 years. Simple excision or cryosurgery is the usual treatment.

Condyloma acuminatum

Condyloma acuminatum, a venereal wart, once was seen infrequently in the oral cavity and was considered a problem primarily of the anogenital region. In some locales this human papillomavirus induced lesion now is perceived as a relatively common lesion of the oral mucosa because of changing sexual practices. Often a history of oral-genital sex can be elicited from the patient. Lesions usually are found on the labial and buccal mucosae, tongue, gingiva, and palate. They begin as small, pink, papillary lesions and progress to white, cauliflower-like growths measuring 0.5 to 1 cm. Often patients have multiple lesions (Swan et al, 1981). The occurrence of condyloma acuminatum in HIV-infected patients is also recognized.

Depending on its stage of evolution, condyloma acuminatum may resemble an enlarged papilla of the tongue or a small papilloma. Later stages appear similar to papillomas, verruciform xanthomas, and verrucous carcinoma (Fig. 76-15). A biopsy is necessary to establish a definitive diagnosis. Simple local excision and cryosurgery have been the most effective forms of therapy. Recurrent disease is not uncommon.

Verruciform xanthoma

Although the nature and cause of verruciform xanthoma is unknown, speculation suggests that ir represents a reactive lesion. Verruciform xanthoma tends to occur mainly in middle-aged persons, with a slight predilection for females. The lesions range in size from a few millimeters to 1 or 2 cm and appear granular or wartlike. The color may be normal, red, or white. They may occur anywhere in the oral cavity but are found most often on the gingiva or alveolar mucosa (Neville and Weathers, 1980).

Lesions of verruciform xanthoma are similar in appearance to papillomas, verruca vulgaris, and squamous cell carcinoma. A biopsy is necessary to make the diagnosis. The principal histologic features include a verrucous epithelium that exhibits uniform elongation of the rete ridges. Large, foamy xanthoma cells fill the connective tissue papillae between the rete ridges. Reports show serum lipid levels of these patients to be normal. Therapy consists of simple excision of the lesion, and recurrence is rare.

Papillary hyperplasia

Papillary hyperplasia occurs primarily in patients who wear maxillary dentures. No specific factor has been identified as producing this lesion, but it tends to be found in patients who wear their dentures continuously or have ill-fitting ones. Occasionally papillary hyperplasia affects patients who are not wearing any dental appliance, and usually they have a candidal infection. The lesions typically are confined to the hard palate. They appear as multiple, small, red, edematous papules with a cobblestone appearance. The lesion may involve only a small focal area, multiple areas, or the entire hard palate (Plate 13, C).

Because of its characteristic appearance and its association with dental appliances, papillary hyperplasia usually is not confused with other lesions. Occasionally a granulomatous infection or carcinoma in situ may have a similar appearance. The histologic changes may be striking, showing a marked pseudocarcinomatous hyperplasia with abundant keratin pearl

formation. Perhaps because of this histologic pattern, it once was thought to represent a precancerous lesion; however, no good evidence exists to support this concept.

Treatment involves resolving the previously identified factors. The patient who wears a denture continuously must remove it a few hours each day, preferably while sleeping, and soak it in a denture cleaner. Ill-fitting dentures must be relined or remade. Complete resolution of the connective tissue hyperplasia usually does not occur; when extensive it should be considered for surgical removal.

Epulis fissuratum

Epulis fissuratum is an *inflammatory fibrous hyperplasia* caused by ill-fitting dentures. The denture flange produces a low-grade chronic irritation of the mucosa in the fornix, which results in a proliferation of soft tissue. This inflammatoy hyperplasia is a relatively slow process. The lesions occur most often in the facial region of the anterior jaws but can be found in any area. Usually they have linear fissures and may be bosselated or ulcerated (Fig. 76-16). The inflammatory response is variable; some swellings are fibrotic, whereas others appear edematous and red. Occasionally the swellings can be quite large and can be mistaken for tumors. The lesions must be excised and new dentures fabricated for the patient.

