15.6 The mouth and salivary glands 2797

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ESSENTIALS Many systemic diseases are associated with oral symptoms or signs, hence thorough examination of the lips, gums, teeth, tongue, and oropharynx should be part of any complete physical examination of a patient. Dental caries, caused by bacterial action, is one of the commonest human diseases and a cause of considerable misery. Chronic periodontal disease is the most important cause of dental loss in adults. In addition to describing these conditions, this chapter also covers potentially malignant lesions of the oral mucosa and oral cancer; viral, fungal, and bacterial infections; oral ulceration; oral manifestations of dermatological, gastroenterological, haematological, and multisystem disorders; orofacial pain syndromes; and salivary gland disorders. Diseases of the teeth, gums,
and supporting tissues Dental caries Dental caries is the destruction of dental hard tissues due to acidic and proteolytic microbial attack. The caries process is initiated in the biofilm (dental plaque) where acidogenic bacteria cause a local pH reduction sufficient to bring about dissolution of the hydroxy- apatite crystals in enamel with resultant demineralization. If the process continues for long enough and sufficient mineral is lost, progressive porosity and weakening of the tooth structure leads to cavitation. Cavitation of the enamel represents the point of no return and leads to further destruction of enamel followed by the dentine and this subsequently leads to involvement of the dental pulp. Pulpal inflammation is initiated by noxious stimuli from the carious lesion and, if the stimulus is not removed, leads to pulpal abscess and subsequent necrosis. Necrotic teeth can lead to infec- tion of the periapical tissues and beyond. Aetiology Dental caries is a multifactorial disease, the complex aetiology of which is represented diagrammatically in Fig. 15.6.1. The pathogenic biofilm Dental plaque is a polymicrobial biofilm which is adherent to the tooth structure. The biofilm is a microenvironment where bac- teria live a symbiotic existence offering mutual protection from the nonspecific immune response of the host as well as from chemicals and antibiotics. The early colonizers in dental plaque include Streptococcus mitis, S. salivarius, and S. oralis. These form the initial adherent layer which facilitates the development of the mature plaque with more patho- genic bacteria capable of rapid and prolonged acid production. The main bacterial species thought to be responsible for dental caries is S. mutans, although lactobacilli are also involved in the caries pro- cess once the lesion progresses into the

dentine. S. mutans cariogenic potency comes from its ability to colonize teeth by adhering to salivary glycoprotein and production of extracellular polysaccharides, 15.6 The mouth and salivary glands John Gibson and Douglas Robertson SES Income Saliva Education Lifestyle Stress Occupation Behaviour Oral hygiene AMPs Cortisol Noradrenaline SIgA Adrenaline Teeth Plaque microorganisms Diet (sugar) Time No caries No caries No caries No caries Caries Fig. 15.6.1 The complex multifactorial nature of dental caries. AMPS, antimicrobial peptides; SES, socioeconomic status; SIgA, secretory immunoglobulin A.

SECTION 15 Gastroenterological disorders 2798 its acidogenic ability to reduce the local pH to just above 4, and its aciduric ability to thrive in low-pH environments. Experimental studies have shown that S. mutans can also induce dental caries in germ-free mice. Recent molecular microbiology investigating the caries microbiome now indicates that S. mutans is not always pre- sent and other acidogenic bacteria can also be involved. Elevated levels of S. salivarius, S. sobrinus, and S. parasanguinis and Veillonella spp. are also associated with dental caries, especially in subjects with no or low levels of S. mutans. Bacterial community diversity is gen- erally reduced in advanced caries compared to health with reduced levels of oral commensals such as the S. mitis group, Neisseria spp., and S. sanguinis. Dental caries probably represents the endpoint of an acidogenic dysbiosis in the oral microbiome leading to cariogenic conditions in the mouth. Source of fermentable carbohydrate Consumption of nonmilk extrinsic sugars produces a rapid fall in the pH at the tooth surface to less than the critical pH of 5.5 at which tooth demineralization occurs. The most common carbohydrates in our diet are starch and sucrose, with smaller amounts of glucose, fructose, and lactose. The most important substrate in the human diet is sucrose which gives rise to heavy plaque formation with con- siderable amounts of extracellular polysaccharide favouring col- onization with aciduric cariogenic bacteria such as S. mutans and lactobacilli. The most important polysaccharide is dextran (glucan), which is synthesized in large amounts by the constitutive enzyme glucosyltransferase. Dextran may give plaque the necessary quality of stickiness to the enamel surface. Streptococci do not possess a cytochrome system but contain the Embden–Meyerhof glyco- lytic enzymes, which will convert glucose to lactic and other or- ganic acids. The pH inside the plaque may fall within 2 to 3 min of rinsing the mouth with glucose or sucrose from a level of about 6.5 to 4.5. The oral environment is therefore in a constant state of flux with changes in oral pH occurring after every ingestion of food leading to disruption of the balance between demineralization and remineralization. There are associations between caries prevalence and quantity of sugar, frequency of sugar more than four times daily, the consistency (i.e. stickiness) of the applied sugar, and the time of exposure, such as prior to sleeping during which salivary flow is reduced. Other modifying factors The tooth may be susceptible due to its anatomy (normal or dis- ordered formation), iatrogenic factors such as filling margins and damaged enamel surfaces, or due to its local environment such as a reduction in salivary quantity or quality. Patients who suffer from xerostomia (dry mouth), due either to the effect of head and neck irradiation, medication, or autoimmune diseases such as Sjögren’s syndrome, are extremely susceptible to caries which can be rapidly destructive. Saliva plays a significant role in the prevention of dental caries both through its high buffering capacity and through growth in- hibition of dental plaque by nonspecific defence proteins such as lysozyme and lactoferrin. Specific antibacterial proteins such as secretory IgA, released through fluid derived from the gum pocket known as gingival crevicular fluid, also play a role in protection of the teeth from the colonization and maturation of plaque bacteria. The effectiveness of these factors varies between individuals. Serum IgG, IgA, and IgM antibodies, as well as cell-mediated immunity to S. mutans, can be

