A clinician attempting to diagnose an ulcerative or vesiculobullous disease of the mouth is confronted with the fact that many diseases have a similar clinical appearance. The oral mucosa is thin, causing vesicles and bullae to break rapidly into ulcers, and ulcers are easily traumatized from teeth and food, and they become secondarily infected by the oral flora. These factors may cause lesions that have a characteristic appearance on the skin to have a nonspecific appearance on the oral mucosa.

Mucosal disorders may occasionally be correctly diagnosed from a brief history and rapid clinical examination, but this approach is most often insufficient and leads to incorrect diagnosis and improper treatment. The history taking is frequently underemphasized, but, when correctly performed, it gives as much information as does the clinical examination. A detailed history of the present illness is of particular importance when attempting to diagnose oral mucosal lesions. A complete review of systems should be obtained for each patient, including questions regarding the presence of skin, eye, genital, and rectal lesions. Questions should also be included regarding symptoms of diseases associated with oral lesions; that is, each patient should be asked about the presence of symptoms such as joint pains, muscle weakness, dyspnea, diplopia, and chest pains. The clinical examination should include a thorough inspection of the exposed skin surfaces; the diagnosis of oral lesions requires knowledge of basic dermatology because many disorders occurring on the oral mucosa also affect the skin. Dermatologic lesions are classified according to their clinical appearance and include the following basic lesions:

1. Macules. Well-circumscribed, flat lesions that are noticeable because of their change from normal skin color. They may be red due to the presence of vascular lesions or inflammation, or pigmented due to the presence of melanin, hemosiderin, and drugs.
2. Papules. Solid lesions raised above the skin surface that are smaller than 1 cm in diameter. Papules may be seen in a wide variety of diseases including erythema multiforme simplex, rubella, lupus erythematosus, and sarcoidosis.

3. Plaques. Solid raised lesions that are over 1 cm in diameter; they are large papules.

4. Nodules. These lesions are present deep in the dermis, and the epidermis can be easily moved over them.

5. Vesicles. Elevated blisters containing clear fluid that are under 1 cm in diameter.

6. Bullae. Elevated blisterlike lesions containing clear fluid that are over 1 cm in diameter.

7. Erosions. Moist red lesions often caused by the rupture of vesicles or bullae as well as trauma.


9. Ulcers. A defect in the epithelium; it is a well-circumscribed depressed lesion over which the epidermal layer has been lost.

10. Purpura. Reddish to purple flat lesions caused by blood from vessels leaking into the subcutaneous tissue. Classified by size as petechiae or ecchymoses, these lesions do not blanch when pressed.

11. Petechiae. Purpuric lesions 1 to 2 mm in diameter. Larger purpuric lesions are called ecchymoses.

A detailed history of the present illness is essential in making the diagnosis of oral mucosal disease. Three pieces of information that should be obtained early in the history will help the clinician rapidly categorize a patient’s disease and simplify the diagnosis: length of time the lesions have been present (acute or chronic lesions), past history of similar lesions (primary or recurrent disease), and number of lesions present (single or multiple). In this chapter, the diseases are grouped according to the information just described. This information serves as an excellent starting point for the student who is just learning to diagnose these disorders, as well as the experienced clinician who is aware of the potential diagnostic pitfalls.

The first section of this chapter describes acute multiple lesions that tend to occur only once, the second portion of the chapter covers recurring oral mucosal syndromes, and the third portion presents the patient with chronic multiple lesions. The final section describes diseases that present as chronic single lesions. It is hoped that classifying the disorders in this way will help the clinician avoid the common diagnostic problem of confusing viral infections with recurring oral syndromes, such as recurrent aphthous stomatitis, or disorders that present as chronic progressive disease, such as pemphigus and pemphigoid.

▼ THE PATIENT WITH ACUTE MULTIPLE LESIONS

The major diseases that cause acute multiple oral lesions include viral stomatitis, allergic reactions (particularly erythema multiforme and contact allergic stomatitis), and lesions caused by cancer chemotherapy or blood dyscrasias.

Herpesvirus Infections

There are 80 known herpesviruses, and eight of them are known to cause infection in humans: herpes simplex virus (HSV) 1 and 2, varicella-zoster virus, Cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 (HHV6). All herpesviruses contain a deoxyribonucleic acid (DNA) nucleus and can remain latent in host neural cells, thereby evading the host immune response. HHV6, a herpesvirus discovered in 1986, has been shown by seroprevalence studies to infect over 80% of the population by adult life. Two variants, HHV6A and HHV6B have been identified. The virus is commonly isolated from saliva and causes roseola infantum (exanthema subitum), a common childhood illness that is characterized by fever and a rash. The virus also is a cause of a mononucleosis-like syndrome in older children and adults. In immunocompromised patients, HHV6 can cause interstitial pneumonitis and bone marrow suppression. HHV7, which is commonly isolated from saliva, is presently not associated with a specific disease, whereas HHV8 has been closely associated with Kaposi’s sarcoma in human immunodeficiency virus (HIV)–infected patients. There is also evidence linking HHV8 to forms of lymphoma and Castleman’s disease.

HSV1, HSV2, and varicella-zoster are viruses that are known to cause oral mucosal disease. Cytomegalovirus is an occasional cause of oral ulceration in immunosuppressed patients, and it is suspected as a cause of salivary gland disease in HIV-infected patients.

The herpes simplex virus is composed of four layers: an inner core of linear double-stranded DNA, a protein capsid, a tegument, and a lipid envelope containing glycoproteins that is derived from the nuclear membrane of host cells. The two major types, HSV1 and 2, can be distinguished serologically or by restriction endonuclease analysis of the nuclear DNA. Classically, HSV1 causes a majority of cases of oral and pharyngeal infection, meningocencephalitis, and dermatitis above the waist; HSV2 is implicated in most genital infections. Although this distinction applies to a majority of cases, changing sexual habits are making that distinction less important. Both types can cause primary or recurrent infection of either the oral or the genital area, and both may cause recurrent disease at either site. Primary infection may also occur concurrently in both oral and genital sites from either HSV1 or HSV2, although HSV1 recurs more frequently in the oral region and HSV2 more frequently in the genital region.

Humans are the only natural reservoir of HSV infection, and spread occurs by direct intimate contact with lesions or secretions from an asymptomatic carrier. This latter method of spread of HSV is common; between 2 and 9% of asymptomatic individuals shed HSV in saliva or genital secretions.

Latency, a characteristic of all herpesviruses, occurs when the virus is transported from mucosal or cutaneous nerve endings by neurons to ganglia where the HSV viral genome remains present in a nonreplicating state. During the latent phase, herpes DNA is detectable, but viral proteins are not produced. Reactivation of the latent virus occurs when HSV switches to a replicative state; this can occur as a result of a
Primary Herpes Simplex Virus Infections

There are approximately 600,000 new cases of primary HSV infections per year in the United States. Primary HSV infection occurs in patients who do not have immunity resulting from previous contact with the virus. HSV is contracted after intimate contact with an individual who has active HSV primary or recurrent lesions. Primary HSV may also be spread by asymptomatic shedders with HSV present in salivary secretions. The majority of oral HSV infections is caused by HSV1, but primary oral HSV2 infections may also occur chiefly as a result of oral-genital contact. Infection of the fingers (herpetic whitlows) of health professionals may occur during treatment of infected patients. Dentists may experience primary lesions of the fingers from contact with lesions of the mouth or saliva of patients who are asymptomatic carriers of HSV, although the incidence of this disorder should be minimal if gloves are worn (Figure 4-1). Use of gloves should also prevent the spread of HSV from the fingers of health care workers infected with herpetic whitlows to patients.

Primary HSV infection of the newborn was previously believed to be caused by direct contact with vaginal HSV lesions during birth, but it has now been established that a majority of mothers giving birth to children with primary HSV are asymptomatic carriers without lesions. These infections of the newborn result in viremia and disseminated infection of the brain, liver, adrenals, and lungs.

Newborns of mothers with antibody titers are protected by placentally transferred antibodies during the first 6 months of life. After 6 months of age, the incidence of primary HSV1 infection increases. The incidence of primary HSV1 infection reaches a peak between 2 and 3 years of age. Incidence of primary HSV2 infection does not increase until the age when sexual activity begins. Studies of neutralizing and complement-fixing antibodies to HSV have shown a continual rise in the percentage of patients who have had contact with the virus until 60 years of age, demonstrating that although the primary infection with HSV1 is chiefly a disease of infants and children, new cases continue to appear during adult life. This is consistent with the many reports of adults with primary herpetic gingivostomatitis.

The incidence of primary herpes infection has been shown to vary according to socioeconomic group. In lower socioeconomic groups, 70 to 80% of the population have detectable antibodies to HSV by the second decade of life, indicating prior HSV infection, whereas, in a group of middle class individuals, only 20 to 40% of the patients in the same age group have evidence of contact with HSV.

A significant percentage of cases of primary herpes are subclinical, although the apparently low incidence of a history of classic primary herpetic gingivostomatitis is also influenced by the young age of patients who develop the infection, by the improper diagnosis of some cases, and by the cases of primary herpetic pharyngitis that cannot be clinically distinguished from other causes of viral pharyngitis.

CLINICAL MANIFESTATIONS OF PRIMARY ORAL HERPES

The patient usually presents to the clinician with full-blown oral and systemic disease, but a history of the mode of onset is helpful in differentiating lesions of primary HSV infection from other acute multiple lesions of the oral mucosa. The incubation period is most commonly 5 to 7 days but may range from 2 to 12 days.

Patients with primary oral herpes have a history of generalized prodromal symptoms that precede the local lesions by 1 or 2 days. This information is helpful in differentiating this viral infection from allergic stomatitis or erythema multiforme, in which local lesions and systemic symptoms appear together. These generalized symptoms include fever, headache, malaise, nausea, and vomiting. A negative past history of recurrent herpes labialis and a positive history of direct intimate contact with a patient with primary or recurrent herpes are also helpful in making the diagnosis.

Approximately 1 or 2 days after the prodromal symptoms occur, small vesicles appear on the oral mucosa; these are thin-walled vesicles surrounded by an inflammatory base (Figure 4-2). The vesicles quickly rupture, leaving shallow round discrete ulcers. The lesions occur on all portions of the mucosa. As the disease progresses, several lesions may coalesce, forming larger irregular lesions.

An important diagnostic criterion in this disease is the appearance of generalized acute marginal gingivitis. The entire gingiva is edematous and inflamed (Figures 4-3, A and...
Ulcerative, Vesicular, and Bullous Lesions

B, and 4-4). Several small gingival ulcers are often present. Examination of the posterior pharynx reveals inflammation, and the submandibular and cervical lymph nodes are characteristically enlarged and tender. On occasion, primary HSV may cause lesions of the labial and facial skin without intraoral lesions.

Primary HSV in otherwise healthy children is a self-limiting disease. The fever ordinarily disappears within 3 or 4 days, and the lesions begin healing in a week to 10 days, although HSV may continue to be present in the saliva for up to a month after the onset of disease.

LABORATORY DIAGNOSIS

The diagnosis of primary herpetic gingivostomatitis is straightforward when patients present with a typical clinical picture of generalized symptoms followed by an eruption of oral vesicles, round shallow symmetric oral ulcers, and acute marginal gingivitis. Laboratory tests are rarely required in these cases. Other patients, especially adults, may have a less typical clinical picture, making the diagnosis more difficult. This is especially important when distinguishing primary herpes from erythema multiforme since proper therapy differs significantly.

The following laboratory tests are helpful in the diagnosis of a primary herpes infection.

Cytology. For cytology, a fresh vesicle can be opened and a scraping made from the base of the lesion and placed on a microscope slide. The slide may be stained with Giemsa, Wright’s, or Papanicolaou’s stain and searched for multinucleated giant cells (Figure 4-5), syncytium, and ballooning degeneration of the nucleus. Fluorescent staining of cytology smears has been shown to be more sensitive (83%) compared with routine cytology (54%); it is the cytologic test of choice, when available.23

HSV Isolation. Isolation and neutralization of a virus in tissue culture is the most positive method of identification and has a specificity and sensitivity of 100%.23 A clinician must remember that isolation of HSV from oral lesions does not necessarily mean that HSV caused the lesions. Patients who have lesions from other causes may also be asymptomatic shedders of HSV.

Antibody Titers. Conclusive evidence of a primary HSV infection includes testing for complement-fixing or neutralizing antibody in acute and convalescent sera. However, it is rarely necessary in routine clinical situations and is often not helpful since the results are not available until the infection is gone. In special circumstances, such as immunocompromised

FIGURE 4-2  A 12-year-old female with primary herpetic gingivostomatitis causing discrete vesicles and ulcers surrounded by inflammation.