Irritation fibroma (traumatic fibroma)

Irritation fibroma is one of the most common soft tissue lesions in the oral cavity and represents a reactive fibrous hyperplasia. It usually occurs in the third, fourth, and fifth decades of life and can affect any area, usually the buccal mucosa, and less frequently the tongue, gingiva, and palate. The lesion usually appears as a sessile nodule with a smooth surface (Fig. 76-17). It may be pink or slightly keratotic, with a soft to rather firm consistency. The fibroma grows very slowly and may range in size from a few millimeters to 1 ro 2 cm.

Any mesenchymal or glandular tumor may look similar and must be considered in a differential diagnosis. Microscopically the lesion consists of relatively acellular collagenous connective tissue that may contain foci of chronic inflammatory cells. The irritation fibroma must be excised, since it will not regress and usually continues to enlarge.

Pyogenic granuloma

Pyogenic granuloma is a reactive lesion, an overgrowth of granulation tissue that can occur at any age but is found more often in the second through fifth decades of life, with a slight predilection for females (Angelopoulos, 1971). The lesion is a red or reddish purple mass with a smooth or slightly nodular surface. This mass is soft, may be ulcerated, and tends to bleed with minimal provocation. The lesion may be found anywhere in the oral cavity, but many occur on the gingival tissue. The facial regions of the anterior jaws are affected frequently; other sites include the tongue, buccal mucosa, and lips. These lesions may grow rapidly, a feature that mimics malignancy. The size may range from a few millimeters to several centimeters.

During pregnancy a clinically and histologically identical lesion may be found on the gingiva and is referred to as a *pregnancy tumor.* An endocrine imbalance may predispose the patient to this lesion. Other gingival swellings similar to pyogenic granuloma include peripheral odontogenic fibroma and peripheral giant cell granuloma. In other sites the pyogenic granuloma may appear similar to Kaposi's sarcoma. Histologically, the pyogenic granuloma has numerous dilated, blood-filled, endothelial-lined vascular spaces and shows marked proliferation of fibroblasts and budding endothelial cells. An infiltrate of both acute and chronic inflammatory cells of variable intensity also is seen.

The pyogenic granuloma must be removed surgically. At times the lesions, especially gingival ones, recur because of inadequate excision.

Mucocele

The mucocele, or *mucous retention phenomenon*, is thought to occur because of traumatic injury to a minor salivary gland duct that allows saliva to escape into the surrounding connective tissue. However, all lesions cannot be explained by trauma, and other factors seem to play a pathogenic role.

Mucoceles may occur at any age but more frequently appear in the first three decades of life. They may be seen in any area where salivary gland tissue is found but occur most often on the mucosa of the lower lip; the lesion here is called a *ranula.* A variant called the "plunging ranula" may produce a neck mass (McClatchey et al, 1984).

The mucocele appears as a soft, compressible swelling that may have a bluish color (Fig. 76-18). It ranges from a few millimeters to 1 or 2 centimeters; when small, it resembles a vesicle. The swelling occurs rather rapidly and persists for weeks to months, depending on its location. Superficial lesions tend to rupture, drain, and then recur. Deeper lesions usually persist, and their consistency may cause them to be mistaken for a lipoma. On occasion patients are seen after the swelling ruptures, discharging a thick, mucoid material, and only a tag of tissue remains. Because of the mucocele's compressible nature and bluish cast, it may be suspected as representing a vascular lesion or a mucoepidermoid carcinoma, which also may be mistaken for a mucocele. The histology shows a cavity filled with an eosinophilic coagulum and lined by connective tissue that consists of granulation tissue.

Occasionally a mucocele ruptures and does not recur; however, it usually is recurrent or persistent and must be excised. Marsupialization has generally proved unsatisfactory.

Retention cyst

Retention cyst involving the minor salivary glands are found infrequently in the labial or buccal mucosa. They are typically detected on palpation of the mucosa and are noted as small nontender, firm nodules. Often an erythematous, slightly dilated duct orifice can be seen on the mucosa overlying the nodule. Slight pressure on the nodule usually expresses a cloudy, mucoid saliva from the orifice.

Small sialoliths may be associated with these retention cysts or occur as separate entitites. These may be demonstrated readily on a dental radiograph with a soft tissue

exposure.