correlated with the DMF (decayed, missing, and filled teeth) index of caries. Salivary IgA antibodies are also found. The induction of salivary IgA antibodies through immunization may be related to a reduction in dental caries. Such salivary IgA antibodies can be induced by direct immunization of the minor salivary glands or by immunization of the gut-associated lymphoid tissue or nasal-associated lymphoid tissue. Systemic im- munization experiments with S. mutans have shown in the rhesus monkey model that caries can be reduced by immunization and the induction of serum IgG antibodies. Salivary or serum-derived anti- bodies may prevent S. mutans from adhering to the tooth surface or inhibit glucosyltransferase activity and thereby prevent caries. Epidemiology Dental caries comprises the most common disease of humankind. In spite of reductions in the rate of decay in some Western societies in the last 50 years, the prevalence of caries in developed countries remains at more than 90% of the population and shows worrying signs of increasing once more. Epidemiologists report caries as DMFT or DMFS which represents the number of decayed, missing, or filled teeth or surfaces respectively. Caries is still increasing in the developing countries with the increased consumption of refined sugars. Caries is a disease of social inequalities and its prevalence is highest in poorer countries and in the lower socioeconomic groups in richer countries. In most populations, 80% of dental caries oc- curs in 20% of the population. The prevalence of caries is greatest in children and young adults where it affects the pits and fissures of the occlusal surfaces, and the enamel of the interproximal surfaces of teeth. Changing population demographics and tooth retention into later life is, however, leading to an increase in the prevalence of root caries (at the neck of the tooth) later in life. Dental caries is associated with socioeconomic factors such as low income, education, dental health attitudes, dental attendance, fluoride exposure, tooth-brushing frequency, presence of fissure sealants, family and past caries experience, and maternal infection with S. mutans. Pathology Dental caries starts as a white spot on teeth which is virtually un- detectable to the untrained eye. It progresses to a brown spot which normally represents the uptake of exogenous stain. Due to the balance between demineralization and remineralization, caries can often take 3 to 4 years to progress through enamel. It is, however, possible for caries to occur within months of tooth eruption in highly caries-active patients. This is due to the nature of newly erupted en- amel which is hypomineralized, lacks demineralization-inhibiting contaminants of the hydroxyapatite lattice such as fluoride, and is often physically within a plaque-trap location in children who may have less than perfect oral hygiene and a diet high in nonmilk ex- trinsic sugars. Early identification and institution of preventative measures that promote remineralization can arrest and reverse this process prior to surface breakdown or cavitation. Once cavitation occurs, there will be changes in the appearance of the tooth including chalky white demineralization, dark staining which can appear as brown or grey, and visible holes in the teeth. This dark stain within the tooth represents spread to the dentine core and will quickly progress to induce a reaction in the pulp below. There is

 a fine balance between the speed of the advancing front of the den- tine lesion and the rate at which pulp-dentine defences can be laid down to reduce the dentine permeability. In response to the micro- bial assault in the dentine, the cells of pulp will lay down a protective layer of tertiary dentine but may also become inflamed, a condition known as pulpitis. Dental caries is not normally painful until the carious lesion is 0.5 mm from the pulp. Depending on the duration and severity of the microbial assault, the developing pulpitis may be either reversible or irreversible depending on the pulp’s health and ability to resolve the inflammation. Acute periapical periodontitis or abscess usually occurs sec- ondary to dental caries and its sequelae (Fig. 15.6.2). After the in- tact pulp chamber is breached, colonization of the root

canals occurs with a diverse mix of anaerobic bacteria. The walls of the necrotic root canals become colonized by a specialized mixed anaerobic bio- film. Asymptomatic necrosis is common and can lead to granuloma or periapical cyst formation but abscess formation occurs when the root canal microbiota and their toxic products enter the periapical tissues via the apical foramen and induce acute inflammation and pus formation. Clinical features Dental caries is diagnosed by visual examination of a clean dry tooth under good illumination and ideally magnification supplemented by intraoral radiographs showing radiolucencies within the crown and tactile investigation by a trained dental professional (Fig. 15.6.3). Sequelae of dental caries Pulpitis is characterized by severe pain in the mouth and jaw, which is stimulated by hot, cold, and sweet stimuli, and in later stages the tooth can feel sore during biting. The pain can be either sharp or dull and poorly localized and can radiate to the ear. It is often worse at night and when lying down. Crucially, there is no bacterial infection of the surrounding tissue, swelling, or suppuration. The inflamma- tion does not respond to antibiotics and analgesia is often ineffective. This condition requires management by a dentist which includes re- moval of dental caries and placement of a sedative dressing before definitive restoration. In cases of irreversible pulpitis, removal of the tooth or extirpation of the pulp (root canal treatment) is indicated. Periapical periodontitis is inflammation of the periodontal liga- ment and alveolar bone surrounding the end of the tooth without pus formation. Pain from periapical periodontitis is not induced by thermal or osmotic stimuli such as sweet foods and is normally well localized to the offending tooth. The treatment is either to carry out root canal treatment or to extract the tooth. The acute periapical (dental) abscess is a localized collection of pus in the alveolar bone and tissues around the tooth. It is character- ized by pain, swelling, erythema, and suppuration usually localized to the affected tooth, Treatment of the localized dental abscess re- quires tooth removal or drainage of pus either through an intraoral incision or the root canal. Occasionally, dental infection can spread through the fascial planes of the head and neck as a spreading cellulitis or abscess (Fig. 15.6.4). These serious infections are potentially life-threatening and are associated with pyrexia, tachycardia or tachypnoea, trismus, Infection via carious cavity or traumatized crown Periodontal ligament Alveolar bone Apical foramen Periapical infection Infected or necrotic pulp Fig. 15.6.2 Periapical abscess formation. (a) (b) Fig. 15.6.3 Dental caries: (a) extensive destruction of the enamel and dentine; (b) cervical caries secondary to xerostomia (affecting the neck of the teeth, slightly above or below the junction between the root cementum and the enamel crown).

 raised tongue and floor of mouth, drooling, periorbital cellulitis, dif- ficulty with speaking, swallowing, and breathing, increased white blood cell count, lymphadenopathy, and dehydration. Such patients should be referred to an oral and maxillofacial surgeon without delay for incision and drainage of collections, tooth extraction, and airway management with adjunctive systemic antibiotics and medical care. Prevention Advice on prevention of dental caries is shown in Box 15.6.1. Gingival and periodontal diseases Gingival and periodontal diseases are a heterogeneous group of dis- eases that affect the supporting structures of the teeth known as the periodontium. The periodontium is made up of the gingivae (gums), cementum, periodontal ligament, and alveolar bone. In health, it is resistant to mechanical, microbiological, and chemical trauma and is responsible for maintaining the attachment of the teeth. The diseases affecting the periodontium encompass a wide range of possible pathologies, the classification of which is listed in Table 15.6.1. But the two most common conditions by far are plaque-induced gingivitis and plaque-induced periodontitis. This chapter will focus on three of the more common conditions, namely plaque-induced gingivitis, plaque-induced

periodontitis, and necrotizing ulcerative gingivitis. Clinicians should also be aware that periodontitis may be a presenting feature of haemato- logical, nutritional, hormonal, and genetic systemic diseases. Periodontal diseases are some of the most common diseases af- fecting mankind resulting in tooth loss with a significant impact on function and quality of life. Plaque-induced gingivitis is the presence of gingival inflammation without loss of the supporting tissues of the periodontium. Once the plaque is removed, the effects are entirely reversed. Plaque-induced periodontitis represents the condition in the periodontium in sites of gingival inflammation where there has been subsequent irreversible bone and connective tissue loss. Nasal passage Orbit Maxillary sinus Maxilla Buccal sulcus Buccinator muscle Buccal sulcus Mandible Oral cavity Tongue Floor of mouth Mylohyoid muscle Fig. 15.6.4 Possible routes of spread of dental infection. Box 15.6.1 Advice on the prevention of dental caries • Teeth should be brushed twice a day using toothpaste containing at least 1000 to 1500 parts per million of fluoride, the toothpaste spat out, and water for rinsing the mouth avoided. Fluoride in toothpaste decreases the incidence of caries in children by up to 40%. • Fissure sealants and professionally applied fluoride varnish applica- tions are also effective. • One part per million of fluoride in the drinking water will decrease the incidence of caries in children by up to 60%. There is no evidence of toxicity from water fluoridation. • Both the quantity and the frequency of sugar intake should be de- creased; in particular sugary snacks should be avoided between meals and immediately before bedtime. • Nonsugar sweeteners should ideally be used in food and drink; if a sweetener is required, consider xylitol. • It is important for patients to register with a dentist and attend ac- cording to individual risk assessment. • Doctors should be aware of the risk of dental caries from sugared medicines and consider this when prescribing. • Nondental professionals should be aware of the noticeably increased risk of dental caries in the presence of dry mouth. • Low-sugar artificial saliva or sugar-free chewing gum should be con- sidered for patients with dry mouth as appropriate. • General practitioners should actively encourage patients at high risk of caries to attend for dental care.