FIGURE 4-3  Acute marginal gingivitis characteristic of primary HSV infection. A, mandibular anterior gingiva; B, vesicles and inflammation around mandibular molars.

FIGURE 4-4  Primary herpes infection in a 17-year-old male. Note the unruptured palatal vesicles and intense marginal gingivitis.
patients, an acute serum specimen should be obtained within 3 or 4 days of the onset of symptoms. The absence of detectable antibodies plus the isolation of HSV from lesions is compatible with the presence of a primary HSV infection. Antibody to HSV will begin to appear in a week and reach a peak in 3 weeks. A convalescent serum can confirm the diagnosis of primary HSV infection by demonstrating at least a fourfold rise in anti-HSV antibody. If anti-HSV antibody titers are similar in both the acute and convalescent sera, then the lesions from which HSV was isolated were recurrent lesions.

TREATMENT

A significant advance in the management of herpes simplex infections was the discovery of acyclovir, which has no effect on normal cells but inhibits DNA replication in HSV-infected cells. Acyclovir has been shown to be effective in the treatment of primary oral HSV in children when therapy was started in the first 72 hours. Acyclovir significantly decreased days of fever, pain, lesions, and viral shedding. Newer antiviral drugs are now available, including valacyclovir and famciclovir. The advantage of the newer drugs is increased bioavailability, allowing for effective treatment with fewer doses. Milder cases can be managed with supportive care only. The use of antiviral drugs in the management of recurrent disease or in immunocompromised patients is discussed later in this chapter in sections on recurrent and chronic HSV.

Routine supportive measures include aspirin or acetaminophen for fever and fluids to maintain proper hydration and electrolyte balance. If the patient has difficulty eating and drinking, a topical anesthetic may be administered prior to meals. Dyclonine hydrochloride 0.5% has been shown to be an excellent topical anesthetic for the oral mucosa. If this medication is not available, a solution of diphenhydramine hydrochloride 5 mg/mL mixed with an equal amount of milk of magnesia also has satisfactory topical anesthetic properties. Infants who are not drinking because of severe oral pain should be referred to a pediatrician for maintenance of proper fluid and electrolyte balance.

Antibiotics are of no help in the treatment of primary herpes infection, and use of corticosteroids is contraindicated. Future therapy may include prevention of the infection with use of a genetically disabled HSV vaccine.

Coxsackievirus Infections

Coxsackieviruses are ribonucleic acid (RNA) enteroviruses and are named for the town in upper New York State where they were first discovered. Coxackieviruses have been separated into two groups, A and B. There are 24 known types of coxsackievirus group A and 6 types of coxsackievirus group B. These viruses cause hepatitis, meningitis, myocarditis, pericarditis, and acute respiratory disease. Three clinical types of infection of the oral region that have been described are usually caused by group A coxackieviruses: herpangina, hand-foot-and-mouth disease, and acute lymphonodular pharyngitis. Types of coxsackievirus A have also been described as causing a rare mumpslike form of parotitis.

HERPANGINA

Coxsackievirus A4 has been shown to cause a majority of cases of herpangina, but types A1 to A10 as well as types A16 to A22 have also been implicated. Because many antigenic strains of coxsackievirus exist, herpangina may be seen more than once in the same patient. Unlike herpes simplex infections, which occur at a constant rate, herpangina frequently occurs in epidemics that have their highest incidence from June to October. The majority of cases affect young children ages 3 through 10, but infection of adolescents and adults is not uncommon.

Clinical Manifestations. After a 2- to 10-day incubation period, the infection begins with generalized symptoms of fever, chills, and anorexia. The fever and other symptoms are generally milder than those experienced with primary HSV infection. The patient complains of sore throat, dysphagia, and occasionally sore mouth. Lesions start as punctate macules, which quickly evolve into papules and vesicles involving the posterior pharynx, tonsils, faucial pillars, and soft palate. Lesions are found less frequently on the buccal mucosa, tongue, and hard palate (Figure 4-6). Within 24 to 48 hours, the vesicles rupture, forming small 1 to 2 mm ulcers. The disease is usually mild and heals without treatment in 1 week.

Herpangina may be clinically distinguished from primary HSV infection by several criteria:

1. Herpangina occurs in epidemics; HSV infections do not.
2. Herpangina tends to be milder than HSV infection.
3. Lesions of herpangina occur on the pharynx and posterior portions of the oral mucosa, whereas HSV primarily affects the anterior portion of the mouth.
4. Herpangina does not cause a generalized acute gingivitis like that associated with primary HSV infection.
5. Lesions of herpangina tend to be smaller than those of HSV.
Laboratory Studies. A smear taken from the base of a fresh vesicle and stained with Giemsa will not show ballooning degeneration or multinucleated giant cells. This helps to distinguish herpangina from herpes simplex and herpes zoster, which do show these changes.

Treatment. Herpangina is a self-limiting disease, and treatment is supportive, including proper hydration and topical anesthesia when eating or swallowing is difficult. Specific antiviral therapy is not available.

ACUTE LYMPHONODULAR PHARYNGITIS
This is a variant of herpangina caused by coxsackievirus A10. The distribution of the lesions is the same as in herpangina, but yellow-white nodules appear that do not progress to vesicles or ulcers. The disease is self-limiting, and only supportive care is indicated.

HAND-FOOT-AND-MOUTH DISEASE
Hand-foot-and-mouth disease is caused by infection with coxsackievirus A16 in a majority of cases, although instances have been described in which A5, A7, A9, A10, B2, or B5 or enterovirus 71 has been isolated. The disease is characterized by low-grade fever, oral vesicles and ulcers, and nonpruritic macules, papules, and vesicles, particularly on the extensor surfaces of the hands and feet. The oral lesions are more extensive than those described for herpangina, and lesions of the hard palate, tongue, and buccal mucosa are common. Severe cases with central nervous system involvement, myocarditis, and pulmonary edema have been reported in epidemics caused by enterovirus 71.27 Adler and colleagues28 studied 20 cases of hand-foot-and-mouth disease. The patients ranged in age from 8 months to 33 years, with 75% of cases occurring below 4 years of age. The clinical manifestations lasted 3 to 7 days. The most common complaint of the 20 patients was a sore mouth, and, clinically, all 20 patients had lesions involving the oral mucosa. Because of the frequent oral involvement, dentists are more likely to see patients with this disease than with herpangina, and they should remember to examine the hands and feet for maculopapular and vesicular lesions when patients present with an acute stomatitis and fever. Treatment is supportive.

Varicella-Zoster Virus Infection
Varicella zoster (VZV) is a herpesvirus, and, like other herpesviruses, it causes both primary and recurrent infection and remains latent in neurons present in sensory ganglia.29 VZV is responsible for two major clinical infections of humans: chickenpox (varicella) and shingles (herpes zoster [HZ]). Chickenpox is a generalized primary infection that occurs the first time an individual contacts the virus. This is analogous to the acute herpetic gingivostomatitis of herpes simplex virus.

After the primary disease is healed, VZV becomes latent in the dorsal root ganglia of spinal nerves or extramedullary ganglia of cranial nerves. A child without prior contact with VZV can develop chickenpox after contact with an individual with HZ.

In 3 to 5 of every 1,000 individuals, VZV becomes reactivated, causing lesions of localized herpes zoster. The incidence of HZ increases with age or immunosuppression.30 Patients who are immunocompromised due to HIV disease, cancer chemotherapy, immunosuppressive drug therapy, or hematologic malignancy have an increased susceptibility to severe and potentially fatal HZ. These HZ infections may be deep-seated and disseminated, causing pneumonia, meningitis, and hepatitis; however, otherwise normal patients who develop HZ do not have a significant incidence of underlying malignancy.

CLINICAL MANIFESTATIONS

General Findings. Chickenpox is a childhood disease characterized by mild systemic symptoms and a generalized intensely pruritic eruption of maculopapular lesions that rapidly develop into vesicles on an erythematosus base. Oral vesicles that rapidly change to ulcers may be seen, but the oral lesions are not an important symptomatic, diagnostic, or management problem.

HZ commonly has a prodromal period of 2 to 4 days, when shooting pain, paresthesia, burning, and tenderness appear along the course of the affected nerve. Unilateral vesicles on an erythematous base then appear in clusters, chiefly along the course of the nerve, giving the characteristic clinical picture of single dermatome involvement. Some lesions spread by viremia occur outside the dermatome. The vesicles turn to scabs in 1 week, and healing takes place in 2 to 3 weeks. The nerves most commonly affected with HZ are C3, T5, L1, L2, and the first division of the trigeminal nerve.

When the full clinical picture of HZ is present with pain and unilateral vesicles, the diagnosis is not difficult. Diagnostic problems arise during the prodromal period, when pain is present without lesions. Unnecessary surgery has been performed because of the diagnosis of acute appendicitis, cholecystitis, or dental pulpitis.31 A more difficult diagnostic problem is pain caused by VZ virus without lesions developing along the course of the nerve (zoster sine herpete; zoster sine...
Diagnosis in these cases is based on clinical symptoms and serologic evidence of a rising antibody titer.

HZ may also occasionally affect motor nerves. HZ of the sacral region may cause paralysis of the bladder. The extremities and diaphragm have also been paralyzed during episodes of HZ.

The most common complication of HZ is postherpetic neuralgia, which is defined as pain remaining for over a month after the mucocutaneous lesions have healed, although some clinicians do not use the term postherpetic neuralgia unless the pain has lasted for at least 3 months after the healing of the lesions. The overall incidence of postherpetic neuralgia is 12 to 14%, but the risk increases significantly after the age of 60 years, most likely due to the decline in cell-mediated immunity. Immunosuppression does not increase the risk of postherpetic neuralgia.

Oral Findings. Herpes zoster involves one of the divisions of the trigeminal nerve in 18 to 20% of cases, but the ophthalmic branch is affected several times more frequently than are the second or third divisions. HZ of the first division can lead to blindness secondary to corneal scarring and should be managed by an ophthalmologist. Facial and intraoral lesions are characteristic of HZ involving the second and third divisions of the trigeminal nerve.

Each individual oral lesion of HZ resembles lesions seen in herpes simplex infections. The diagnosis is based on a history of pain and the unilateral nature and segmental distribution of the lesions (Figures 4-7 and 4-8). When the clinical appearance is typical and vesicles are present, oral HZ can be distinguished clinically from other acute multiple lesions of the mouth, which are bilateral and are not preceded or accompanied by pain along the course of one trigeminal nerve branch (Figure 4-9).

HZ has been associated with dental anomalies and severe scarring of the facial skin when trigeminal HZ occurs during tooth formation. Pulpal necrosis and internal root resorption have also been related to HZ. In immunocompromised patients, large chronic HZ lesions have been described that have led to necrosis of underlying bone and exfoliation of teeth.

HZ of the geniculate ganglion, Ramsay Hunt syndrome, is a rare form of the disease characterized by Bell’s palsy, unilateral vesicles of the external ear, and vesicles of the oral mucosa.

Because oral lesions occurring without facial lesions are rare, isolated oral HZ can be misdiagnosed, particularly when erythema, edema, and nonspecific ulceration are seen without the presence of intact vesicles. In these cases, a cytology smear or viral culture is often necessary for diagnosis. An incorrect diagnosis can be made when prodromal pain is present prior to the appearance of the characteristic lesions. During this period, endodontic therapy, extractions, or other surgery may be performed unnecessarily. Similar problems occur in zoster sine eruptione.
LABORATORY FINDINGS

Cytology is a rapid method of evaluation that can be used in cases in which the diagnosis is uncertain. Fluorescent-antibody stained smears using fluorescein conjugated monoclonal antibodies is more reliable than is routine cytology and is positive in over 80% of cases. The most accurate method of diagnosis is viral isolation in tissue culture, but this test is more expensive and the results take days rather than hours. Demonstration of a rising antibody titer is rarely necessary for diagnosis except in cases of zoster sine eruptione, when it is the only means of confirming suspected cases.

TREATMENT

Management should be directed toward shortening the course of the disease, preventing postherpetic neuralgia in patients over 50 years of age, and preventing dissemination in immunocompromised patients. Acyclovir or the newer antiviral drugs valacyclovir or famciclovir accelerate healing and reduce acute pain, but they do not reduce the incidence of postherpetic neuralgia. The newer drugs have greater bioavailability and are more effective in the treatment of HZ.

The use of systemic corticosteroids to prevent postherpetic neuralgia in patients over 50 years of age is controversial; a recent review of the data indicated a reduction of pain and disability during the first 2 weeks but no effect on the incidence or severity of post-herpetic neuralgia. Some clinicians advocate the use of a combination of intralesional steroids and local anesthetics to decrease healing time and prevent postherpetic neuralgia, but a controlled study of this therapy has not been performed.