The clinical examination usually reveals these lesions. If any doubt exists, they should be excised because minor salivary gland tumors have similar clinical features. Because of their benign and asymptomatic nature, treatment is optional.

Palatal and mandibular tori

Bony tori are found on the palate and mandible with some frequency. Although not conclusive, the evidence suggesting that these are hereditary conditions is strong (Gould, 1964). Palatal tori appear in approximately 20% of the population, more frequently in females. Typically they are midline swellings that range from a small nodule to diffuse enlargements that involve almost the entire palate. A torus may be smooth, lobulated, sessile, or pedunculated (Fig. 76-19). Surprisingly patients often are unaware of its presence. A palatal torus may appear very similar to the swelling produced by a minor salivary gland tumor; however, the bony hardness and consistent midline location of the torus help confirm the diagnosis.

Mandibular tori occur far less frequently and may or may not be associated with a palatal torus. Usually the tori appear as smooth swellings on the lingual surface of the mandible in the bicuspid region. As with the palatal torus, they also can vary in size and shape. Infrequently only a unilateral exostosis may exist. Because of their unique and consistent location, mandibular tori should not pose a diagnostic problem.

Occasionally, bony exostoses occur elsewhere on the alveolar process of the jaws and produce a nodular excrescence of bone. These develop bilaterally and usually involve the facial alveolus in the moral region. The tori and exostoses are asymptomatic unless the overlying mucosa is traumatized and becomes ulcerated. Healing may take longer than usual because of the location. Removal of tori or exostoses usually is not necessary unless they interfere with dental prosthetic appliances.

Pemphigus

Current evidence suggests that pemphigus is an autoimmune disease characterized by serum antibodies directed against an intercellular substance of the epidermis and mucosa. Of the four major types, *pemphigus vulgaris* is the only form seen with any frequency in the oral cavity. It is reported that more than 50% of the patients have oral lesions as the initial manifestation of the disease, and these may precede the cutaneous lesions by as much as 2 years. In most cases the oral lesions have a slow and mild onset; often several months pass before multiple sites are involved. The average age of patients is 55, with those in the fifth, sixth, and seventh decades affected most often. A slight female predilection exists. The characteristic bulla usually is present only a short time. The lesion then appears as a rather superficial, ragged, eroded area. The surrounding mucosa is friable and can be dislodged with minimal pressure or trauma (Fig. 76-20). Lesions most often involve the palate, buccal mucosa, and tongue (Laskaris et al, 1982).

At times the disease waxes and wanes in severity, creating the impression that it may be resolving. Diseases to be considered in a differential diagnosis are benign mucous membrane pemphigoid, bullous lichen planus, erythema multiforme, and drug reactions. Histologically the diagnostic features are suprabasilar acantholysis, with acantholytic cells present in the bulla that develops. Direct and indirect immunofluorescence, which primarily demonstrate immunoglobulin G (IgG) directed against the intercellular spaces of the epithelium, should be used to verify the diagnosis.

Pemphigus vulgaris usually can be controlled with systemic corticosteroids. Unfortunately, high doses often are necessary, and patients develop complications of steroid therapy. To reduce the likelihood of this problem, gold, methotrexate, cyclophosphamide, and azathioprine may be used with steroids so that therapeutic steroid levels can be reduced.

Cicatricial pemphigoid

Because deposits of IgG and C3 complement are found in the basement membrane zone of cicatricial pemphigoid (benig mucous membrane pemphigoid (BMMP), ocular pemphigoid), it has been speculated that this is also an autoimmune disease. Pemphigoid is seen in an older age group of patients; the average age is 66, and females are affected more frequently. Lesions occur most often in the oral cavity, with the conjunctiva second. Skin lesions are seen infrequently. The initial oral lesion is a blister of variable size that may be clear or hemorrhagic, with a surrounding erythematous mucosa.