 Periodontitis can be classified as either chronic or aggressive. Chronic periodontitis is the most common and is generally con- sidered to be a slowly progressing form of the disease. Chronic periodontitis may be further described as mild, moderate, or severe. Aggressive periodontitis is a severe and widespread form of periodontal disease which is characterized by rapid attachment loss and bone destruction from an early age. The patient will be healthy apart from the periodontitis and there is a propensity to familial aggregation. Aggressive periodontitis is commonly diag- nosed in teenagers and young adults and can lead to early tooth loss. The effects of chronic periodontitis increase with age and un- treated this will progress slowly through life in a pattern of cyclical bursts of disease progression and quiescence resulting in a linear loss of attachment over time. The distinction between aggressive and chronic forms of disease is related to the earlier age of onset or detection, the more rapid rate of progression, the pattern of destruction with molars and incisors affected more severely, es- pecially in localized aggressive periodontitis, the signs of inflam- mation, and the relative amounts of plaque and calculus which are generally lower. Aetiology Plaque-induced gingivitis and periodontitis are an inflammatory response to the accumulation of dental plaque on the teeth. While dental plaque is required, it is in itself not sufficient to cause peri- odontitis and acts as an initiating factor in susceptible individuals. Theories on the effect of plaque in periodontitis have varied over the years from the nonspecific plaque hypothesis which suggested that all plaque would lead to periodontitis over time, to the spe- cific plaque hypothesis which suggested that only infection with specific periodontal pathogens would lead to periodontitis. There is good evidence that Porphyomonas

gingivalis, Tanerella forsy thensis, Treponema denticola, and Aggregatibacter actinomycetem comitans are associated with periodontitis and each have potent periodontopathic potential. However, the periodontal microbiome is incredible complex with hundreds of species of bacteria found in the mouth, half of which are yet to be cultured. The current view is that both of these views are simplistic and microbiome analysis now suggests polymicrobial synergy and dysbiosis as the current model. This hypothesis suggests that breakdown of periodontal host–microbe homeostasis (i.e. ‘healthy plaque’) occurs due to in- fection with a keystone pathogen such as P. gingivalis or the occur- rence of immunoregulatory defects in the host response and this precipitates a dysbiosis (pathogenic plaque) and periodontitis in susceptible hosts. P. gingivalis is the predominant organism iso- lated from periodontal disease; it is capable of invasion and pro- duces powerful extracellular toxins. Smoking is a significant cause of periodontitis with odds ratios of between 1.2 and 7.1 reported, depending on smoking exposure. The mechanisms by which smoking has been proposed to damage the periodontium include alterations in the vasculature of the peri- odontal tissues in smokers, reduced neutrophil transmigration across the periodontal microvasculature, suppression of neutrophil chemokinesis, chemotaxis, and phagocytosis. Large studies of populations have found that periodontal dis- ease is affected by a number of risk factors including increasing age, smoking, psychosocial stress, genetics, race, sex, oral hygiene, socioeconomic status, obesity, hormonal changes, psychosocial stress, osteopenia and osteoporosis, Down’s syndrome, diabetes mellitus, as well as host genetic factors which predispose to an inef- fective, excessive, or inappropriate inflammatory response. Table 15.6.1 Classification of periodontal conditions I. Gingival diseases A. Dental plaque-induced gingival diseasesa

1. Gingivitis associated with dental plaque only a. without other local contributing factors b. with local contributing factors
2. Gingival diseases modified by systemic factors a. associated with the endocrine system
3. puberty-associated gingivitis
4. menstrual cycle-associated gingivitis
5. pregnancy-associated a. gingivitis b. pyogenic granuloma
6. diabetes mellitus-associated gingivitis b. associated with blood dyscrasias
7. leukaemia-associated gingivitis
8. other
9. Gingival diseases modified by medications
10. Gingival diseases modified by malnutrition B. Non-plaque-induced gingival lesions II. Chronic periodontitis A. Localized B. Generalized III. Aggressive periodontitis A. Localized B. Generalized IV. Periodontitis as a manifestation of systemic diseases A. Associated with haematological disorders
11. Acquired neutropenia 2. Leukemias 3. Other B. Associated with genetic disorders
12. Familial and cyclic neutropenia 2. Down syndrome 3. Leukocyte adhesion deficiency syndromes 4. Papillon–Lefèvre syndrome 5. Chediak–Higashi syndrome 6. Histiocytosis syndromes 7. Glycogen storage disease 8. Infantile genetic agranulocytosis 9. Cohen syndrome 10. Ehlers–Danlos syndrome (types IV and VIII) 11. Hypophosphatasia 12. Other C. Not otherwise specified V. Necrotizing periodontal diseases A. Necrotizing ulcerative gingivitis B. Necrotizing ulcerative periodontitis VI. Abscesses of the periodontium VII. Periodontitis associated with endodontic lesions A. Combined periodontic-endodontic lesions VIII. Developmental or acquired deformities and conditions a Can occur on a periodontium with no attachment loss or on a periodontium with attachment loss that is

not progressing. Source data from Armitage GC (1999). Development of a classification system for periodontal diseases and conditions. Ann Periodontol, 4, 1–6.

SECTION 15 Gastroenterological disorders 2802 Epidemiology Gingivitis is found in most adults while periodontitis is found in about one-half of the middle-aged or older population. Periodontitis is the most important cause of loss of teeth after the age of 40 years, when the incidence of dental caries has greatly diminished. Across the whole adult population between 5 and 20% of the population are affected. In most populations there are groups of individuals who are (1) strongly periodontally resistant (10%), (2) highly periodontally susceptible (10%), and (3) mod- erately periodontally susceptible (80%) despite poor oral hygiene. There is evidence that the prevalence of periodontitis in developed countries is reducing slightly although changes in patient prefer- ence for tooth retention and an ageing population could affect this trend. The prevalence of chronic periodontitis is higher in Asian, Hispanic, and African patients even in migrant populations, thus pointing to a genetic predisposition. Aggressive periodontitis There is a low prevalence of aggressive periodontitis in those under 35 years. Aggressive periodontitis was found in 0.1% of teenagers but the severity and extent increases in young adulthood; for ex- ample, in one study in young adults, the prevalence rose to 3.6%. Population studies have reported varying low levels of aggressive periodontitis in children throughout the world of less than 1% apart from Africa where the prevalence was 3.4% of the population. Studies show lower levels of aggressive periodontitis in Caucasians compared with other races. Pathology Periodontitis develops in well-described histological stages as a re- sult of initial plaque accumulation and subsequent development of a pathogenic dysbiosis in the biofilm. Gingivitis Gingivitis develops after 7 to 14 days of plaque accumulation with pronounced vascular changes and an increase in extra- vascular neutrophils. The inflammatory infiltrate consists of numerous lymphocytes, predominantly T lymphocytes, im- mediately below the proliferating basal cells of the junctional epithelium. In order to facilitate the migration of neutrophils and lymphocytes, destruction of the gingival connective tissue occurs through apoptosis of fibroblasts and a reduction in the collagen fibre network of the marginal gingivae, via host- and pathogen-derived matrix metalloproteinases. As the lesion be- comes more established, there is a shift in the cell population in the inflammatory infiltrate with large numbers of plasma cells being the main histological feature in older patients; in younger patients, the infiltrate continues to be dominated by lympho- cytes. The inflammatory infiltrate becomes more pronounced and clinically noticeable. T and B lymphocytes and antibodies and complement are present in the inflamed marginal gingivae and gingival sulcus. The junctional epithelium becomes hyperplastic and ulcerated at this stage and bleeding occurs on gentle probing or brushing. Chronic gingivitis always preceded periodontitis but may persist for many years without destruction of the periodontal ligament and supporting bone. Periodontitis Periodontitis occurs when the inflammatory lesion extends into the periodontal ligament and alveolar bone and there is destruction of connective tissue attachment to the tooth. The epithelium migrates down the root surface to form a periodontal pocket. While there is some evidence that highly virulent strains of bac- teria can invade the tissues this is not normally the case. Progression of periodontal destruction occurs largely as a result of an inappro- priate and ineffective host response leading to bystander damage. Some direct tissue damage can occur through direct cytotoxicity of bacterial products such as proteinases, collagenases, epitheliotoxin, cytolethal distending toxin, haemolysin, hydrogen sulphide, and ammonia. Dysregulation of host derived factors such as protein- ases and proteinase inhibitors, matrix metalloproteinases and tissue inhibitors of metalloproteinases, proinflammatory cytokines such as interleukin (IL)-1α, IL-1β, tumour necrosis factor (TNF)-α and others,