Effective therapy for postherpetic neuralgia includes application of capsaicin, a substance extracted from hot chili peppers. Topical capsaicin is safe but must be used for a prolonged period to be effective and may cause a burning sensation of the skin. When topical capsaicin therapy is ineffective, use of a tricyclic antidepressant or gabapentin is indicated. Chemical or surgical neurolysis may be necessary in refractory cases (see Chapter 11, Orofacial Pain).

Erythema Multiforme

Erythema multiforme (EM) is an acute inflammatory disease of the skin and mucous membranes that causes a variety of skin lesions—hence the name “multiforme.” The oral lesions, typically inflammation accompanied by rapidly rupturing vesicles and bullae, are often an important component of the clinical picture and are occasionally the only component. Erythema multiforme may occur once or recur, and it should be considered in the diagnosis of multiple acute oral ulcers whether or not there is a history of similar lesions. There is also a rare chronic form of EM. EM has several clinical presentations: a milder self-limiting form and severe life-threatening forms that may present as either Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN).

ETIOLOGY

EM is an immune-mediated disease that may be initiated either by deposition of immune complexes in the superficial microvasculature of skin and mucosa, or cell-mediated immunity. Kazmierowski and Wuepper studied specimens of lesions less than 24 hours old from 17 patients with EM; 13 of the 17 had deposition of immunoglobulin (Ig) M and complement (C) 3 in the superficial vessels. Other health care workers have detected elevated levels of immune complexes and decreased complement in fluid samples taken from vesicles.

Although the histopathology is not specific, two major histologic patterns have been described: an epidermal pattern characterized by lichenoid vasculitis and intraepidermal vesicles, and a dermal pattern characterized by lymphocytic vasculitis and subepidermal vesiculation.

The most common triggers for episodes of EM are herpes simplex virus and drug reactions. The drugs most frequently associated with EM reactions are oxycam nonsteroidal anti-inflammatory drugs (NSAIDs); sulfonamides; anticonvulsants such as carbamazepine, phenobarbital, and phenytoin; trimethoprim-sulfonamide combinations, allopurinol, and penicillin. A majority of the severe cases of Stevens-Johnson syndrome or TEN are caused by drug reactions.

The relationship of HSV to episodes of EM has been known for over 50 years, but improved diagnostic techniques, including polymerase chain reaction (PCR) and in situ hybridization have demonstrated that herpes-associated EM is a common form of the disease, accounting for at least 20 to 40% of the cases of single episodes of EM and approximately 80% of recurrent EM (Figures 4-10 and 4-11). Herpes antigens have been demonstrated in the skin and immunocomplexes obtained from patients with EM. Many investigators now believe that the major cause of EM is a cellular immune response to HSV antigens deposited in keratinocytes of the skin and mucosa. The tendency to develop mucous membrane lesions during episodes of herpes-associated EM appears to be genetically determined and related to specific human leukocyte antigen (HLA) types. Oral mucosal lesions were detected in 8 of 12 children with HSV-associated EM. Other triggers for EM include progesterone, Mycoplasma benign and malignant tumors, radiotherapy, Crohn’s disease, sarcoidosis, histoplasmosis, and infectious mononucleosis.
Many cases of EM continue to have no obvious detectable cause after extensive testing for underlying systemic disease and allergy and are labeled idiopathic.

**CLINICAL MANIFESTATIONS**

**General Findings.** EM is seen most frequently in children and young adults and is rare after age 50 years. It has an acute or even an explosive onset; generalized symptoms such as fever and malaise appear in severe cases. A patient may be asymptomatic and in less than 24 hours have extensive lesions of the skin and mucosa. EM simplex is a self-limiting form of the disease and is characterized by macules and papules 0.5 to 2 cm in diameter, appearing in a symmetric distribution.

The most common cutaneous areas involved are the hands, feet, and extensor surfaces of the elbows and knees. The face and neck are commonly involved, but only severe cases affect the trunk. Typical skin lesions of EM may be nonspecific macules, papules, and vesicles. More typical skin lesions contain petechiae in the center of the lesion. The pathognomonic lesion is the target or iris lesion, which consists of a central bulla or pale clearing area surrounded by edema and bands of erythema (Figure 4-12).

The more severe vesiculobullous forms of the disease, Stevens-Johnson syndrome and TEN, have a significant mortality rate. EM is classified as Stevens-Johnson syndrome when the generalized vesicles and bullae involve the skin, mouth, eyes, and genitals (Figure 4-13). The most severe form of the disease is TEN, (toxic epidermal necrolysis), which is usually secondary to a drug reaction and results in sloughing of skin and mucosa in large sheets. Morbidity, which occurs in 30 to 40% of patients, results from secondary infection, fluid and electrolyte imbalance, or involvement of the lung, liver, or kidneys. Patients with this form of the disease are most successfully managed in burn centers, where necrotic skin is removed under general anesthesia and healing takes place under sheets of porcine xenografts.

**Oral Findings.** Oral lesions commonly appear along with skin lesions in approximately 70% of EM patients (Figure 4-14). In some cases, oral lesions are the predominant or single site of disease. When the oral lesions predominate and no target lesions are present on the skin, EM must be differentiated from other causes of acute multiple ulcers, especially primary herpes simplex infection. This distinction is important because corticosteroids may be the treatment of choice in EM, but they are specifically contraindicated in primary herpes simplex infections. When there are no skin lesions and the oral lesions are mild, diagnosis may be difficult and is usually made by exclusion of other diseases. Cytologic smears and virus isolation may be done to eliminate the possibility of primary herpes infection. Biopsy may be performed when acute pemphigus is suspected. The histologic picture of oral EM is not considered specific, but the finding of a perivascular lymphocytic infiltrate and epithelial edema and hyperplasia is considered suggestive of EM.

The diagnosis is made on the basis of the total clinical picture, including the rapid onset of lesions. The oral lesions start as bullae on an erythematous base, but intact bullae are rarely seen by the clinician because they break rapidly into irregular ulcers. Viral lesions are small, round, symmetric, and shallow, but EM lesions are larger, irregular, deeper, and often bleed. Lesions may occur anywhere on the oral mucosa with EM, but involvement of the lips is especially prominent, and gingival involvement is rare. This is an important criterion for distinguishing EM from primary herpes simplex infection, in which generalized gingival involvement is characteristic.

In full-blown clinical cases, the lips are extensively eroded, and large portions of the oral mucosa are denuded of epithelium. The patient cannot eat or even swallow and drools blood-tinged saliva. Within 2 or 3 days the labial lesions begin to crust. Healing occurs within 2 weeks in a majority of cases, but, in some severe cases, extensive disease may continue for several weeks.

**TREATMENT**

Mild cases of oral EM may be treated with supportive measures only, including topical anesthetic mouthwashes and a soft or liquid diet. Moderate to severe oral EM may be treated with a
short course of systemic corticosteroids in patients without significant contraindications to their use. Systemic corticosteroids should only be used by clinicians familiar with the side effects, and, in each case, potential benefits should be carefully weighed against potential risks. Young children treated with systemic steroids for EM appear to have a higher rate of complications than do adults, particularly gastrointestinal bleeding and secondary infections. Adults treated with short-term systemic steroids have a low rate of complications and a shorter course of EM. The protein-wasting and adrenal-suppressive effects of systemic steroids are not significant when used short-term, and the clinical course of the disease may be shortened. An initial dose of 30 mg/d to 50 mg/d of prednisone or methylprednisolone for several days, which is then tapered, is helpful in shortening the healing time of EM, particularly when therapy is started early in the course of the disease. It should be noted that the efficacy of this treatment has not been proven by controlled clinical trials and is controversial.

Patients with severe cases of recurrent EM have been treated with dapsone, azathioprine, levamisole, or thalidomide. EM triggered by progesterone, also referred to as autoimmune progesterone dermatitis and stomatitis, has been treated successfully with tamoxifen. In resistant cases, oophorectomy has been necessary to cure the disorder. Anthrherpes drugs such as acyclovir or valacyclovir can be effective in preventing susceptible patients from developing herpes-

**FIGURE 4-13** Labial (A), skin (B), and penile (C) lesions in a 17-year-old male with Stevens-Johnson form of erythema multiforme. The lesions began to arise less than 12 hours before the pictures were taken.

**FIGURE 4-14** Intraoral lesions of erythema multiforme in an 18-year-old male.
associated EM, if the drug is administered at the onset of the recurrent HSV lesion. Prophylactic use of antiherpes drugs is effective in preventing frequent recurrent episodes of HSV-associated EM.\textsuperscript{56,58} Systemic steroids are recommended for management of Stevens-Johnson syndrome and are considered life saving in severe cases.\textsuperscript{59,60}

**Contact Allergic Stomatitis**

Contact allergy results from a delayed hypersensitivity reaction that occurs when antigens of low molecular weight penetrate the skin or mucosa of susceptible individuals. These antigens combine with epithelial-derived proteins to form haptens that bind to Langerhans’ cells in the epithelium. The Langerhans’ cells migrate to the regional lymph nodes and present the antigen to T lymphocytes, which become sensitized and undergo clonal expansion. After re-exposure to the antigen, sensitized individuals develop an inflammatory reaction confined to the site of contact. Since the reaction resulting from contact allergy appears as nonspecific inflammation, contact dermatitis or stomatitis may be difficult to distinguish from chronic physical irritation. The incidence of contact stomatitis is unknown, but it is believed to be significantly less common than contact dermatitis for the following reasons:

1. Saliva quickly dilutes potential antigens and physically washes them away and digests them before they can penetrate the oral mucosa.
2. Since the oral mucosa is more vascular than the skin, potential antigens that do penetrate the mucosa are rapidly removed before an allergic reaction can be established.
3. The oral mucosa has less keratin than does the skin, decreasing the possibility that haptens will be formed.

Contact stomatitis may result from contact with dental materials, oral hygiene products, or foods. Common causes of contact oral reactions are cinnamon or peppermint, which are frequently used flavoring agents in food, candy, and chewing gum, as well as oral hygiene products such as toothpaste, mouthwash and dental floss\textsuperscript{61} (Figure 4-15).

Dental materials that have been reported to cause cases of contact allergic stomatitis include mercury in amalgam, gold in crowns, free monomer in acrylic, and nickel in orthodontic wire.\textsuperscript{62–64} Pyrophosphates and zinc citrate, which are components of tartar control toothpaste, cause superficial peeling of the mucosa in some users, but this reaction is believed to be caused by physical irritation rather than an allergic reaction.\textsuperscript{65}

**CLINICAL MANIFESTATIONS**

The clinical signs and symptoms of contact oral allergy are nonspecific and are frequently difficult to distinguish from physical irritation. The reaction occurs only at the site of contact and includes a burning sensation or soreness accompanied by erythema, and occasionally the formation of vesicles and ulcers. Burning sensations without the presence of lesions is not a result of contact allergy, and obtaining allergy tests for patients with burning mouth syndrome with normal-appearing mucosa is not indicated.

Lesions that appear lichenoid both clinically and histologically may also be a result of contact allergy when the lichenoid lesion is in direct contact with the potential allergen. These lesions occur most frequently as a result of mercury in amalgam, and appear on the buccal mucosa and lateral border of the tongue in direct contact with the restoration. These lesions disappear when the amalgam is removed. It should be emphasized that there is no evidence that generalized lesions of oral lichen planus not in direct contact with restorations heal when amalgam restorations are removed.

Another oral manifestation of contact allergy is plasma cell gingivitis, which is characterized by generalized erythema and edema of the attached gingiva, occasionally accompanied by cheilitis and glossitis\textsuperscript{66} (Figure 4-16). The histopathology is described as sheets of plasma cells that replace normal connective tissue. Some cases have been related to an allergen present in toothpaste, chewing gum, or candy, whereas other cases remain of unknown etiology even after extensive allergy testing. Plasma cell gingivitis must be distinguished from neoplastic plasma cell diseases such as plasmacytoma or multiple myeloma.

**FIGURE 4-15** Contact allergy of the labial mucosa, due to peppermint.

**FIGURE 4-16** Plasma cell gingivitis of unknown etiology.
DIAGNOSIS
Contact allergy is most accurately diagnosed by the use of a patch test.67 This test is performed by placing the suspected allergens in small aluminum disks, called Finn chambers, which are taped onto hairless portions of the skin. The disks remain in place for 48 hours. A positive response to a contact allergen is identified by inflammation at the site of the test, which is graded on a scale of 0 to 3. Patch tests should be performed by clinicians trained and experienced in using the test, so the results are interpreted accurately.

TREATMENT
Management of oral contact allergy depends on the severity of the lesions. In mild cases, removal of the allergen suffices. In more severe symptomatic cases, application of a topical corticosteroid is helpful to speed healing of painful lesions.