After the blister ruptures, the mucosa may persist as a shaggy membrane covering the blister site, or it may be lost, leaving an erythematous, eroded area (Plate 14, A). The buccal mucosa, gingiva, and palate are involved most often (Laskaris et al, 1982). The gingival lesions may be present with other mucous membrane involvement or may be the only manifestation of the disease. Gingival involvement appears as a diffuse, edematous redness. The gingival mucosa is extremely friable and hemorrhagic. Areas of necrosis and sloughing also may be seen (Plate 14, B).

Oral lesions may be relatively asymptomatic, even though they appear painful. The disease may improve slightly but seldom goes into remission; usually it becomes more severe with time. A differential diagnosis must include pemphigus vulgaris, bullous pemphigoid, bullous lichen planus, and erythema multiforme. Histologically the changes are nonspecific, showing only a subepithelial clefting. Direct immunofluorescency is necessary to make a diagnosis and demonstrates linear deposits of IgG and C3 in the basement membrane zone.

Topical corticosteroids have been used with limited success in treatment of cicatricial pemphigoid. Systemic corticosteroids usually are necessary to control the disease and at times are not effective. Dapsone also has been used with some success (Rogers et al, 1982).

Primary herpetic gingivostomatitis

The herpes simplex virus is responsible for an initial or primary infection of the oral cavity, herpetic gingivostomatitis. Either type 1 or type 2 virus may cause such a "primary" infection; however, type 1 is much more frequently responsible for oral disease, whereas type 2 is seen in the gential region. Primary herpetic gingivostomatitis once was considered mainly

pediatric disease, occurring most often in patients between ages 2 and 6. Presumably, because of improved hygiene and living standards, fewer adults have antibodies to the herpes simplex virus and thus may have primary infections caused by the herpes virus. Approximately 10% of the population has a clinical history of primary herpetic gingivostomatitis (Juretic, 1966).

The disease course is variable, ranging from a patient who has a few, mildly painful ulcers to one who is ill and complains of fever, malaise, sore throat, headache, and cervical lymphadenopathy. Vesicles appear 1 to 2 days after onset of symptoms and persist for another 1 to 2 days; they may affect any area of the oral cavity. Usually the gingiva becomes red and edematous.

Often patients are not seen during the vesicular stage. When examined, they have numerous 2- to 4-mm ulcers with a tan-yellow base and erythematous halo. Some ulcers coalesce to produce large lesions. At this stage the oral lesions of herpes essentially are identical to those seen in patients with aphthous ulcers (Fig. 76-21). This similarity has resulted in the misdiagnosis of recurrent aphthous ulcers as recurrent herpes.

Diseases that may have oral lesions similar to primary herpes are herpangina, varicella, herpes zoster, an hand-foot-and-mouth disease. Often other clinical features, such as cutaneous lesions, help distinguish one from the other. Several recurrent diseases also have oral lesions similar to those of primary herpes and should be included in a differential diagnosis because a patient with an initial episode of one of these diseases could not provide a history of recurrent episodes. Additional diseases that should be included are minor aphthous ulcers, herpetiform ulcers, Behçet's syndrome, cyclic neutropenia, and erythema multiforme. A diagnosis of herpes can be verified by exfoliative cytology, a culture for the virus, or immunofluorescence for the herpes antigen. The clinical course of primary herpetic gingivostomatitis usually lasts from 1 to 2 weeks. Supportive care may be necessary for patients with severe infections.

Recurrent intraoral herpes appears to be an infrequent problem. The lesions are characteristic and can usually be distinguished from others. They occur as a cluster of 10 to 20 small vesicles, which rupture within a few hours. Often the only evidence of disease is a cluster of small, superficial ulcerations (Fig. 76-22). The lesions' restriction to keratinizing tissue (the attached gingiva and hard palate) has diagnostic significance in that recurrent aphthous ulcerations ("canker sores") would not occur at these sites. Patients may have some mild discomfort, but often the lesions are relatively asymptomatic. The lesions may persist for 3 to 10 days (Weathers and Griffin, 1970).