prostaglandins, and the products of polymorphonuclear leucocytes lead to damage to the connective tissue attachment. This is particularly the case where the immunoinflammatory response is unsuccessful in containing the bacterial biofilm and its products. Bone is destroyed through normal biological mechanisms involving physiological bone turnover and impaired repair. The alveolar bone is resorbed by osteoclasts creating a ‘safety zone’, 0.5 to 1 mm in width, of uninfiltrated connective tissue. Periodontitis represents a significant microbial and inflammatory burden to the host and there are a number of systemic diseases that seem to be adversely affected by the condition of the periodontium. These include atherosclerosis, diabetes mellitus, adverse pregnancy outcomes, obesity, metabolic syndrome, chronic kidney disease, and rheumatoid arthritis. Clinical features The symptoms of chronic gingivitis or periodontitis are usually so mild that they go unnoticed by the patient until at an advanced stage (Fig. 15.6.5). The symptoms and signs of periodontitis are described in Box 15.6.2. Differential diagnosis Chronic gingivitis is relatively painless. It can be differentiated from acute ulcerative gingivitis (see later) by the sudden onset, malaise, characteristic halitosis, pain, and ulceration of the gingiva in the latter. Herpetic gingivostomatitis occurs predominantly in children and again the onset is acute, with fever, malaise, pain, and ulceration of the gingiva and oral mucosa (see later). Desquamative gingivitis usually involves the full thickness of the gingivae and is associated with lichen planus or mucous membrane pemphigoid (see later) as well as several other diseases and may cause difficulties in differen- tial diagnosis. The points to bear in mind are that the attached gin- giva shows diffuse erosive areas and there may be evidence of lesions elsewhere in the oral mucosa. Management Gingivitis and periodontitis can largely be prevented by excellent oral hygiene with twice-daily tooth-brushing and daily flossing and interdental brush use. Because severe periodontitis only occurs in a subgroup of the population, individual risk assessment by a dentist is important.

 Once deep periodontal pockets have been formed, the contamin- ated root surface must be debrided and the biofilm disrupted. The dental plaque below the gum line is removed using scalers which may be manual or powered. Systemic and, to a lesser degree, local antibiotics are used in cases of aggressive periodontitis and in those unresponsive to initial nonsurgical therapy. Periodontal surgery to access the root surfaces is also occasionally indicated. Host modula- tion therapies are also available, for example, the matrix metallopro- teinase inhibitor, low-dose doxycycline. Course and prognosis If the bacterial plaque is not removed, the gingivitis may progress to periodontitis and after many years will progress to loss of teeth and resultant loss of function. This process may, however, be arrested by excellent plaque control and professional root surface debridement, as long as there is sufficient bone to support the teeth. Patients with widespread severe or aggressive disease and those who continue to smoke are at high risk of recurrence. Necrotizing periodontal diseases The necrotizing periodontal diseases include necrotizing ulcerative gingivitis (synonyms: Vincent’s gingivitis or acute fusospirochaetal gingivitis) and necrotizing ulcerative periodontitis. Both are char- acterized by necrosis but there is no permanent damage to the periodontium in necrotizing ulcerative gingivitis. Aetiology Necrotizing ulcerative gingivitis is caused by a complex mixture of spirochaetes and fusiforms aided by other Gram-negative species. Fusobacterium and Treponema vincenti have been favoured on account of their presence in large numbers in direct examination of smears from the lesions. Prevotella intermedia, Porphyromonas gingivalis, Leptotrichia spp., and Selenomonas spp. can also com- monly be found. Whatever role microorganisms may play, a number of local and systemic predisposing factors are recognized. Of the local factors, poor oral hygiene, pre-existing gingivitis, and smoking are most important. Necrotizing periodontal diseases are associated with nutritional

deficiency, smoking, stress, debilitating disease, and HIV/AIDS. A lowered systemic resistance may also predispose to the disease, as was commonly seen in trench war- fare during the First World War which is where the term ‘trench mouth’ derives. Pathology The necrotizing ulcerative gingivitis lesion is a nonspecific, acute necrotizing inflammation of the gingivae which involves the underlying connective tissue as well as the epithelium. There is an intense polymorphonuclear response and fibrinous exudate. This soon leads to necrosis of the epithelium, thrombosis of the small blood vessels, and replacement with a meshwork of bacteria, fibrin, necrotic epithelial cells, and polymorphonuclear neutrophils. This appears clinically as a pseudomembrane. Epidemiology Necrotizing ulcerative gingivitis occurs most commonly in pa- tients between 15 and 30 years of age. It is more common in lower socioeconomic groups and in developing countries, especially in Africa where it can also progress to necrotizing ulcerative peri- odontitis and cancrum oris or ‘noma’ in malnourished children. Epidemic-like outbreaks can occur in populations although it has not been shown to be contagious. Clinical features Necrotizing ulcerative gingivitis is readily recognized by the sudden onset of painful, bleeding gums and a characteristic foul breath and metallic taste. It is also characterized by pyrexia, re- gional lymphadenitis, leucocytosis, loss of appetite, and significant malaise. Oral examination reveals grey, necrotic, punched-out crater-like ulcers covered in a grey pseudomembrane predominantly affecting the interdental gingiva and a generalized gingivitis (Fig. 15.6.6). (a) (b) Fig. 15.6.5 (a) Chronic gingivitis, with erythema and oedema of the gingival margin of the lower teeth and especially the right upper lateral incisor; (b) drug-induced gingival hyperplasia due to ciclosporin. Box 15.6.2 Symptoms and signs of periodontitis • Occasional redness or bleeding of gums while brushing teeth, using dental floss or biting into hard food (e.g. apples) • Occasional gum swelling • Halitosis or bad breath • Persistent bad taste in the mouth • Recession of gums resulting in apparent lengthening of teeth (which may also be caused by heavy-handed brushing) • Periodontal pockets between the teeth and the gums • Spacing of teeth • Loose, shaky teeth in later stages