Oral Ulcers Secondary to Cancer Chemotherapy
Chemotherapeutic drugs are frequently used to effect remission of both solid tumors, hematologic malignancies, and bone marrow transplantation. Similar drugs are used for patients with bone marrow transplants. One of the common side effects of the anticancer drugs is multiple oral ulcers. Dentists who practice in hospitals where these drugs are used extensively may see oral ulcers secondary to such drug therapy more frequently than any other lesion described in this chapter.68,69

Anticancer drugs may cause oral ulcers directly or indirectly. Drugs that cause stomatitis indirectly depress the bone marrow and immune response, leading to bacterial, viral, or fungal infections of the oral mucosa. Others, such as methotrexate, cause oral ulcers via direct effect on the replication and growth of oral epithelial cells by interfering with nucleic acid and protein synthesis, leading to thinning and ulceration of the oral mucosa.

A recent publication by Sonis describes a new hypothesis that explains the severe stomatitis observed in patients receiving cytotoxic drugs for stem cell transplantation.70 It is noted that an inflammatory reaction precedes ulceration and that anti-inflammatory drugs may be useful in minimizing bone marrow–related ulceration.

Details of the diagnosis and management of these lesions are discussed in Chapters 19, Transplantation Medicine, and 16, Hematologic Disease.

Acute Necrotizing Ulcerative Gingivitis
Acute necrotizing ulcerative gingivitis (ANUG) is an endogenous oral infection that is characterized by necrosis of the gingiva. Occasionally, ulcers of the oral mucosa also occur in patients with hematologic disease or severe nutritional deficiencies (see Chapter 16).

ANUG became known notoriously as “trench mouth” during World War I because of its prevalence in the combat trenches, and it was incorrectly considered a highly contagious disease. Since then, studies have shown that the disease is accompanied by an overgrowth of organisms prevalent in normal oral flora and is not transmissible. The organisms most frequently mentioned as working symbiotically to cause the lesions are the fusiform bacillus and spirochetes.

Plaque samples taken from ANUG patients demonstrate a constant anaerobic flora of Treponema spp, Selenomonas spp, Fusobacterium spp, and Bacteroides intermedius.71 The tissue destruction is thought to be caused by endotoxins that act either directly on the tissues or indirectly by triggering immunologic and inflammatory reactions.

Classic ANUG in patients without an underlying medical disorder is found most often in those between the ages of 16 and 30 years, and it is associated with three major factors:

1. Poor oral hygiene with pre-existing marginal gingivitis or faulty dental restorations
2. Smoking
3. Emotional stress

Systemic disorders associated with ANUG are diseases affecting neutrophils (such as leukemia or aplastic anemia), marked malnutrition, and HIV infection. Malnutrition–associated cases are reported from emergent countries where the untreated disease may progress to noma, a large necrotic ulcer extending from the oral mucosa through the facial soft tissues.

The prevalence of the disease was reported by Giddon and colleagues,72 who studied the prevalence of ANUG in 12,500 students served by the Harvard University Dental Health Service. About 0.9% of the total sample developed ANUG during the period of study. A 4% prevalence in those students who made use of the dental clinic was observed. Members of the junior class were most often affected. A relation to stress was noted by an increased frequency during examination and vacation periods. Studies of military trainees or college students demonstrated a prevalence of 5 to 7%.

There are three forms of periodontal diseases observed in patients with acquired immunodeficiency syndrome (AIDS): linear gingival erythema (LGE), necrotizing ulcerative gingivitis (NUG), and necrotizing ulcerative periodontitis (NUP).

LGE is an intense red band involving the marginal gingiva that does not resolve with standard oral hygiene procedures. Some cases are believed to be caused by candidal overgrowth, and these cases resolve with antifungal therapy. NUG and NUP are clinically similar to ANUG; the term “NUG” is used when the disease involves only the gingiva, and “NUP” involves a loss of periodontal attachment.73,74 There is evidence that, in patients with AIDS, the host response in the gingival crevice is altered. Levels of proinflammatory cytokines such as interleukin-1 β are increased in the gingival crevice of patients with human immunodeficiency virus (HIV), which alters the regulation of neutrophils. This alteration in neutrophil function may explain the increase in NUP–related organisms including fusobacteria and Candida, which results in the rapid necrosis of gingival tissues.75

A fulminating form of ulcerative stomatitis related to ANUG is noma (cancrum oris), which predominantly affects children in sub-Saharan Africa. This disease is characterized by...
extensive necrosis that begins on the gingiva and then progresses from the mouth through the cheek to the facial skin, causing extensive disfigurement (Figure 4-17). The major risk factors associated with noma include malnutrition, poor oral hygiene, and concomitant infectious diseases such as measles. Living in close proximity to livestock is also believed to play a role, and *Fusobacterium necrophorum*, a pathogen associated with disease in livestock, has been isolated from over 85% of noma lesions. The mortality rate without appropriate therapy exceeds 70%.

**CLINICAL MANIFESTATIONS**

The onset of acute forms of ANUG is usually sudden, with pain, tenderness, profuse salivation, a peculiar metallic taste, and spontaneous bleeding from the gingival tissues. The patient commonly experiences a loss of the sense of taste and a diminished pleasure from smoking. The teeth are frequently thought to be slightly extruded, sensitive to pressure, or to have a “woody sensation.” At times they are slightly movable. The signs noted most frequently are gingival bleeding and blunting of the interdental papillae (Figure 4-18).

The typical lesions of ANUG consist of necrotic punched-out ulcerations, developing most commonly on the interdental papillae and the marginal gingivae. These ulcerations can be observed most easily on the interdental papillae, but ulceration may develop on the cheeks, the lips, and the tongue, where these tissues come in contact with the gingival lesions or following trauma. Ulcerations also may be found on the palate and in the pharyngeal area (Figure 4-19). When the lesions have spread beyond the gingivae, blood dyscrasias and immunodeficiency should be ruled out by ordering appropriate laboratory tests, depending upon associated signs and symptoms.

The ulcerative lesions may progress to involve the alveolar process, with sequestration of the teeth and bone. When gingival hemorrhage is a prominent symptom, the teeth may become superficially stained a brown color, and the mouth odor is extremely offensive.

The tonsils should always be examined since these organs may be affected. The regional lymph nodes usually are slightly enlarged, but occasionally the lymphadenopathy may be marked, particularly in children.

The constitutional symptoms in primary ANUG are usually of minor significance when compared with the severity of the oral lesions. Significant temperature elevation is unusual, even in severe cases, and, when it exists, other accompanying or underlying diseases should be ruled out, particularly blood dyscrasias and AIDS. HIV-infected patients with NUG have rapidly progressing necrosis and ulceration first involving the gingiva alone, and then NUP with the periodontal attachment and involved alveolar bone. The ulcerated areas may be localized or generalized and often are very painful. In severe cases, the underlying bone is denuded and may become sequestrated, and the necrosis may spread from the gingiva to other oral tissues.

**TREATMENT**

The therapy of ANUG uncomplicated by other oral lesions or systemic disease is local débridement. At the initial visit, the gingivae should be débrided with both irrigation and periodontal curettage. The extent of the débridement depends on the soreness of the gingivae. The clinician should remember that the more quickly the local factors are removed, the faster is the resolution of the lesions. Special care should be taken by the clinician to débride the area just below the marginal gin-
givae. Complete debridement may not be possible on the first visit because of soreness. The patient must return, even though the pain and other symptoms have disappeared, to remove all remaining local factors.

Treatment of ANUG is not finished until there has been a complete gingival curettage and root planing, including removal of overhanging margins and other predisposing local factors. After the first visit, careful home care instruction must be given to the patient regarding vigorous rinsing and gentle brushing with a soft brush. Patients should be made aware of the significance of such factors as poor oral hygiene, smoking, and stress.

Antibiotics are usually not necessary for routine cases of ANUG confined to the marginal and interdental gingivae. These cases can be successfully treated with local debridement, irrigation, curettage, and home care instruction including hydrogen peroxide (approximately 1.5 to 2% in water) mouth rinses three times a day and chlorhexidine 12% rinses. Antibiotics should be prescribed for patients with extensive gingival involvement, lymphadenopathy, or other systemic signs, and in cases in which mucosa other than the gingivae is involved. Metronidazole and penicillin are the drugs of choice whose lesions have extended from the gingivae to the buccal mucosa, tongue, palate, or pharynx should be placed on antibiotics and should have appropriate studies to rule out blood dyscrasias or AIDS. After the disease is resolved, the patient must return for a complete periodontal evaluation.

After the disease is resolved, the patient should return, even though the pain and other symptoms have disappeared, to remove all remaining local factors.

The current concept is that RAS is a clinical syndrome with several possible causes. The major factors identified include heredity, hematologic deficiencies, and immunologic abnormalities. The best documented factor is heredity. Miller and colleagues studied 1,303 children from 530 families and demonstrated an increased susceptibility to RAS among children of RAS-positive parents. A study by Ship and associates showed that patients with RAS-positive parents had a 90% chance of developing RAS, whereas patients with no RAS-positive parents had a 20% chance of developing the lesions. Further evidence for the inherited nature of this disorder results from studies in which genetically specific HLAs have been identified in patients with RAS, particularly in certain ethnic groups.

Hematologic deficiency, particularly of serum iron, folate, or vitamin B12, appears to be an etiologic factor in a subset of patients with RAS. The size of the subset is controversial, but most estimates range from 5 to 15%. A study by Rogers and Hutton reported clinical improvement in 75% of patients with RAS when a specific hematologic deficiency was detected and corrected with specific replacement therapy. Some cases of nutritional deficiency, such as celiac disease, are reported to be secondary to malabsorption syndrome.

Most of the research into the etiology of RAS centers on immunologic abnormalities. Early work suggested either an autoimmune disorder or hypersensitivity to oral organisms such as Streptococcus sanguis. Investigations using more sophisticated immune assays have not supported the early work and suggest a role of lymphocytotoxicity, antibody-dependent cell-mediated cytotoxicity, and defects in lymphocyte cell subpopulations. Burnett and Wray showed that sera and monocytes induced significantly more cytology in patients with RAS than in control patients. Thomas and colleagues showed that T lymphocytes from patients with RAS had increased cytotoxicity to oral epithelial cells. Work by Pedersen and colleagues and other studies demonstrated an alteration in CD4:CD8 lympha-
Recurrent aphthous stomatitis of the tongue and floor of the mouth increases the frequency and severity of RAS. In cases of allergy to foods such as milk, cheese, wheat, and flour, elimination diet in some patients with suspected or proven refractory disease, Hay and Reade reported the benefit of an elimination diet in some patients with suspected or proven allergy to foods such as milk, cheese, wheat, and flour.

A detergent present in toothpaste, sodium lauryl sulfate (SLS), was suspected as an etiologic factor in RAS development, but a recent double-blind crossover study showed that use of an SLS-free toothpaste had no significant effect on ulcer development.

**CLINICAL MANIFESTATIONS**

The first episodes of RAS most frequently begin during the second decade of life and may be precipitated by minor trauma, menstruation, upper respiratory infections, or contact with certain foods. The lesions are confined to the oral mucosa and begin with prodromal burning any time from 2 to 48 hours before an ulcer appears. During this initial period, a localized area of erythema develops. Within hours, a small white papule forms, ulcerates, and gradually enlarges over the next 48 to 72 hours. The individual lesions are round, symmetric, and shallow (similar to viral ulcers), but no tissue tags are present from ruptured vesicles (this helps to distinguish RAS from disease with irregular ulcers such as EM, pemphigus, and pemphigoid). Multiple lesions are often present, but the number, size, and frequency of them vary considerably (Figure 4-20). The buccal and labial mucosae are most commonly involved. Lesions are less common on the heavily keratinized palate or gingiva. In mild RAS, the lesions reach a size of 0.3 to 1.0 cm and begin healing within a week. Healing without scarring is usually complete in 10 to 14 days.

Most patients with RAS have between two and six lesions at each episode and experience several episodes a year. The disease is an annoyance for the majority of patients with mild RAS, but it can be disabling for patients with severe frequent lesions, especially those classified as major aphthous ulcers. Patients with major ulcers develop deep lesions that are larger than 1 cm in diameter and may reach 5 cm (Figure 4-21, A and B). Large portions of the oral mucosa may be covered with large deep ulcers that can become confluent. The lesions are extremely painful and interfere with speech and eating. Many of these patients continually go from one clinician to another, looking for a “cure.” The lesions may last for months and sometimes be misdiagnosed as squamous cell carcinoma, chronic granulomatous disease, or pemphigoid. The lesions heal slowly and leave scars that may result in decreased mobility of the uvula and tongue and destruction of portions of the oral mucosa. The least common variant of RAS is the herpetiform type, which tends to occur in adults. The patient presents with small punctate ulcers scattered over large portions of the oral mucosa.