Hand-foot-and-mouth disease

Hand-foot-and-mouth disease usually is caused by a group A coxsackievirus and primarily affects children. It is characterized by a vesicular eruption that appears in specific sites on the skin, hands, feet, and occasionally the buttocks. Oral lesions are found in 90% of the patients and may be the only evidence of disease in 15% (Alder et al, 1970). The intraoral vesicles are found most often on the palate, tongue, and buccal mucosa. The degree of involvement may vary from a few isolated lesions to a marked stomatitis. Clinical symptoms may include fever, malaise, coryza, diarrhea, abdominal pain, conjunctival infection, and headache; cervical lymphadenopathy is an uncommon finding. When the

disease is confined to the oral cavity, it cannot be distinguished from primary herpetic gingivostomatitis. To confirm a diagnosis, it is necessary to culture for the virus or examine the serum for antibody titers during the acute phase of the disease.

Herpangina

Herpangina has characteristic oropharyngeal lesions but is not a specific disease because several different coxsackieviruses and enteric cytopathogenic human orphan (ECHO) viruses have been associated with it. It primarily affects children and typically occurs during the summer and early fall. The condition usually is mild, but patients may complain of sudden fever, anorexia, neck pain, and headache. Multiple, small, gray-white papules and vesicles with an erythematous base appear and usually are confined to the soft palate, uvula, and tonsillar pillars. The vesicles rupture within 2 to 3 days, leaving ulcers that may enlarge. The cervical nodes may be enlarged and tender. Oral lesions seldom persist for more than a week. The diagnosis is made primarily on a clinical basis, with virus isolation necessary to confirm it (Cherry and Jahn, 1965).

Erythema multiforme

The specific cause of erythema multiforme is unknown, but several precipitating factors have been identified, including recurrent herpes simplex infections, *Mycoplasma pneumoniae* infections, and drugs such as sulfonamides. The disease has been separated into two forms: the classic disease, initially described by Hebra, is the *minor* form; the more severe disease, reported by Stevens and Johnson (1922) and characterized by marked mucosal involvement, is the *major* form. The oral mucosa is more likely to be involved in the major than the minor form.

Erythema multiforme is a disease of younger persons; most patients are between ages 10 and 30. It is much more common in males. The oral lesions have been described as progressing through five stages: macular, bullous, sloughing, pseudomembranous, and healing (Wooten et al, 1967). Although new lesions may develop during the course of the disease, the macular and bullous stages seldom are observed. The sloughing stage is marked by the collapsed covering mucosa, which is white and friable; it usually can be removed, leaving a red, raw surface. A fibrinous exudate appears on this surface, producing the pseudomembranous stage. The erosive areas vary in size and may range from several millimeters to diffuse involvement of a mucosal surface. Any area of the oral cavity may be affected, but the most common sites are the lips, buccal mucosa, and tongue. The gingivae usually are spared, whereas the lips frequently have a hemorrhagic crust, a distinctive feature of the disease (Huff et al, 1983).

Oral lesions occur in the absence of skin involvement in 25% or more of these patients. This makes establishing a diagnosis difficult becase no specific test exist for erythema multiforme. The diagnosis must be made from the history and clinical features. Other diseases with similar oral lesions inclde pemphigus vulgaris, bullous pemphigoid, cicatricial pemphigoid, and bullous lichen planus.

Erythema multiforme is a self-limiting disease, with the mild form lasting 2 to 3 weeks and the more severe form lasting up to 6 weeks. Therapy usually is not necessary for the mild form. In patients with more severe forms corticosteroids have been used to provide symptomatic relief.

Lesions With a Depressed Surface

Most lesions with depression of their surface morphology are clinically ulcerations. Usually color changes are associated with such lesions because of the yellowish white fibrinous exudate, which fills the epithelial defect, and the peripheral erythema, which is characteristic of the accompanying inflammation. Other conditions may exhibit ulceration secondary to a vesiculobullous process and are considered elsewhere.

Traumatic ulcer

Ulcers secondary to trauma are very common and not restricted to any particular age, sex, or racial group. These may be caused by injury from biting, from coarse foods, or from an external object. Usually but always the patient can remember the initial injury. Clinically these lesions frequently exhibit an irregularly shaped, slightly elevated or rolled, erythematous border. The central portion of the lesion usually is depressed and may appear either granular and erythematous because of granulation tissue or yellowish white because of a fibrinous pseudomembrane. Sometimes pain is present, although tenderness is more characteristic. Usually these lesions heal spontaneously within 1 or 2 weeks; however, they may persist for as long as several months, particularly if the patient continually irritates the lesion or if other problems exist, such as xerostomia or immunosuppression.