 If untreated, necrotizing ulcerative gingivitis can lead on to peri- odontal destruction (necrotizing ulcerative periodontitis), recession and loss of the necrotic papilla. Management Necrotizing ulcerative gingivitis/periodontitis can respond to gentle local debridement alone and this can be carried out with ultra- sonic scalers and chlorhexidine gluconate or hydrogen peroxide mouthwash. If it does not respond to this then a short course of metronidazole is effective. Given that it is a disease of immunosup- pression, it is important to identify the underlying cause, especially in recurrent cases. Pericoronitis Pericoronitis is inflammation of the soft tissues associated with the crown of a partially erupted tooth (‘operculum’) and is seen most commonly in relation to the mandibular third molar teeth and gen- erally occurs at the time of their eruption (15–24 years). Clinical features Pericoronitis is associated with a complex mixture of Gram-positive and Gram-negative bacteria. Risk factors include the presence of partially erupted teeth with deep gum pocketing around the crown, trauma from contact with the opposing tooth, and poor oral hygiene. Pericoronitis may remain localized or may develop into a spreading infection involving the deep surgical spaces with associated systemic upset. Symptoms include pain, swelling and pus from the pericoronal tissues, trismus, bad taste/breath, and lymphadenopathy. Management Treatment includes irrigation of pericoronal space with a sterile irrigant such as chlorhexidine, water, saline, or local anaesthetic agent, or local agents to cauterize the soft tissues. The opposing tooth can be removed if it is causing trauma. Patients should be prescribed nonsteroidal anti-inflammatory drugs unless contraindicated and should use a 0.2% chlorhexidine mouthwash twice daily. A broad- spectrum antibiotic should be prescribed only in

cases of severe local disease not responding to local measures or if there are signs of systemic upset (e.g. fever). Repeated episodes of pericoronitis are an indication for removal of the affected tooth. Potentially malignant lesions of the oral mucosa and oral cancer Potentially malignant lesions of the oral mucosa The World Health Organization (WHO) Collaborating Centre for Oral Cancer and Precancer has identified several oral mucosal disorders as potentially malignant. These include leucoplakia, erythroplakia, lichen planus, oral submucous fibrosis, discoid lupus erythematosus, and the hereditary disorders of dyskeratosis congenita and epidermolysis bullosa. This section will deal specific- ally with leucoplakia and erythroplakia. Epidemiology Detailed studies into the incidence and prevalence of leucoplakia and erythroplakia are surprisingly uncommon with the majority of such studies being carried out in India or Sri Lanka. Thus estimates on the incidence and prevalence of these conditions vary signifi- cantly depending on which population group or country is being studied. Combining the Indian studies, the incidence of leucoplakia ranged from 0.6 per 1000 to 30.2 per 1000 depending on the use of tobacco or other substances of habit. The prevalence of leucoplakia and erythroplakia is around 1 to 5% of the population, again depending on the population examined, with leucoplakia being significantly commoner than erythroplakia. There have been brave attempts to define the term leucoplakia over several decades with the WHO in 1978 defining leucoplakia as ‘white patch or plaque that cannot be characterized clinically or pathologically as any other disease’. This definition has changed over the years with a more modern definition now being ‘a white plaque of questionable risk having excluded (other) known diseases or dis- orders that carry no increased risk for mouth cancer’. As such, it is clearly important to identify any other potential differential diag- nosis and potential positive factors. A biopsy is therefore mandatory where a lesion persists, despite intervention, for 3 weeks in order to rule out other mucosal conditions and to assess the risk of malignant transformation. Aetiology The natural history of leucoplakias and erythroplakias remains largely unknown. However, it seems that the majority of such lesions have involvement of tobacco, alcohol, or betel quid (or other recre- ational substance or drug). Pathogenesis and pathology It is important to appreciate that the terms leucoplakia and erythroplakia are clinical terms with no specific histological fea- tures. The lesions may show atrophy or hyperplasia of the prickle cell layer of the oral epithelium and may or not show epithe- lial dysplasia. Historically, two types of leucoplakias have been described—homogeneous and nonhomogeneous. It is thought that nonhomogeneous lesions carry a much higher risk of malig- nant transformation. These include ‘speckled’ variants, also called erythroleucoplakia. Clinical features These lesions, by definition, are white, red, or speckled. They can be flat, nodular, or verrucous. Fig. 15.6.6 Acute necrotizing ulcerative gingivitis.

 Differential diagnosis A number of oral mucosal lesions require to be excluded in order to make a diagnosis of leucoplakia. These include white sponge naevus, frictional keratosis, leukoedema, cheek biting and chemical injury from substances such as aspirin, candidosis, lichen planus and lichenoid tissue reactions, discoid lupus erythematosus, hairy leucoplakia, and stomatitis nicotina (hyperkeratosis of the palatal mucosa related to tobacco use). A number of clinical features are considered important in predicting the risk of malignant transformation of leucoplakias and erythroplakias. These include duration, older age of patient, being female, clinical subtype (with nonhomogeneous lesions being more prone to transformation than homogeneous lesions), being sited on the lateral borders of the tongue, ventral surface of the tongue, and floor of mouth, a previous diagnosis of head and neck cancer and, surprisingly, the absence of smoking habits. It has been reported in some studies that larger lesions are more prone

to malignant transformation. Other predictive factors, in recent studies, have suggested that the presence and severity of grade of epithelial dysplasia and/or the presence of Candida albicans also predict that the lesion may show malignant transformation at a future date. Clinical investigation Biopsy of an identified leucoplakia or erythroplakia of the oral mucosa is mandatory. Some studies have suggested that the use of diagnostic aids such as toluidine blue may be helpful in identifying the salient site for biopsy. The emergence of data to support the rou- tine use of such aids has not been forthcoming to date. Management Patients should be encouraged to stop smoking as a matter of priority and it is frequently noted that smoking cessation can re- sult in the significant regression or disappearance of such lesions in short order. Surgical treatment of leucoplakia, either by ex- cision or laser ablation, appears to offer little protection for the future development of mouth cancer within the affected mouth. Similarly, there is little evidence that long-term follow up pro- grammes for patients with oral leucoplakia or erythroplakia are very effective in preventing oral cancers developing. Regardless, practitioners and patients should be educated to look out for any change in the clinical appearance of these lesions, seeking early referral as soon as possible thereafter. There is much debate as to whether patients with potentially malignant lesions of the oral mucosa should be followed up by any primary or secondary care setting. Prognosis and outcome It is estimated that the risk of malignant transformation of oral leucoplakias is around 2% per annum and this represents a sig- nificant increase over the general population. The risk of malig- nant transformation is even higher in those with erythroplakia. As such, patients with these lesions identified in their mouths should be informed of the increased risk of mouth cancer and of the need to self-monitor the oral mucosa and report any changes to a doctor or dentist with some urgency. Oral cancer Mouth cancers include those arising on the lip, the intraoral mu- cosal structures, and oropharyngeal—arising from the tonsils or posterior one-third of tongue. The WHO's tenth edition of the International Classification of Diseases (ICD-10) classifies cancers of the lip, tongue, and mouth as ICD-10: C00-06, and oropharynx as ICD-10: C09-10. Salivary gland tumours are classified under the ICD coding as C07-08 with other pharyngeal sites as C11-13. The most common cancers of the head and neck are those arising from the mouth with the sides of the tongue the most common site. Epidemiology Head and neck cancers, including those affecting the oral cavity and pharynx, are increasingly common with around 0.5 million new cases annually across the world and 300 000 deaths. The poor out- come with mouth cancer is largely related to delay in diagnosis with around 50% of patients having metastatic disease at the time of pres- entation. Therefore, the early diagnosis of oral cancer is crucial. Aetiology The majority of mouth cancers are squamous cell carcinomas, that is, arising from the epithelial keratinocytes. Such cancers are com- moner in people who smoke tobacco, use betel, and consume al- cohol to excess. There are concerns about mouth cancer occurring in younger age groups but, currently, the majority of patients with oral squamous cell carcinoma (OSCC) are older men. There is also an increased risk of OSCC in those with a previous experience of a cancer within the aero-digestive tract or other sites within the gastrointestinal system. OSCC is also commoner in patients with a past history of potentially malignant lesions of the oral mucosa, including erythroplakia, leucoplakia, submucous fibrosis, lichen planus, and discoid lupus erythematosus. It has also been identified that lower educational status and lower income levels are associated with increased risk of developing mouth cancer. These variables are independent of smoking and alcohol consumption. Several genetic polymorphisms involved with the regulation of metabolic pathways are currently under consideration as being influential in the aeti- ology of mouth cancer. Higher levels of consumption of fruit and vegetables have been reported as significantly reducing the risk for mouth cancer. Pathogenesis and pathology The vast majority of mouth cancers are squamous cell