**DIAGNOSIS**

RAS is the most common cause of recurring oral ulcers and is essentially diagnosed by exclusion of other diseases. A detailed history and examination by a knowledgeable clinician should distinguish RAS from primary acute lesions such as viral stomatitis or from chronic multiple lesions such as pemphigoid, as well as from other possible causes of recurring ulcers, such as connective tissue disease, drug reactions, and dermatologic disorders. The history should emphasize symptoms of blood dyscrasias, systemic complaints, and associated skin, eye, genital, or rectal lesions. Laboratory investigation should be used when ulcers worsen or begin past the age of 25 years. Biopsies are only indicated when it is necessary to exclude other diseases, particularly granulomatous diseases such as Crohn’s disease or sarcoidosis.

Patients with severe minor aphthae or major aphthous ulcers should have known associated factors investigated, including connective-tissue diseases and abnormal levels of serum iron, folate, vitamin B₁₂, and ferritin (Figure 4-22). Patients with abnormalities in these values should be referred to an internist to rule out malabsorption syndromes and to initiate proper replacement therapy. The clinician may also choose to have food allergy or gluten sensitivity investigated in severe cases resistant to other forms of treatment. HIV-infected patients, particularly those with CD4 counts below 100/mm³, may develop major aphthous ulcers (Figure 4-23).

**TREATMENT**

Medication prescribed should relate to the severity of the disease. In mild cases with two or three small lesions, use of a protective emollient such as Orabase (Bristol-Myers Squibb, Princeton, NJ) or Zilactin (Zila Pharmaceuticals, Phoenix, AZ) is all that is necessary. Pain relief of minor lesions can be obtained with use of a topical anesthetic agent or topical diclofenac, an NSAID frequently used topically after eye surgery. In more severe cases, the use of a high-potency topical steroid preparation, such as fluocinonide, betamethasone or clobetasol, placed directly on the lesion shortens healing time and reduces the size of the ulcers. The effectiveness of the topical steroid is partially based upon good instruction and
patient compliance regarding proper use. The gel can be carefully applied directly to the lesion after meals and at bedtime two to three times a day, or mixed with an adhesive such as Orabase prior to application. Larger lesions can be treated by placing a gauze sponge containing the topical steroid on the ulcer and leaving it in place for 15 to 30 minutes to allow for longer contact of the medication. Other topical preparations that have been shown to decrease the healing time of RAS lesions include amlexanox paste and topical tetracycline, which can be used either as a mouth rinse or applied on gauze sponges. Intralosomal steroids can be used to treat large indolent major RAS lesions. It should be emphasized that no available topical therapy decreases the onset of new lesions. In patients with major aphthae or severe cases of multiple minor aphthae not responsive to topical therapy, use of systemic therapy should be considered. Drugs that have been reported to reduce the number of ulcers in selected cases of major aphthae include colchicine, pentoxifylline, dapsone, short bursts of systemic steroids, and thalidomide. Each of these drugs has the potential for side effects, and the clinician must weigh the potential benefits versus the risks. Thalidomide has been shown to reduce both the incidence and severity of major RAS in both HIV-positive and HIV-negative patients, but this drug must be used with extreme caution in women during childbearing years owing to the potential for severe life-threatening and deforming birth defects. All clinicians prescribing thalidomide in the United States must be registered in the STEPS (System for Thalidomide Education and Prescribing Safety) program, and patients receiving the drug must be thoroughly counseled regarding effective birth control methods that must be used whenever thalidomide is prescribed. For example, two methods of birth control must be used, and the patient must have a pregnancy test monthly. Other side effects of thalidomide include peripheral neuropathy, gastrointestinal complaints, and drowsiness.

**Behçet’s Syndrome**

Behçet’s syndrome, described by the Turkish dermatologist Hulüsi Behçet, was classically described as a triad of symptoms including recurring oral ulcers, recurring genital ulcers, and
Aphthous-like lesion in a patient with Behçet's syndrome. A positive pathergy test defined as an inflammatory reaction forming within 24 hours of a needle puncture, scratch, or saline injection.

Arthritis occurs in greater than 50% of patients and most frequently affects the knees and ankles. The affected joint may be red and swollen as in rheumatoid arthritis, but involvement of small joints of the hand does not occur, and permanent disability does not result.

In some patients, central nervous system involvement is the most distressing component of the disease. This may include brainstem syndrome, involvement of the cranial nerves, or neurologic degeneration resembling multiple sclerosis that can be visualized by magnetic resonance imaging of the brain. Other reported signs of Behçet’s syndrome include thrombophlebitis, intestinal ulceration, venous thrombosis, and renal and pulmonary disease. Involvement of large vessels is life threatening because of the risk of arterial occlusion or aneurysms.

Behçet’s syndrome in children, which most frequently presents between the ages of 9 and 10 years, has similar manifestations as does the adult form of the disease, but oral ulcers are a more common presenting sign in children, and uveitis is less common.

Oral lesions are the presenting symptom in over 95% of children with Behçet’s syndrome. A variant of Behçet’s syndrome, MAGIC syndrome, has been described. It is characterized by Mouth And Genital ulcers with Inflamed Cartilage.

**DIAGNOSIS**

Because the signs and symptoms of Behçet’s syndrome overlap with those of several other diseases, particularly the connective-tissue diseases, it has been difficult to develop criteria that meet with universal agreement. Five different sets of diagnostic criteria have been in use during the past 20 years. In 1990, an international study group reviewed data from 914 patients from seven countries. A new set of diagnostic criteria was developed that includes recurrent oral ulceration occurring at least three times in one 12-month period plus two of the following four manifestations:

1. Recurrent genital ulceration
2. Eye lesions including uveitis or retinal vasculitis
3. Skin lesions including erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules in postadolescent patients not receiving corticosteroids
4. A positive pathergy test

**TREATMENT**

The management of Behçet’s syndrome depends on the severity and the sites of involvement. Patients with sight-threatening eye involvement or central nervous system lesions require more aggressive therapy with drugs with a higher potential for serious side effects. Azathioprine combined with prednisone has been shown to reduce ocular disease as well as oral and genital involvement. Pentoxifylline, which has fewer side effects than do immunosuppressive drugs or systemic steroids, has also been reported to be effective in decreasing disease activity, particularly
eye involvement. Cyclosporine or colchicine in combination with corticosteroids has also been shown to be useful in severe disease. Colchicine and thalidomide have been shown to be useful in mucocutaneous and gastrointestinal manifestations. Systemic corticosteroids remain a mainstay of treatment and are particularly useful in rapidly controlling the disease until immunosuppressive agents begin to work. Plasmapheresis has also been used successfully in emergencies.

Oral mucosal lesions not adequately controlled by systemic therapy may be treated with topical or intralesional steroids in regimens described in the section on RAS.

Recurrent Herpes Simplex Virus Infection

Recurrent herpes infection of the mouth (recurrent herpes labialis [RHL]; recurrent intraoral herpes simplex infection [RIH]) occurs in patients who have experienced a previous herpes simplex infection and who have serum-antibody protection against another exogenous primary infection. In otherwise healthy individuals, the recurrent infection is confined to a localized portion of the skin or mucous membranes. Recurrent herpes is not a re-infection but a reactivation of virus that remains latent in nerve tissue between episodes in a non-replicating state. Herpes simplex has been cultured from the trigeminal ganglion of human cadavers, and recurrent herpes lesions commonly appear after surgery involving the ganglion. Recurrent herpes may also be activated by trauma to the lips, fever, sunburn, immunosuppression, and menstruation. The virus travels down the nerve trunk to infect epithelial cells, spreading from cell to cell to cause a lesion.

The published evidence demonstrating that RAS is not caused by herpesvirus induced many to believe that recurrent herpes infection of the oral region occurred only on the lips and not on the oral mucosa; this has been shown to be false. RAS and herpes lesions can both exist intraorally and are two separate and distinct disease processes.

All patients who experience primary herpes infection do not experience recurrent herpes. The number of patients with a history of primary genital infection with HSV1 who subsequently experience recurrent HSV infections is approximately 15%. The recurrence rate for oral HSV1 infections is estimated to be between 20 and 40%.

Studies have suggested several mechanisms for reactivation of latent HSV, including low serum IgA, decreased cell-mediated immunity, decreased salivary antiherspes activity, and depression of ADCC (antibody-dependent cell-mediated cytotoxicity) and interleukin-2 caused by prostaglandin release in the skin.

Individuals with T-lymphocyte deficiencies owing to AIDS or transplant or cancer chemotherapy may develop large chronic lesions (see “Herpes Simplex Virus Infection in Immunosuppressed Patients,” below) or, rarely, disseminated HSV infection.

CLINICAL MANIFESTATIONS

RHL, the common cold sore or fever blister, may be precipitated by fever, menstruation, ultraviolet light, and perhaps emotional stress. The lesions are preceded by a prodromal period of tingling or burning. This is accompanied by edema at the site of the lesion, followed by formation of a cluster of small vesicles (Figure 4-25). Each vesicle is 1 to 3 mm in diameter, with the size of the cluster ranging from 1 to 2 cm. Occasionally, the lesions may be several centimeters in diameter, causing discomfort and disfigurement. These larger lesions are more common in immunosuppressed individuals. The frequency of recurrences varies.

RIH lesions in otherwise normal patients are similar in appearance to RHL lesions, but the vesicles break rapidly to form ulcers. The lesions are typically a cluster of small vesicles or ulcers, 1 to 2 mm in diameter, clustered on a small portion of the heavily keratinized mucosa of the gingiva, palate, and alveolar ridges, although RIH lesions can occasionally involve other mucosal surfaces (Figure 4-26). In contrast, lesions of RAS tend to be larger, to spread over a larger area of mucosa, and to have a predilection for the less heavily keratinized buccal mucosa, labial mucosa, or floor of the mouth.

DIAGNOSIS

If laboratory tests are desired, RIH can be distinguished from RAS by cytology smears taken from the base of a fresh lesion. Smears from herpetic lesions show cells with ballooning degeneration and multinucleated giant cells; those from RAS lesions do not. For more accurate results, cytology smears may also be tested for HSV using fluorescein-labeled HSV antigen. Viral cultures also are used to distinguish herpes simplex from other viral lesions, particularly varicella-zoster infections.

TREATMENT

Recurrent herpes infections of the lips and mouth are seldom more than a temporary annoyance in otherwise normal individuals and should be treated symptomatically. Patients who experience frequent, large, painful, or disfiguring lesions may request professional consultation. The clinician should first attempt to minimize obvious triggers. Some recurrences can be eliminated by the wearing of sunblock during intense sun exposure.
Drugs are available that suppress the formation and shorten the healing time of new recurrent lesions. Acyclovir, the original antiviral drug, has been shown to be both safe and effective. The newer antiviral drugs such as valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir, have greater bioavailability than does acyclovir, but they do not eliminate established latent HSV. However, in the mouse model, famciclovir appeared to decrease the rate of HSV latency. The clinical importance of this finding in human HSV infection is not known. The effectiveness of these antiviral drugs to prevent recurrences of genital HSV has been studied extensively. Acyclovir 400 mg twice daily, valacyclovir 250 mg twice daily, and famciclovir 250 mg were each highly effective in preventing genital recurrences. The use of antiviral nucleoside analogues to prevent and treat RHL in otherwise normal individuals is controversial. Systemic therapy should not be used to treat occasional or trivial RHL in otherwise healthy individuals, but episodic use to prevent lesions in susceptible patients before high-risk activities such as skiing at high altitudes or before undergoing procedures such as dermabrasion or surgery involving the trigeminal nerve is justifiable. Some clinicians advocate the use of suppressive antiviral therapy for the small percentage of RHL patients who experience frequent deforming episodes of RHL. Acyclovir 400 mg twice daily has been shown to reduce the frequency and severity of RHL in this group of patients. Both acyclovir and penciclovir are available in topical formulations, but use of these preparations shortens the healing time of RHL by less than 2 days.

The Patient with Chronic Multiple Lesions

Patients with chronic multiple lesions are frequently misdiagnosed for weeks to months since their lesions may be confused with recurring oral mucosal disorders. The clinician can avoid misdiagnosis by carefully questioning the patient on the initial visit regarding the natural history of the lesions. In recurring disorders such as severe aphthous stomatitis, the patient may experience continual ulceration of the oral mucosa, but individual lesions heal and new ones form. In the category of disease described in this section, the same lesions are present for weeks to months. The major diseases in this group are pemphigus vulgaris, pemphigus vegetans, bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease, and erosive lichen planus. Herpes simplex infections may cause chronic lesions in patients immunocompromised by cancer chemotherapy, immunosuppressive drugs, or HIV infection.