Administration of a protective agent such as carboxymethylcellulose paste or an antibiotic, such as tetracycline syrup, may aid healing. Corticosteroids probably should not be used to treat these lesions because many steroidal properties can inhibit healing. Infrequently, excisional biopsy of the lesion may be performed, particularly if the lesion has been present for a significant time. Microscopic examination helps rule out other lesions in the differential diagnosis, such as squamous cell carcinoma, syphilis, histoplasmosis, or tuberculosis. Primary closure of the biopsy wound usually results in healing of the lesion site.

Primary syphilis

Although the majority of primary syphilitic lesions, also known as *chancres,* are seen in the genital region, perioral and oropharyngeal lesions are being identified with increasing frequency. Approximately 3 weeks following exposure to the causative organism, *Treponema pallidum,* an ulcerated papule develops at the site of the spirochete's initial penetration. Such lesions typically are painless and are associated with significant regional lymphadenopathy. Diagnosis at this stage may be difficult because serology frequently is negative. If dark-field microscopy is used as a diagnostic aid, care must be taken to avoid contaminating the material with saliva because *Treponema microdentium* is a common inhabitant of the oral microflora that may be mistaken for *T. pallidum.* Examination of biopsy material reveals an ulceration with an intense plasmacytic infiltrate. A special silver stain such as the Warthin-Starry must be used to identify the organism in tissue sections.

Perleche

The term *perleche* has been used since the mid-nineteenth century to describe fissured lesions at the corners of the mouth. Also called *angular cheilitis,* this condition is seen with some frequency, particularly in elderly patients whose dentures do not provide the appropriate support for the facial contours. As a result, creases in the facial skin develop at the commissures. These creases remain continually moist with saliva, creating an environment that is favorable to infection by yeasts, primarily *Candida albicans,* and other microorganisms such as *Staphylococcus aureus* (Ohman et al, 1986). Frequently the condition clears following treatment with antifungal cream such as nystatin; however, if the skin crease is allowed to persist, the condition will return. Lesions of perleche also should suggest the presence of other candidal lesions of the oral mucosa. Recurrence may be expected if the oral reservoir of *C. albicans* is not treated.

Recurrent aphthous ulcerations

Recurrent aphthous ulcers (RAU), known as "canker sores" in lay terminology, are a very common problem that usually affects a younger population, but no age group is immun. The etiology of RAU is unknown at present, although cell-mediated hypersensitivity to oral mucosa has been suggested as a probable cause. Alternately, aphthous ulcers may represent several entities with a similar clinical appearance. One study has shown that the tendency to develop these lesions may be inherited (Miller et al, 1980). Other suggested etiologic or contributing factors include microbial agents (L form of streptococcus), hormonal changes, nutritional deficiencies (vitamin B12, folic acid, iron), hypersensitivity states (gluten-sensitive enteropathy), and stress (Rennie et al, 1985).

Clinically, aphthous ulcers may appear as solitary lesions, or several may develop simultaneously. The frequency of episodes and the size of the lesions may vary consierably from patient to patient, and three categories have been described based on the clinical presentation. *Minor aphthae* are by far the most commonly seen form, appearing as 2- to 10-mm ulcerations that exhibit a yellowish white central fibrinous pseudomembrane and an erythematous periphery. The central area frequently is depressed, and the rim of the ulcer usually is smooth (Fig. 76-23). The ulcer typically is painful, and although a mild cervical lymphadenopathy may be found, these patients rarely have a fever. Healing occurs over 10 to 14 days. Sometimes the patient can attribute the development of aphthous ulcers to such factors as stress, minor trauma, or menses.

In contrast to minor aphthae, the *major aphthous ulcer* typically is much larger, at times attaining a size of 2 to 3 cm (Fig. 76-24). Often these patients are afflicted constantly with these lesions; when one resolves, another begins. Scarring may be seen after healing, and this probably relates to the size rather than any intrinsic property of the lesion.