in origin with a multifactorial aetiology including genetic and environmental factors. Clinical features The classical appearance of an OSCC is that of an indurated (hard), exophytic (outward growing) lump or nodule with an area of asso- ciated chronic ulceration. Often the ulcer has a rolled, raised border and the tissues often friable, bleeding easily on touching (Fig. 15.6.7). However, increasingly, the topography of mouth cancer is changing with all red, white, and speckled patches of the oral mucosa which lasts for 3 weeks or more being viewed with suspi- cion. Similarly, any unexplained lumps or bumps around the oral mucosa and unexplained lymphadenopathy of the head and neck

 should be considered suspicious with investigations instituted within a 3-week time frame. Differential diagnosis A differential diagnosis for OSCC would include benign and malig- nant tumours arising from other tissue types, including lymphoma and melanoma. A smaller cohort of mouth cancers arising from the keratinocyte are known as verrucous carcinomas and these tend to be chronic, slow-growing lesions with local destructive invasion and little opportunity for metastasis. Clinical investigation Biopsy is mandatory with staging of the tumour being made under the TNM (tumour, node, metastases) classification. Examination under anaesthesia allows the full extent of the lesion to be identi- fied, along with any other coexisting primary tumours. MRI and CT scanning will allow fuller delineation of the tumour locally with the identification of nodal or distant metastatic spread. Management The identification of potential aetiological factors with rapid cessation of such factors is required. This will include advice on smoking cessation and moderation of alcohol consumption. Similarly, where the use of other recreational drugs or ethnicity- based substances (e.g. betel) is identified, cessation advice should be offered. Treatment of OSCC is centred on local excision, with or without neck dissection. The TNM staging and the tumour hist- ology will determine whether radiotherapy, chemotherapy, or chemoradiotherapy is appropriate. Prognosis and outcome Advancements in surgical techniques mean a gradually improving 5-year survival rate for patients with OSCC. However, the 5-year survival rate still sits at around 50%. Regardless, current management strategies, including prosthetic rehabilitation, mean that even those patients with disseminated disease should have a decent quality of life throughout their remaining years. Special circumstances A particular type of oral cavity cancer, oropharyngeal cancer, ap- pears to be becoming more prevalent. This is also a squamous cell carcinoma and affects primarily the lymphoid tissue of the oro- pharynx and the posterior one-third of tongue. The increasing prevalence of oropharyngeal cancer is thought to be related to an increase in carriage rates of human papilloma virus (HPV), par- ticularly serotypes 16 and 18. It is now routine practice to assess biopsy and resection specimens for the presence of HPV DNA. Such tumours tend to be of better prognosis. It is unclear how the current vaccination programme against HPV in teenage girls in some countries such as the United Kingdom for the prevention of cervical cancer may affect the prevalence of oropharyngeal cancer in the long term. Some countries, such as Australia, are assessing the veracity of a similar programme of vaccination against HPV in boys. Viral infections A number of viruses are responsible for manifestations around the head and neck. These are particularly the herpes group vir- uses (herpes simplex virus (HSV)-1, HSV-2, varicella zoster virus, human herpes virus 8, cytomegalovirus (CMV), and Epstein–Barr virus), the group A Coxsackie viruses, and HIV. On an historic note, the Koplik's spots associated with the measles virus acute infection are now very rarely seen in those countries where the mumps, mea- sles, and rubella vaccination programme is in place. Herpes simplex virus 1 and 2 HSV-1 and -2 are DNA viruses with high seroprevalence rates across all populations. Historically, HSV-1 has been predominantly found in the tissues of the head and neck with HSV-2 in the genital

tissues as a sexually acquired infection. However, with changing sexual practices, HSV-1 and -2 are now known to cause primary infections and reactivations both orally and genitally. That said, HSV-1 is still the predominant serotype identified with lesions of the head and neck. Epidemiology Around 70% of adults show seropositivity for HSV-1. In addition, some 70% of the population have been shown to shed HSV-1 in their saliva, regardless of seropositivity. Primary infection Aetiology A primary herpetic infection in the first 6 months of life is rare because of the transfer of neutralizing IgG antibodies to the virus transferred across the placenta in utero. Primary herpetic gingivostomatitis is the primary presentation, normally in children following exposure to the HSV-1 virus. For those subsequently ex- posed to HSV-2, a further primary herpetic gingivostomatitis may Fig. 15.6.7 Squamous cell carcinoma on the ventral surface of the tongue showing a necrotic centre and rolled indurated margins.