Pemphigus

Pemphigus is a potentially life-threatening disease that causes blisters and erosions of the skin and mucous membranes. These epithelial lesions are a result of autoantibodies that react with desmosomal glycoproteins that are present on the cell surface of the keratinocyte. The immune reaction against these glycoproteins causes a loss of cell-to-cell adhesion, resulting in the formation of intraepithelial bullae. There are 0.5 to 3.2 cases reported each year per 100,000 population, with the highest incidence occurring in the fifth and sixth decades of life, although rare cases have been reported in children and the elderly. Pemphigus occurs more frequently in the Jewish population, particularly among Ashkenazi Jews, in whom studies have shown a strong association with major histocompatibility complex (MHC) class II alleles HLA-DR4 and DQW3. Familial pemphigus has also been reported.

The major variants of pemphigus are pemphigus vulgaris (PV), pemphigus vegetans, pemphigus foliaceus, pemphigus erythematous, paraneoplastic pemphigus (PNPP), and drug-related pemphigus. Pemphigus vegetans is a variant of pemphigus vulgaris, and pemphigus erythematous is a variant of pemphigus foliaceus. Each form of this disease has antibodies directed against different target cell surface antigens, resulting in a lesion forming in different layer of the epithelium. In pemphigus foliaceus, the blister occurs in the superficial granular cell layer, whereas, in pemphigus vulgaris, the lesion is deeper, just above the basal cell layer. Mucosal involvement is not a feature of the foliaceus and erythematous forms of the disease.

Pemphigus Vulgaris

PV is the most common form of pemphigus, accounting for over 80% of cases. The underlying mechanism responsible for causing the intraepithelial lesion of PV is the binding of IgG autoantibodies to desmoglein 3, a transmembrane glycoprotein adhesion molecule present on desmosomes. The presence of desmoglein 1 autoantibodies is a characteristic of pemphi-
Histologic picture of pemphigus vulgaris. The bulla is intraepithelial because of acantholysis (×32 original magnification). (Courtesy of Margaret Wood, MD)

Clinical Manifestations. The classical lesion of pemphigus is a thin-walled bulla arising on otherwise normal skin or mucosa. The bulla rapidly breaks but continues to extend peripherally, eventually leaving large areas denuded of skin (Figure 4-28). A characteristic sign of the disease may be obtained by application of pressure to an intact bulla. In patients with PV, the bulla enlarges by extension to an apparently normal surface. Another characteristic sign of the disease is that pressure to an apparently normal area results in the formation of a new lesion. This phenomenon, called the Nikolsky sign, results from the upper layer of the skin pulling away from the basal layer. The Nikolsky sign is most frequently associated with pemphigus but may also occur in epidermolysis bullosa.

Oral Manifestations. Eighty to ninety percent of patients with pemphigus vulgaris develop oral lesions sometime during the course of the disease, and, in 60% of cases, the oral lesions are the first sign. The oral lesions may begin as the classic bulla on a noninflamed base; more frequently, the clinician sees shallow irregular ulcers because the bullae rapidly break. A thin layer of epithelium peels away in an irregular pattern, leaving a denuded base. The edges of the lesion continue to extend peripherally over a period of weeks until they involve large portions of the oral mucosa. Most commonly the lesions start on the buccal mucosa, often in areas of trauma along the occlusal plane. The palate and gingiva are other common sites of involvement.

It is common for the oral lesions to be present up to 4 months before the skin lesions appear. If treatment is instituted during this time, the disease is easier to control, and the chance for an early remission of the disorder is enhanced. Frequently, however, the initial diagnosis is missed, and the lesions are misdiagnosed as herpes infection or candidiasis. Zegarelli and Zegarelli studied 26 cases of intraoral PV. The average time from onset of the disease to diagnosis was 6.8 months. They also noted that several patients had coexisting candidiasis, which sometimes masked the typical clinical picture of the pemphigus lesions. There is also a subgroup of pemphigus patients whose disease remains confined to the oral mucosa. These patients often have negative results on direct immunofluorescence (DIF).

If a proper history is taken, the clinician should be able to distinguish the lesions of pemphigus from those caused by acute viral infections or erythema multiforme because of the acute nature of the latter diseases. It is also important for the clinician to distinguish pemphigus lesions from those in the RAS category. RAS lesions may be severe, but individual lesions heal and recur. In pemphigus, the same lesions continue to extend peripherally over a period of weeks to months. Lesions of pemphigus are not round and symmetric like RAS lesions but are shallow and irregular and often have detached epithelium at the periphery (see Figure 4-27). In early stages of the disease, the sliding away of the oral epithelium resembles skin peeling after a severe sunburn. In some cases, the lesions may start on the gingiva and be called desquamative gingivitis. It should be remembered that desquamative gingivitis is not a diagnosis in itself; these lesions must be biopsied to rule out the possibility of PV as well as bullous pemphigoid, mucous membrane pemphigoid, and erosive lichen planus.

Laboratory Tests. PV is diagnosed by biopsy. Biopsies are best done on intact vesicles and bullae less than 24 hours old; however, because these lesions are rare on the oral mucosa, the
biopsy specimen should be taken from the advancing edge of the lesion, where areas of characteristic suprabasilar acantholysis may be observed by the pathologist. Specimens taken from the center of a denuded area are nonspecific histologically as well as clinically. Sometimes several biopsies are necessary before the correct diagnosis can be made. If the patient shows a positive Nikolsky sign, pressure can be placed on the mucosa to produce a new lesion; biopsy may be done on this fresh lesion.

A second biopsy, to be studied by DIF, should be performed whenever pemphigus is included in the differential diagnosis. This study is best performed on a biopsy specimen that is obtained from clinically normal-appearing perilesional mucosa or skin. In this technique for DIF, fluorescein-labeled antihuman immunoglobulins are placed over the patient’s tissue specimen. In cases of PV, the technique will detect antibodies, usually IgG and complement, bound to the surface of the keratinocytes.

Indirect immunofluorescent antibody tests have been described that are helpful in distinguishing pemphigus from pemphigoid and other chronic oral lesions and in following the progress of patients treated for pemphigus. In this technique, serum from a patient with bullous disease is placed over a prepared slide of an epidermal structure (usually monkey esophagus). The slide is then overlaid with fluorescein-tagged antihuman gamma globulin. Patients with pemphigus vulgaris have antikeratinocyte antibodies against intercellular substances that show up under a fluorescent microscope. The titer of the antibody has been directly related to the level of clinical disease. An ELISA (enzyme-linked immunosorbent assay) has been developed that can detect desmoglein 1 and 3 in serum samples of patients with PV. These laboratory tests should provide a new tool for the accurate diagnosis of PV and may also prove useful in monitoring the progress of the disease.156,157

**Treatment.** An important aspect of patient management is early diagnosis, when lower doses of medication can be used for shorter periods of time to control the disease. The mainstay of treatment remains high doses of systemic corticosteroids, usually given in dosages of 1 to 2 mg/kg/d. When steroids must be used for long periods of time, adjuvants such as azathioprine or cyclophosphamide are added to the regimen to reduce the complications of long-term corticosteroid therapy. Prednisone is used initially to bring the disease under control, and, once this is achieved, the dose of prednisone is decreased to the lowest possible maintenance levels. Patients with only oral involvement also may need lower doses of prednisone for shorter periods of time, so the clinician should weigh the potential benefits of adding adjuvant therapy against the risks of additional complications such as blood dyscrasias, hepatitis, and an increased risk of malignancy later in life. There is no one accepted treatment for pemphigus confined to the mouth, but one 5-year follow-up study of the treatment of oral pemphigus showed no additional benefit of adding cyclophosphamide or cyclosporine to prednisone versus prednisone alone, and it showed a higher rate of complications in the group taking the immunosuppressive drug.158 Most studies of pemphigus of the skin show a decreased mortality rate when adjuvant therapy is given along with prednisone.159 One new immunosuppressive drug, mycophenolate, has been effective when managing patients resistant to other adjuvants.160 The need for systemic steroids may be lowered further in cases of oral pemphigus by combining topical with systemic steroid therapy, either by allowing the prednisone tablets to dissolve slowly in the mouth before swallowing or by using potent topical steroid creams. Other therapies that have been reported as beneficial are parenteral gold therapy, dapsone, tetracycline, and plasmapheresis.161 Plasmapheresis is particularly useful in patients refractory to corticosteroids. A therapy described by Rook and colleagues involves administration of 8-methoxypsoralen followed by exposure of peripheral blood to ultraviolet radiation.162

**PARANEoplastIC Pemphigus**

PNPP is a severe variant of pemphigus that is associated with an underlying neoplasm—most frequently non-Hodgkin’s lymphoma, chronic lymphocytic leukemia, or thymoma.
Ulcerative, Vesicular, and Bullous Lesions

Castleman’s disease and Waldenström’s macroglobulinemia are also associated with cases of PNPP. Patients with this form of pemphigus develop severe blistering and erosions of the mucous membranes and skin. Treatment of this disease is difficult, and most patients die from the effects of the underlying tumor, respiratory failure due to acantholysis of respiratory epithelium, or the severe lesions that do not respond to the therapy successful in managing other forms of pemphigus.163,164

Histopathology of lesions of PNPP includes inflammation at the dermal-epidermal junction and keratinocyte necrosis in addition to the characteristic acantholysis seen in PV. The results of direct and indirect immunofluorescence also differ from those in PV. DIF shows deposition of IgG and complement along the basement membrane as well as on the keratinocyte surface. Indirect immunofluorescence demonstrates antibodies that not only bind to epithelium but to liver, heart, and bladder tissue as well.

PEMPHIGUS VEGETANS

Pemphigus vegetans, which accounts for 1 to 2% of pemphigus cases, is a relatively benign variant of pemphigus vulgaris because the patient demonstrates the ability to heal the denuded areas. Two forms of pemphigus vegetans are recognized: the Neumann type and the Hallopeau type. The Neumann type is more common, and the early lesions are similar to those seen in pemphigus vulgaris, with large bullae and denuded areas. These areas attempt healing by developing vegetations of hyperplastic granulation tissue. In the Hallopeau type, which is less aggressive, pustules, not bullae, are the initial lesions. These pustules are followed by verrucous hyperkeratotic vegetations.

Biopsy results of the early lesions of pemphigus vegetans show suprabasilar acantholysis.165 In older lesions, hyperkeratosis and pseudopitheliomatous hyperplasia become prominent. Immunofluorescent study shows changes identical to those seen in PV.

Oral Manifestations. Oral lesions are common in both forms of pemphigus vegetans and may be the initial sign of disease.166 Gingival lesions may be lace-like ulcers with a purulent surface on a red base or have a granular or cobblestone appearance (Figure 4-29). Oral lesions that are associated with inflammatory bowel disease and resemble pemphigus vegetans both clinically and histologically are referred to by some authors as pyostomatitis vegetans.167

Treatment. Treatment is the same as that for PV.

Subepithelial Bullous Dermatoses

Subepithelial bullous dermatoses are a group of mucocutaneous autoimmune blistering diseases that are characterized by a lesion in the basement membrane zone. The diseases in this group include bullous pemphigoid (BP), mucous membrane (cicatricial) pemphigoid (MMP), linear IgA disease (LAD), chronic bullous dermatosis of childhood (CBDC), and erosive and bullous lichen planus. There is significant overlap among these diseases, and the diagnosis often depends on whether the disease is categorized by clinical manifestations combined with routine histopathology or the newer techniques of molecular biology. Recent research into pathologic mechanisms is defining the specific antigens in the basement membrane complex involved in triggering the autoantibody response.

BULLOUS PEMPHIGOID

BP, which is the most common of the subepithelial blistering diseases, occurs chiefly in adults over the age of 60 years; it is self-limited and may last from a few months to 5 years. BP may be a cause of death in older debilitated individuals.168 BP has occasionally been reported in conjunction with other diseases, particularly multiple sclerosis and malignancy, or drug therapy, particularly diuretics.169 In pemphigoid, the initial defect is not intraepithelial as in PV, but it is subepithelial in the lamina lucida region of the basement membrane170 (Figure 4-30). There is no acantholysis, but the split in the basement membrane is accompanied by an inflammatory infiltrate that is characteristically rich in eosinophils.
Direct immunofluorescent study of a biopsy specimen demonstrates deposition of IgG bound to the basement membrane. Indirect immunofluorescent study of serum obtained from patients with BP demonstrates IgG antibodies bound to the epidermal side of salt-split skin onto antigens that have been named BP antigens 1 and 2. This latter test is particularly useful in distinguishing BP from another subepithelial bullous disease, epidermolysis bullosa aquisita, which has IgG antibodies localized to the dermal side of the salt-split skin.