Herpetiform ulcerations, as the name suggests, may mimic a primary herpes simplex infection. These lesions appear as numerous 1- to 2-mm ulcerations, which may be clustered in one area of the mucosa or distributed more widely (Plate 14, C). Unlike primary herpes, the lesions typically recur periodically. Viral cultures are consistently negative, and cytologic or histologic examination shows no evidence of viral cytopathic effect.

Differentiation of aphthous ulcerations from herpetic and other viral infections is important but may be difficult at times; however, several features should distinguish the lesions. First, aphthous ulcerations are frequently recurrent, whereas viral infections in the oral cavity are not. Second, aphthous ulcerations are found almost exclusively on non-keratinized mucosa, whereas viral lesions typically affect both keratinized (hard palate and attached gingiva) and non-keratinized mucosa. Third, aphthous ulcerations rarely cause systemic signs and symptoms, whereas viral infections frequently are associated with elevated temperature and malaise.

Management of the aphthous ulcerations is empirical and depends somewhat on the severity of disease. Isolated lesions respond well to application of a topical steroid, such as triamcinolone acetonide in a protective dental paste (Kenalog in Orabase). More diffuse lesions may require a steroid mouth rinse, such as betamethasone syrup. Severe involvement may require systemic steroid therapy for the first 3 to 4 days in addition to the topical therapy. Herpetiform ulcerations may respond to tetracycline, and often episodes of minor aphthae can be managed with tetracycline syrup, used as a mouth rinse and swallowed.

Behçet's syndrome

A Turkish dermatologist initially described the condition known as Behçet's syndrome. A major component is aphthouslike lesions of the oral mucosa. Certain groups such as the Japanese are more prone to develop the condition; in the USA Behçet's syndrome is relatively rare. In addition to oral lesions, these patients may develop genital ulcerations, uveitis, pustular vasculitis of the skin, synvitis, and meningoencephalitis. Two of these signs must be present with the oral lesions to make the diagnosis of Behçet's syndrome; however, oral aphthae alone have been known to precede development of the complete syndrome by years.

Reiter's syndrome

Oral ulcerations may appear as a component of Reiter's syndrome, a symptom complex characterized by conjunctivitis, nonbacterial urethritis, and arthritis. The etiology is unknown, although antecedent diarrheal illness and an increased incidence of human lymphocyte antigen B27 (HLA-B27) have been related to the disease. Historically Reiter's syndrome has been described as affecting primarily young men; however, recent studies have not found this to be true in a civilian population Neuwelt et al, 1982).

Wegener's granulomatosis

Wegener's granulomatosis is a disease of unknown etiology that affects multiple areas of the body, although the respiratory tract and the kidneys are the most significant sites of injury. The condition usually develops in adults, and no sex predilection is seen. The nasal cavity, sinuses, or oral cavity may be the initial site of injury, where an ulceration usually appears. The tissue destruction is probably secondary to the necrotizing vasculitis and granulomatous inflammation that histologically characterize the disease. Occasionally a diffuse papillary enlargement of the gingiva is associated with Wegener's granulomatosis (Edwards and Buckerfield, 1978). Recognition of this disease is important because most patients die of kidney failure unless treatment with an immunosuppressive regimen consisting of prednisone and cyclophosphamide is instituted.

Gingival Lesions

Desquamative gingivitis (gingivosis)

Desquamative gingivitis once was considered a degenerative disease of uncertain etiology; current studies indicate that it represents the clinical manifestation of several different diseases. Most of these patients display a unique oral appearance of chronic dermatoses such as cicatricial pemphigoid, lichen planus, pemphigus vulgaris, and bullous pemphigoid (Sklavounou and Laskaris, 1983). Not all patients show evidence of these diseases, however, suggesting that other factors exist. Also, a question about the role of hormonal influences still remains, since many patients are postmenopausal women. The gingiva shows a variable degree of edema and erythema, which may be somewhat focal or diffuse. With severe involvement the gingiva is very friable and bleeds with minimal trauma. The gingiva can be separated from the connective tissue with digital pressure or a jet of air from an air syringe. Bullae usually are not seen on the gingival tissues.