 then occur—often in adulthood corresponding with the onset of sexual activity. Pathogenesis and pathology Infection starts with HSV-1 gaining entry into the epithelial cells of the mouth with subsequent viral replication taking place inside the nucleus. With progressively more epithelial cells becoming infected, dramatic degenerative and oedematous changes occur within each cell and in the affected tissues, giving rise to vesicle formation with subsequent breakdown to form erosions or ulceration. Where ves- icle formation does not occur, the oral soft tissues simply become red and oedematous. Clinical features Clinically, the affected patient is irritable and lethargic with the onset of a sore throat, fever, and lymphadenitis. Subsequently, the gingivae (gums) become bright red with the development of vesicles. A similar picture is repeated on any or all oral mucosal surfaces. The patient refuses to eat due to oral discomfort and dehydration is a very real problem. The vesicles deroof to become erosions of ulcers, these coalescing into larger areas of tissue sloughing. Differential diagnosis The clinical picture is largely diagnostic but early phases may be con- fused with other upper aerodigestive tract viral infections. There is potential for confusion with acute Coxsackie virus infections but these tend to present with lesions in the posterior part of the mouth and pharynx, whereas a primary herpetic gingivostomatitis occurs throughout the mouth. Severe recurrent aphthous stomatitis may also be confused with a primary herpetic gingivostomatitis, save for the extensive gingival involvement in the viral infection. Clinical investigation Where doubt exists, culture of the virus may assist in the diag- nosis but, as noted previously, there is also extensive shedding of the herpes virus in asymptomatic carriers. The conventional rise in antibody titre at 2 to 3 weeks after infection allows a retrospective diagnosis to be made as required. Management The mainstay of treatment is rest with an emphasis on adequate oral fluid intake. Healthcare practitioners should have a low threshold for referral to secondary care where adequate oral hydration cannot be guaranteed. Similarly, where there is any risk of associated her- petic keratitis or encephalitis, early referral is warranted. Pain control is normally achieved with a simple analgesic such as paracetamol elixir. An antiviral preparation such as aciclovir in elixir or tablet form at a dose of 200 mg five times daily is used for adults and children over the age of 2 years. Under the age of 2, the dose is halved. The antiviral preparation is normally continued for 5 days but may be extended if new lesions appear during treatment or if the healing phase is prolonged. Prognosis and outcome Patients with primary herpetic gingivostomatitis will normally be completely well again within 10 days. Reactivation HSV-1 is a latent neurotropic virus, lying latent in the neuronal tissue of the corresponding dermatome or mucosatome affected in the pri- mary event. Reactivation can occur in four forms—recurrent herpes labialis (cold sore), recurrent intraoral herpes, lower motor neuron facial nerve palsy and, rarely, a trigeminal sensory neuropathy. Aetiology It is anticipated that

reactivation of the HSV-1 occurs following an appropriate triggering event—such as intercurrent illness, signifi- cant trauma, emotional distress, menstruation, or high levels of sun- light exposure. It has been suggested that reactivation of the virus may occur due to a defect in the local cell-mediated immunological response at the neuroepithelial junction. There is no evidence that any impairment in antibody response to the HSV is responsible for reactivation and, indeed, there is little evidence of an antibody re- sponse during episodes of reactivation. Clinical features The lesion of a cold sore tends to occur as a small, single blister, or groups of blisters on the vermillion border of the lips, although it can occur anywhere on the facial skin and nose. The lesions tend to heal within 7 to 10 days, although frequent recurrences can be very distressing and problematic. Recurrent intraoral herpes tends to occur in a localized area of the oral mucosa with ulceration or erosions which are frequently very painful. There is increasing evidence in the literature that reactivation of HSV-1 within the facial nerve may result in a lower motor neuron palsy. This appears to occur due to inflammation of the facial nerve as it passes through the stylomastoid foramen with resultant pressure effects on the nerve within the canal leading to axonal dysfunction. Trigeminal sensory neuropathies tend to be commoner in the spring and summer with the gradual onset of facial pain of limited duration. This presentation is infrequently associated with any mu- cosal or skin manifestations of viral reactivation. Erythema multiforme (EM) may be triggered, sometimes recur- rently, by reactivation of HSV-1. Management There is little evidence that topical preparations of anything other than antiviral agents have any effect on cold sores. Aciclovir cream (5%) or penciclovir cream (1%) may be applied to the developing cold sore lesions as soon as possible in the prodromal phase—every 4 h in the case of aciclovir and every 2 h with penciclovir. Where recurrent episodes of cold sores become the cause of stress or re- lationship difficulties, then prophylactic systemic antiviral prepar- ations may be offered. This is also true of recurrent intraoral herpes infection and recurrent EM. Aciclovir may be prescribed at a dose of 400 mg twice daily and valaciclovir at a dose of 500 mg daily. With regard to the management of Bell’s palsy (lower motor neuron facial nerve palsy) associated with reactivation of HSV-1, antiviral therapy has been identified as unhelpful with regard to prognosis in several studies. Instead, in uncomplicated Bell’s palsy, the literature supports the prescription of oral corticosteroids within 72 h of symptom onset.

 Prognosis and outcome Where sunlight is known to be a precipitant for recurrent cold sores, then an appropriate barrier cream may be applied to the lips before sun exposure. Herpes zoster infection The varicella zoster virus has a primary form (chicken pox) with the recurrent type causing shingles (herpes zoster infection). Once again, after primary infection, the virus shows latency, lying dormant in neuronal tissues of the dorsal root ganglia or cranial nerve ganglia. Reactivation is relatively uncommon and it is antici- pated that shingles will become increasingly rarer as a result of vac- cination programmes in many countries across the world. Reactivation of the virus initially causes altered sensation along the distribution of the affected cranial nerve with vesicles appearing within 5 days on the corresponding dermatome or mucosatome. When shingles affects the ophthalmic division of the trigeminal nerve, the risk of damage to the eye is possible and so consultation with an ophthalmologist is appropriate. When reactivation of the virus affects the geniculate ganglion of the facial nerve, the so-called Ramsay Hunt syndrome may occur with vesicle formation within the external auditory meatus and ip- silateral oropharynx (Fig. 15.6.8), along with a lower motor neuron facial palsy on the same side. Management Early treatment of active shingles infection is most important with an appropriate antiviral preparation being administered systemic- ally as soon as possible. This may be in the form

of aciclovir at a dose of 800 mg five times daily for 7 days, famciclovir at a dose of 500 mg three times daily for 7 days, or valaciclovir at a dose of 1 g three times daily for 7 days. Cytomegalovirus Although CMV infection in neonates may cause devastating results, CMV infection in otherwise healthy children and adults is largely asymptomatic but can include the features of a generalized viraemia with mild pharyngitis and regional lymph node enlargement. CMV infection in immunocompromised patients can be life- threatening. The features include salivary gland enlargement and large irregular ulcers affecting the oral mucosa. Epstein–Barr virus Close contact with the oral secretions of an infected individual or asymptomatic carrier may cause the features of infectious mono- nucleosis in teenagers and adults. This causes acute sore throat, fever, and regional lymph node enlargement. Associated features are oral ulcers and petechiae—both tending to affect the palatal mucosa. Enlargement of the spleen and liver with deranged liver functions tests are not uncommon features. Oral hairy leucoplakia is also caused by Epstein–Barr virus with these corrugated white lesions tending to affect the lateral surfaces of the tongue (Fig. 15.6.9). It was originally felt that oral hairy leucoplakia was pathognomonic of HIV disease but, more recently, this condition has been found in other causes of immunosuppres- sion and, in particular, local immunosuppression due to the use of corticosteroid inhalers in patients with asthma. Human herpes virus 8 This virus is associated with Kaposi's sarcoma in immunosuppressed patients, particularly those with HIV. Within the mouth, Kaposi's sarcoma tends to be found on the palate and the maxillary gingivae (Fig. 15.6.10). Fig. 15.6.8 Herpes zoster of the maxillary branch of the trigeminal nerve showing vesicular eruption on half of the palate. (a) (b) Fig. 15.6.9 (a) Oral hairy leucoplakia. Note the vertical lines of keratosis on the side of the tongue. These are characteristically bilateral. (b) Histological examination reveals frequent swollen epithelial cells due to infection by Epstein–Barr virus in addition to acanthosis.