**Clinical Manifestations.** The characteristic skin lesion of BP is a blister on an inflamed base that chiefly involves the scalp, arms, legs, axilla, and groin (Figure 4-31). Pruritic macules and papules may also be a presenting sign. The disease is self-limiting but can last for months to years without therapy. Patients with BP may experience one episode or recurrent bouts of lesions. Unlike pemphigus, BP is rarely life threatening since the bullae do not continue to extend at the periphery to form large denuded areas, although death from sepsis or cardiovascular disease secondary to long-term steroid use has been reported to be high in groups of sick elderly patients.

**Oral Manifestations.** Oral involvement is common in BP. Lever reported 33 patients with bullous pemphigoid. Oral lesions were present in 11. In 3 of the cases, the oral lesions preceded the skin lesions, most frequently on the buccal mucosa. Venning and colleagues reported oral lesions in 50% (18 of 36) of BP patients studied.

The oral lesions of pemphigoid are smaller, form more slowly, and are less painful than those seen in pemphigus vulgaris, and the extensive labial involvement seen in pemphigus is not present. Desquamative gingivitis has also been reported as a manifestation of BP. The gingival lesions consist of generalized edema, inflammation, and desquamation with localized areas of discrete vesicle formation. The oral lesions are clinically and histologically indistinguishable from oral lesions of mucous membrane pemphigoid, but early remission of BP is more common.

**Treatment.** Patients with localized lesions of BP may be treated with high-potency topical steroids, whereas patients with severe disease require use of systemic corticosteroids alone or combined with immunosuppressive drugs such as azathioprine, cyclophosphamide, or mycophenolate. Patients with moderate levels of disease may avoid use of systemic steroids by use of dapsone or a combination of tetracycline and nicotinamide.

**MUCOUS MEMBRANE PEMPHIGOID (CICATRICIAL PEMPHIGOID)**

MMP is a chronic autoimmune subepithelial disease that primarily affects the mucous membranes of patients over the age of 50 years, resulting in mucosal ulceration and subsequent scarring. The primary lesion of MMP occurs when autoantibodies directed against proteins in the basement membrane zone, acting with complement (C3) and neutrophils, cause a subepithelial split and subsequent vesicle formation (Figure 4-32). The antigens associated with MMP are most frequently present in the lamina lucida portion of the basement membrane, but recent research has demonstrated that the identical antigen is not involved in all cases, and the lamina densa may be the primary site of involvement in some cases. The circulating autoantibodies are not the same in all cases, and subsets of MMP have been identified by the technique of immunofluorescent staining of skin that has been split at the basement membrane zone with the use of sodium chloride. The majority of cases of MMP demonstrate IgG directed against antigens on the epidermal side of the salt-split skin, which have been identified as BP 180 (also called type XVII collagen); however, cases of MMP have also been identified where the antigen is present on the dermal side of the split. This latter antigen has been identified as epiligrin (laminin 5), an adhesion molecule that is a component of the anchoring filaments of the basement membrane.
**Clinical Manifestations.** The subepithelial lesions of MMP may involve any mucosal surface, but they most frequently involve the oral mucosa. The conjunctiva is the second most common site of involvement and can lead to scarring and adhesions developing between the bulbar and palpebral conjunctiva called symblepharon (Figure 4-33, A and B). Corneal damage is common, and progressive scarring leads to blindness in close to 15% of patients. Lesions may also affect the genital mucosa, causing pain and sexual dysfunction. Laryngeal involvement causes pain, hoarseness, and difficulty breathing, whereas esophageal involvement may cause dysphagia, which can lead to debilitation and death in severe cases. Skin lesions, usually of the head and neck region, are present in 20 to 30% of patients.

**Oral Manifestations.** Oral lesions occur in over 90% of patients with MMP. Desquamative gingivitis is the most common manifestation and may be the only manifestation of the disease (Figure 4-34). Since these desquamative lesions resemble the lesions of erosive lichen planus and pemphigus, all cases of desquamative gingivitis should be biopsied and studied with both routine histology and direct immunofluorescence to determine the correct diagnosis. Lesions may present as intact vesicles of the gingival or other mucosal surfaces, but more frequently they appear as nonspecific-appearing erosions (Figure 4-35). The erosions typically spread more slowly than pemphigus lesions and are more self-limiting.

**Diagnosis.** Patients with MMP included in the differential diagnosis must have a biopsy done for both routine and direct immunofluorescent study. Routine histopathology shows subbasilar cleavage. Using the direct immunofluorescent technique (see “Laboratory Tests” under “Pemphigus Vulgaris” for description), biopsy specimens taken from MMP patients demonstrate positive fluorescence for immunoglobulin and complement in the basement membrane zone in 50 to 80% of patients. Splitting the biopsy specimen at the basement membrane zone with 1 M NaCl prior to direct immunofluorescence increases the sensitivity of the test. The direct immunofluorescent technique is excellent for distinguishing MMP from pemphigus, and specimens obtained show immunoglobulin and complement deposition in the intercellular substance of the prickle cell layer of the epithelium. Only 10% of MMP patients demonstrate positive indirect immunofluorescence for circulating antibasement membrane-zone antibodies; however, use of salt-split skin as a substrate increases the sensitivity of this test.

**Treatment.** Management of MMP depends on the severity of symptoms. When the lesions are confined to the oral mucosa, systemic corticosteroids will suppress their formation, but the clinician must weigh the benefits against the hazards from side effects of the drug. Unlike pemphigus, MMP is not a fatal disease, and long-term use of steroids for this purpose must be carefully evaluated, particularly because most cases are chronic, most patients are elderly, and treatment is required for a long period of time.

Patients with mild oral disease should be treated with topical and intralesional steroids. Desquamative gingivitis can often be managed with topical steroids in a soft dental splint that covers the gingiva, although the clinician using topical steroids over large areas of mucosa must closely monitor the patient for side effects such as candidiasis and effects of systemic absorption. When topical or intralesional therapy is not successful, dapsone therapy may be attempted. Rogers and Mehregan have developed a protocol for use of dapsone in patients with MMP. The effectiveness of this protocol for the management of MMP was recently confirmed by Ciarrocca and Greenberg. Since dapsone causes hemolysis and methemoglobinemia, glucose-6-phosphate dehydrogenase deficiency must be ruled out, and the patient’s hemoglobin must be closely monitored. Methemoglobinemia can be reduced with the use of cimetidine and vitamin E. Another rare side effect of dapsone is dapsone hypersensitivity syndrome, an idiosyncratic disorder characterized by fever, lymphadenopathy, skin eruptions, and occasional liver involvement. Patients resistant to dapsone should be treated with a combination of systemic corticosteroids and immunosuppressive drugs, particularly when there is risk of blindness from conjunctival involvement,
or significant laryngeal or esophageal damage. Reports suggest that tetracycline and nicotinamide may also be helpful in controlling the lesions of MMP.\(^{179,180}\)

**LINEAR IGA DISEASE**

LAD is characterized by the deposition of IgA rather than IgG at the basement membrane zone, and the clinical manifestations may resemble either dermatitis herpetiformis or pemphigoid. The cause of the majority of cases is unknown, but a minority of cases have been drug induced.\(^{181}\) As in MMP, the antigens associated with LAD are heterogeneous and may be found in either the lamina lucida or lamina densa portions of the basement membrane.\(^{182,183}\)

The skin lesions of LAD may resemble those observed in patients with dermatitis herpetiformis, which are characterized by pruritic papules and blisters at sites of trauma such as the knees and elbows. Other patients have bullous skin lesions similar to those seen in patients with bullous pemphigoid.

Oral lesions are common in LAD and may be seen in up to 70% of patients. These lesions are clinically indistinguishable from the oral lesions of MMP, with blisters and erosions of the mucosa frequently accompanied by desquamative gingivitis.

Diagnosis and Management of Oral and Salivary Gland Diseases

The oral lesions of LAD may be managed with the use of topical steroids, but dapsone is effective therapy for more severe cases. Resistant cases may require systemic corticosteroids.

**CHRONIC BULLOUS DISEASE OF CHILDHOOD**

CBDC is another blistering disorder, which chiefly affects children below the age of 5 years. It is characterized by the deposition of IgA antibodies in the basement membrane zone,\(^{184}\) which are detected by direct immunofluorescence on the epidermal side of salt-split skin or mucosa. The onset of the disease may be precipitated by an upper respiratory infection or drug therapy.\(^{185}\) The characteristic lesion of CBDC is a cluster of vesicles and bullae on an inflamed base. The genital region is involved; conjunctival, rectal, and oral lesions may also be present. Oral mucosal involvement is present in up to 50% of cases, and the oral lesions are similar to those observed in patients with MMP.

Diagnosis is made by biopsy demonstrating a subepithelial lesion on routine histology and by deposition of IgA in the basement membrane zone on direct immunofluorescence. Indirect immunofluorescence demonstrates circulating IgA in 80% of cases.\(^{186}\) This disease is self-limiting, and the lesions characteristically heal within 2 years. As with LAD, the lesions are responsive to sulfapyridine or dapsone therapy. Corticosteroids may be required for severe cases.

**EROSIVE LICHEN PLANUS**

The majority of cases of lichen planus present as white lesions (discussed in detail in Chapter 5). An erosive and bullous form of this disease presents as chronic multiple oral mucosal ulcers. Erosive and bullous lesions of lichen planus occur in the severe form of the disease when extensive degeneration of the basal layer of epithelium causes a separation of the epithelium from the underlying connective tissue.\(^{187,188}\) In some cases, the lesions start as vesicles or bullae—this has been classified as “bullous lichen planus”; in a majority of cases, the disease is characterized by ulcers and is called “erosive lichen planus.” Both of these disorders are variations of the same process and should be considered together. The erosive form of lichen planus has been associated with drug therapy, underlying medical disorders, and reactions to dental restorations.\(^{189}\) The drugs most commonly associated with severe lichenoid reactions include NSAIDs, hydrochlorothiazide, penicillamine, and angiotensin-converting enzyme inhibitors. The most frequently reported underlying disease associated with oral lichenoid reactions is chronic hepatitis caused by hepatitis C, particularly in Japan and the Mediterranean region.\(^{190,191}\)

Contact allergic reactions to flavoring agents such as cinnamon and peppermint and to dental materials such as mercury in amalgam may also result in lichenoid reactions of the oral mucosa.\(^{192,193}\) Lichen planus lesions suspected of being caused by contact allergy should be in direct contact with the suspected allergen. Graft-versus-host disease due to bone marrow transplantation also causes oral lichenoid lesions.\(^{194}\)

The association between erosive lichen planus and squamous cell carcinoma remains controversial. There have been
Ulcerative, Vesicular, and Bullous Lesions

many case reports of carcinoma developing in areas of lichen planus.\textsuperscript{195–198} A case by Massa and colleagues shows histologic progression from lichen planus, lichen planus with epithelial atypia, and frank squamous cell carcinoma.\textsuperscript{199} Reviews of large numbers of patients with lichen planus by Silverman and colleagues and Murti and associates show an association between the two diseases of between 0.4 and 1.2\%.\textsuperscript{200,201} Affected patients were frequently tobacco users; this leads to speculation that lichen planus is a cofactor in malignant transformation.

**Clinical Manifestations.** Erosive lichen planus is characterized by the presence of vesicles, bullae, or irregular shallow ulcers of the oral mucosa\textsuperscript{187} (Figures 4-36 and 4-37). The lesions are usually present for weeks to months and thus can be distinguished from those of aphthous stomatitis, which form and heal in a period of 10 days to 2 weeks. A significant number of cases of erosive lichen planus present with a picture of desquamative gingivitis\textsuperscript{202} (Figure 4-38). It is important to remember that desquamative gingivitis is not a disease entity but a sign of disease that can be caused by erosive lichen planus, pemphigus vulgaris, or cicatricial pemphigoid. Desquamative gingivitis caused by lichen planus may be accompanied by characteristic Wickham’s striae, simplifying the diagnosis, or they may be present without other lesions.

**Diagnosis.** A diagnosis of erosive lichen planus should be suspected when erosive or bullous lesions are accompanied by typical lichenoid white lesions. Biopsy is necessary for definitive diagnosis. Biopsy of the erosive lesions shows hydropic degeneration of the basal layer of epithelium. This can help to distinguish it from mucous membrane pemphigoid, which is also a subepithelial lesion but which shows an intact basal layer, or from pemphigus vulgaris, in which acantholysis is demonstrated. Direct immunofluorescence should be performed on biopsy specimens when pemphigus, pemphigoid, or discoid lupus erythematosus is included in the differential diagnosis.