This chronic problem may wax and wane in severity. The lesions may remain confined to the gingiva for prolonged periods before involving other areas of the oral cavity. To determine whether the gingival disease reflects one of the dermatoses, immunofluorescent studies on gingival biopsy specimens are necessary. Topical corticosteroids have been beneficial in some cases. At times systemic corticosteroids may be required.

Fistula and parulis

Inflammatory disease of either odontogenic or periodontal origin may result in a draining fistula on the alveolar process. This fistula is associated with a tooth that has either apical periodontitis because of marked pulp disease or severe periodontal involvement. It usually is found on the facial gingiva or alveolar mucosa near the involved tooth. A papule or small nodule that may be umbilicated is the typical lesion (Fig. 76-25). The inflammatory response can vary, resulting is little or marked redness of the fistula and surrounding tissue. A purulent discharge may be expressed from the lesion.

Occasionally a small abscess, referred to as a "gum boil" or parulis, develops on the alveolar process. This ruptures and persists as a fistula. To resolve these lesions, the offending tooth must be treated, usually with endodontic or periodontal management.

Gingival enlargement

The gingival tissues may show marked and diffuse enlargement because of a variety of conditions, some of which reflect systemic disease. Often poor oral hygiene and local factors contribute to the problem. Because of endocrine changes during puberty and pregnancy, gingival enlargement may occur. A more regional enlargement of the gingiva may also be seen in patients with diabetes mellitus and regional enteritis (Crohn's disease). A diffuse and boggy swelling affects patients with myelogenous and monocytic leukemia.

A marked and extensive proliferation of the gingival tissues may be seen in patients who are taking phenytoin or who have fibromatosis gingiva. This proliferation may be so extensive that the crowns of the teeth are covered. Two other drugs that have also been shown

to produce gingival hyperplasia are cyclosporin A (Wysocki et al, 1983) and the calcium-channel-blocking agents such as nifedipine (Lederman et al, 1984). Fibromatosis gingiva, also known as *hereditary gingibal fibromatosis*, may have an autosomal dominant mode of inheritance. This gingival enlargement is reported to be associated with hyertrichosis, epilepsy, and mental retardation.

A pebbly enlargement of the gingiva that may have an associated fine papillomatosis of the oral mucosa is seen in patients with *Cowden's disease* (multiple hamartoma and neoplasia syndrome) (Fig. 76-26). Multiple facial trichilemmomas usually are present. These patients may have fibrocystic disease of the breast, thyroid goiters or adenomas, multiple polyposis of the gastrointestinal tract, and ovarian cysts. In female patients there is an increased prevalence of malignant disease in the breasts and thyroid gland (Salem and Steck, 1983).

The patient's oral hygiene habits and local factors such as calculus and irregular restorations influence many of these gingival enlargements. Good oral care often stabilizes the condition or results in some improvement. If the gingival proliferation is marked, surgical excision (gingivectomy) is necessary to restore the tissues to normal.

Acute necrotizing ulcerative gingivitis

Acute necrotizing ulcerative gingivitis (Vincent's angina, trenchmouth) has been attributed to a fusiform bacillus and a spirochete, *Borrelia vincentii.* Stress often has been implicated as a modifying factor, and a recent study supports this theory (Cogen et al, 1983). Young adults and teenagers are affected most often, and an increased frequency of this condition is seen in HIV-infected individuals.

The classic feature of the disease is ulceration of the interdental papillae, which has been described as having a "punched out" appearance. The problem may be limited to a few areas or may be generalized. When the disease is more extensive, the free gingival margins also become ulcerated and covered by a necrotic membrane (Fig. 76-27). The adjacent gingiva often is edematous and erythematous. Patients frequently complain of severe pain. The problem can spread to the adjacent soft tissues, producing areas of erythema and ulceration. When the condition is mild, debridement and cleaning of the affected dentition usually is sufficient to resolve the disease. In more severe cases rinses and antibiotics are necessary.