**Management.** Patients with severe lichen planus should have drug therapy and underlying disease ruled out as possible causes. The bullous and erosive forms of lichen planus can be distressingly painful. The treatment of choice is topical corticosteroids (Figure 4-39). Intraleisonal steroids can be used for indolent lesions, and, in cases of severe exacerbation, systemic steroids may be considered for short periods of time. Cyclosporine rinses may be effective for patients with severe erosions resistant to topical steroids, although the expense may be a limiting factor.\textsuperscript{203,204} Tacrolimus, another immunosuppressive drug, has recently been marketed in a topical form and has been reported useful in the management of oral erosive lichen planus. Systemic etretinate, dapsone, or photochemotherapy have also been reported to be effective in severe resistant cases.\textsuperscript{205–207} Because patients with oral lichen planus appear to be in a higher risk group for development of squamous cell carcinoma, it is prudent to periodically evaluate all patients with erosive and bullous forms of lichen planus for the presence of suspicious lesions requiring biopsy (Figure 4-40).

**Herpes Simplex Virus Infection in Immunosuppressed Patients**

Immunosuppressed patients may develop an aggressive or chronic form of herpes infection; therefore, herpes simplex infection should be included in the differential diagnosis when immunosuppressed patients develop chronic oral

\textbf{FIGURE 4-36} Erosive lichen planus of the labial mucosa.

\textbf{FIGURE 4-37} Palatal lesions of erosive lichen planus.

\textbf{FIGURE 4-38} Desquamative gingival lesions in a patient with erosive lichen planus.
ulcers. The chronic form of herpes is a variation of recurrent herpes simplex infection rather than a primary infection. AIDS patients, transplant patients taking immunosuppressed drug therapy, patients with leukemia, lymphoma, or other disorders that alter the T-lymphocyte response are those most susceptible to aggressive HSV lesions.

Lesions appear on the skin or the mucosa of the mouth, rectal, or genital area. They begin as an ordinary recurrent herpes infection but remain for weeks to months and develop into large ulcers up to several centimeters in diameter (Figure 4-42). Chronic herpes simplex infection has been reported with both type 1 and type 2 herpesviruses. This disease causes significant local morbidity and occasional dissemination.

**ORAL MANIFESTATIONS**

Lesions of chronic or aggressive recurrent HSV may occur on the lips or intraoral mucosa. Schneidman and colleagues reviewed 18 cases of chronic herpes infection; 7 cases occurred in renal transplant patients, and 8 occurred in patients with hematologic malignancies. Fourteen of the 18 patients had oral or perioral lesions. Greenberg and colleagues studied 98 immunosuppressed patients: 68 renal transplant patients and 30 acute leukemic patients receiving chemotherapy. Fifty percent of the leukemic patients and 15% of the transplant patients developed aggressive or chronic recurrent HSV. HSV was the most common cause of oral lesions in both groups, producing lesions that were previously thought to be due to the toxic effects of chemotherapy or bacterial infection. The oral lesions may be small, round, symmetric, and associated with recurrent herpes infection, or they may be large and deep and often confused with lesions of other diseases (see Figure 4-41, A and B). The lesions last from weeks to months and may reach several centimeters in diameter. The larger lesions often have raised white borders composed of small vesicles (Figure 4-42).

**DIAGNOSIS**

HSV must be ruled out whenever oral mucosal vesicles or ulcers occur in immunosuppressed or myelosuppressed patients. Both a cytology for staining with fluorescent HSV antibody and a viral culture should be obtained. If these lesions occur in a patient without an obvious known cause, they should be thoroughly evaluated for an immunologic deficiency disease.

**TREATMENT**

Immunosuppressed patients with HSV infection respond well to acyclovir administered orally or intravenously. Occasional cases of acyclovir-resistant HSV have been reported in AIDS patients. Foscarnet has been effective therapy for these patients.

▼ **THE PATIENT WITH SINGLE ULCERS**

The most common cause of single ulcers on the oral mucosa is trauma. Trauma may be caused by teeth, food, dental appliances, dental treatment, heat, chemicals, or electricity (Figure 4-43). The diagnosis is usually not complicated and is based on the history and physical findings. The most important differentiation is to distinguish trauma from squamous cell carcinoma. The dentist must examine all single ulcers for significant healing in 1 week; if healing is not evident in this time, a biopsy should be done to rule out cancer. (Cancer of the mouth is discussed in detail in Chapter 8.)

Infections that may cause a chronic oral ulcer include the deep mycoses histoplasmosis, blastomycosis, mucormycosis, aspergillosis, cryptococcosis, and coccidioidomycosis as well as a chronic herpes simplex infection. Syphilis, another infection that may cause a single oral ulcer in the primary and tertiary stages, is described in Chapter 20.

The deep mycoses were rare causes of oral lesions prior to HIV infection and immunosuppressive drug therapy. The dentist must consider this group of diseases in the differential diagnosis whenever isolated ulcerative lesions develop in known or suspected immunosuppressed patients. Biopsy of
suspected tissue, accompanied by a request for appropriate stains, is necessary for early diagnosis (Figure 4-44). Deep mycoses in immunosuppressed patients are discussed in greater detail in Chapters 16 and 18.

**Histoplasmosis**

Histoplasmosis is caused by the fungus *Histoplasma capsulatum*, a dimorphic fungus that grows in the yeast form in infected tissue. Infection results from inhaling dust contaminated with droppings, particularly from infected birds or bats. An African form of this infection is caused by a larger yeast, which is considered a variant of *H. capsulatum* and is called *H. duboisii*.

Histoplasmosis is the most common systemic fungal infection in the United States; in endemic areas such as the Mississippi and Ohio River valleys, serologic evidence of previous infection may be found in 75 to 80% of the population. In most cases, particularly in otherwise normal children, primary infection is mild, manifesting as a self-limiting pulmonary disease that heals to leave fibrosis and calcification similar to tuberculosis. In a small percentage of cases, progressive disease results in cavitation of the lung and dissemination of the organism to the liver, spleen, adrenal glands, and meninges. Patients with the disseminated form of the disease may develop anemia and leukopenia secondary to bone marrow involvement. Immunosuppressed or myelosuppressed patients are more likely to develop the severe disseminated form of the disease. During the past decade, most reported cases of oral lesions of histoplasmosis have been reported in HIV-infected individuals who live in or have visited endemic areas.

**ORAL MANIFESTATIONS**

Oral involvement is usually secondary to pulmonary involvement and occurs in a significant percentage of patients with disseminated histoplasmosis. Oral mucosal lesions may appear as a papule, a nodule, an ulcer, or a vegetation. If a single lesion is left untreated, it progresses from a firm papule to a nodule, which ulcerates and slowly enlarges. The cervical lymph nodes are enlarged and firm. The clinical appearance of the lesions, as well as the accompanying lymphadenopathy, often resembles that of squamous cell carcinoma, other chronic fungal infections, or even Hodgkin’s disease.
Cases of oral histoplasmosis have been reported as the initial sign of HIV infection. The most common oral lesion of histoplasmosis in patients with HIV is an ulcer with an indurated border, which is most commonly seen on the gingiva, palate, or tongue. These oral histoplasmosis lesions in patients with HIV may occur alone or as part of a disseminated infection.

**DIAGNOSIS**

Definitive diagnosis of histoplasmosis is made by a culture of infected tissues or exudates on Sabouraud’s dextrose agar or other appropriate media. Biopsy of infected tissue shows small oval yeasts within macrophages and reticuloendothelial cells as well as chronic granulomas, epithelioid cells, giant cells, and occasionally caseation necrosis. Skin tests and serology are not definitive because of significant numbers of false-negative and false-positive reactions.

**TREATMENT**

Mild to moderate cases of histoplasmosis can be treated with ketoconazole or itraconazole for 6 to 12 months. Immunosuppressed patients or patients with severe disease require intravenous amphotericin B for up to 10 weeks.

**Blastomycosis**

Blastomycosis is a fungal infection caused by Blastomyces dermatitidis. This dimorphic organism can grow in either a yeast or a mycelial form. The organism is found as a normal inhabitant of soil; therefore, the highest incidence of this infection is found in agricultural workers, particularly in the middle Atlantic and southeastern portions of the United States. This geographic distribution of the infection has led to the designation by some as “North American blastomycosis.” Infection by the same organism, however, has also been found in Mexico and Central and South Americas.

Infection with Blastomyces begins in a vast majority of cases by inhalation; this causes a primary pulmonary infection. Although an acute self-limiting form of the disease exists, the infection commonly follows a chronic course beginning with mild symptoms such as malaise, low-grade fever, and mild cough. If the infection goes untreated, the symptoms worsen to include shortness of breath, weight loss, and production of blood-tinged sputum. Infection of the skin, mucosa, and bone may also occur, resulting from metastatic spread of organisms from the pulmonary lesions through the lymphatic system. The skin and mucosal lesions start as subcutaneous nodules and progress to well-circumscribed indurated ulcers.

**ORAL MANIFESTATIONS**

Oral lesions are rarely the primary site of infection. When oral lesions have been reported as a first sign of blastomycosis, they have occurred in patients with mild pulmonary symptoms that have been overlooked by the patient or physician. Most cases of oral involvement demonstrate concomitant pulmonary lesions on chest radiographs.

The most common appearance of the oral lesions of blastomycosis is a nonspecific painless verrucous ulcer with indurated borders, often mistaken for squamous cell carcinoma. Occasionally, this mistake is perpetuated by an inexperienced histopathologist who confuses the characteristic pseudoeptitheliomatous hyperplasia with malignant changes.

Other oral lesions that have been reported include hard nodules and radiolucent jaw lesions. Page and colleagues reported two cases of painless oral mucosal ulcers as the first sign of blastomycosis; in both cases, a careful history taking revealed mild respiratory symptoms. Bell and colleagues reported 7 cases of oral lesions occurring in patients with blastomycosis; 4 presented as chronic oral ulcers and 3 as radiolucent bone lesions. Chest radiographs showed concomitant pulmonary involvement in all cases.

Dentists should include the diagnosis of blastomycosis in the differential diagnosis of a chronic oral ulcer. The diagnosis cannot be made on clinical grounds alone. The index of suspicion should increase when a chronic painless oral ulcer appears in an agricultural worker or when the review of systems reveals pulmonary symptoms. Diagnosis is made on the basis of biopsy and on culturing the organism from tissue. The histologic appearance shows pseudoeptitheliomatous hyperplasia with a heavy infiltrate of chronic inflammatory cells and microabscesses.

**TREATMENT**

Treatment for blastomycosis is similar to that described for histoplasmosis.

**Mucormycosis**

Mucormycosis (phycomycosis) is caused by an infection with a saprophytic fungus that normally occurs in soil or as a mold on decaying food. The fungus is nonpathogenic for healthy individuals and can be cultured regularly from the human nose, throat, and oral cavity. (The organism represents an opportunistic rather than a true pathogen.) Infection occurs in individuals with decreased host resistance, such as those with poorly controlled diabetes or hematologic malignancies,
or those undergoing cancer chemotherapy or immunosuppressive drug therapy. In the debilitated patient, mucormycosis may appear as a pulmonary, gastrointestinal, disseminated, or rhinocerebral infection.

The rhinomaxillary form of the disease, a subdivision of the rhinocerebral form, begins with the invasion of the fungus by a susceptible individual. The fungus invades arteries and causes damage secondary to thrombosis and ischemia. The fungus may spread from the oral and nasal region to the brain, causing death in a high percentage of cases. Symptoms include nasal discharge caused by necrosis of the nasal turbinates, ptosis, proptosis secondary to invasion of the orbit, fever, swelling of the cheek, and paresthesia of the face.

ORAL MANIFESTATIONS

The most common oral sign of mucormycosis is ulceration of the palate, which results from necrosis due to invasion of a palatal vessel. The lesion is characteristically large and deep, causing denudation of underlying bone (Figure 4-45). Ulcers from mucormycosis have also been reported on the gingiva, lip, and alveolar ridge. The initial manifestation of the disease may be confused with dental pain or bacterial maxillary sinusitis caused by invasion of the maxillary sinus. The clinician must include mucormycosis in the differential diagnosis of large oral ulcers occurring in patients debilitated from diabetes, chemotherapy, or immunosuppressive drug therapy.

Early diagnosis is essential if the patient is to be cured of this infection. Negative cultures do not rule out mucormycosis because the fungus is frequently difficult to culture from infected tissue; instead, a biopsy must be performed when mucormycosis is suspected. The histopathologic specimen shows necrosis and nonseptate hyphae, which are best demonstrated by a periodic acid–Schiff stain.

TREATMENT

When diagnosed early, mucormycosis may be cured by a combination of surgical débridement of the infected area and systemic administration of amphotericin B for up to 3 months. Proper management of the underlying disorder is an important aspect affecting the final outcome of treatment. All patients given amphotericin B must be closely observed for renal toxicity by repeated measurements of the blood urea nitrogen and creatinine.

REFERENCES