15.6 The mouth and salivary glands 2809 Coxsackie virus infections Herpangina This is a relatively rare infection caused by group A Coxsackie vir- uses with small vesicles, and subsequently ulcers, affecting the oral mucosa posteriorly—particularly the soft palate and oropharynx. Children tend to be affected more often than adults with a similar presentation to that of primary herpetic gingivostomatitis, albeit that the lesions of primary herpetic gingivostomatitis tend to be significantly more widespread in the mouth. The diagnosis can be firmly established by isolating the virus from a lesion or by showing an increase in antibody titre. Importantly, the symptoms and signs are self-limiting and no specific treatments, except for rest and oral analgesics, is required. Hand, foot, and mouth disease This is another viral infection caused by group A Coxsackie viruses— notably A5, A10, and A16. It is a relatively common infection, mild in presentation but sometimes causing small epidemics among school children. Once again, the mouth is uncomfortable or sore due to multiple small vesicles, which turn into ulcers. These lesions most commonly affect the hard palate, the tongue, and the buccal mucosae. Associated with these oral lesions are similar lesions affecting the skin of the hands and feet. As before the diagnosis is largely clinical but can be confirmed either by isolating the virus from lesional tissue or by demonstrating an increase in antibody titre over 2 to 3 weeks. The disease is largely self-limiting within 10 to 14 days with no specific treatment required except for rest and oral analgesics. Human immunodeficiency virus The epidemiology, aetiology, and pathogenesis of HIV infection is discussed in Chapter 8.5.23. The at-risk populations for the trans- mission of HIV are well established. The specific significance to dentists of the potential for oral transmission of HIV is self-evident, working as they do with saliva and causing bleeding of the oral soft tissues. However, despite extensive studies across the world, there has been no confirmed case of a dental

healthcare worker infected with HIV causing onward transmission of the virus to a patient during the course of normal professional activities. HIV affects predominantly CD4+ lymphocytes, causing significant dysfunction of these cells and their role in the wider immune system. The resultant immunodeficiency allows coinfection with several other viruses, bacteria and fungi. There is evidence to suggest that HIV also adversely affects local innate immunity within the oral cavity. Epidemiology The advent of highly active antiretroviral therapy (HAART) has changed the prevalence and type of the oral manifestations of HIV very significantly. Although oral lesions (HIV-OLs) are still helpful pointers to the possibility of HIV, particularly to dentists and mem- bers of the wider oral healthcare team, once treatment begins with HAART, the HIV-OLs in an individual patient change. Lack of ad- herence to strict definitions of the oral manifestations of HIV and indeed HAART versus antiretroviral therapy, variation between adult and paediatric populations and countries, and the duration of treatment makes sensible interpretation of the worldwide data on the prevalence of HIV-OLs somewhat difficult, with studies re- porting anything from 5 to 75%. Pathogenesis/pathology It is often difficult or impossible to define the exact route of HIV transmission in a patient with HIV disease. However, the risk of oral transmission of HIV during orogenital contact, even with ejaculation of infected semen into the recipient's mouth, remains low. Similarly, there is little evidence to suggest that transfer of the virus occurs in saliva, which makes the risk of transferring HIV in a social setting with talking, coughing, and even kissing very low or negligible. The antiviral factors in saliva and the other secretions which make up the oral fluid pool (e.g. gingival crevicular fluid and blood from gingival bleeding), such as lysozyme and secretory leucocyte pro- tease inhibitor, make contact with saliva, in even the most intimate circumstances, an unlikely route of HIV transmission. Nonetheless, the presence of HIV in the oral fluid pool makes the risk of transmis- sion of HIV in saliva possible and so individuals may prefer to take appropriate precautions. Clinical features of HIV/AIDS It is remarkable to note that, with some minor alterations to the classification of periodontal diseases, the classification of the oral manifestations of HIV-related disease remains unchanged from (a) (b) Fig. 15.6.10 (a) Early Kaposi's sarcoma on the palate. (b) Established Kaposi's sarcoma on the gingiva.

 1993 when the classification and diagnostic criteria for oral lesions in HIV infection under the auspices of the EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus was published. The HIV-OLs are classified according to their relative frequency: Group 1: lesions strongly associated with HIV infection (Fig. 15.6.11) Group II: lesions less commonly associated with HIV infection Group III: lesions seen in HIV infection This classification in given in Boxes 15.6.3, 15.6.4, and 15.6.5. Differential diagnosis The disadvantage of an updated classification of HIV-OLs is that changes are taking place in the number and type of HIV-OLs—for example, hairy leucoplakia is now seen relatively commonly in non- HIV settings such as in long-term corticosteroid inhaler users; also, the pattern of HPV-related lesions is changing, with some evidence that such lesions may be re-emerging in patients on HAART. Clinical investigation Clearly, establishing the reason for the clinical presentation will be required, including an HIV test, along with viral load. However, other reasons for immunosuppression should be considered and it must always be remembered that HIV-positive patients are subject to other diseases in the same way as the general population (e.g. dia- betes and oral candidosis). With an increasing pattern of resistance emerging in the HIV- positive population to drugs such as the triazole antifungal drugs, Box 15.6.3 Group 1: lesions strongly associated with HIV infection • Candidiasis: — Erythematous — Pseudomembraneous • Hairy leucoplakia • Kaposi's sarcoma •

Non-Hodgkin’s lymphoma • Periodontal disease: — Linear gingival erythema — Necrotizing (ulcerative) gingivitis — Necrotizing (ulcerative) periodontitis Box 15.6.4 Group II: lesions less commonly associated with HIV infection • Bacterial infections: — Mycobacterium avium-intracellulare — Mycobacterium tuberculosis • Melanotic hyperpigmentation • Necrotizing (ulcerative) stomatitis • Salivary gland disease: — Dry mouth due to decreased salivary flow rate — Unilateral or bilateral swelling of major salivary glands • Thrombocytopenic purpura • Ulceration NOS (not otherwise specified) • Viral infections: — Herpes simplex virus — Human papilloma virus (warty-like lesions): — Condyloma acuminatum — Focal epithelial hyperplasia — Verruca vulgaris — Varicella zoster virus: — Herpes zoster — Varicella (a) (b) (c) Fig. 15.6.11 Candidiasis in HIV-positive patients. (a) Erythematous candidiasis of the dorsum of the tongue.
(b) Pseudomembranous candidiasis of the lower alveolus. (c) Chronic hyperplastic candidiasis of the dorsum of the tongue.

 appropriate microbiological sampling with a request for sensitivity testing is required, particularly in cases of nonresponse to empirical therapy. Management As stated before, the HIV-OLs change with the commencement of HAART in the individual patient, often ‘melting away’. However, where HIV-OLs remain or re-emerge subsequently, appropriate therapy targeted at the HIV-OLs should be commenced with the proviso that HAART comes with myriad interactions so these should be checked carefully before prescribing. Prognosis Before the commencement of HAART, the prognosis for HIV- positive patients was always guarded; however, the prognosis is now very good for those who adhere to, and cope with, prescribed HAART. The emergence of a changing pattern of HIV-OLs in patients on long-term HAART with the apparent re-emergence of some of the ‘old guard’ of HIV-OLs means that vigilance is required in moni- toring the oral manifestations of HIV diseases into the future. Fungal infections Candidosis Oral, and indeed orofacial, candidosis is common; also called can- didiasis or moniliasis. ‘Thrush’ is often used by healthcare workers and patients alike to refer to anything ‘white’ in the mouth and there is no doubt that oral candidosis is overdiagnosed by medical and dental practitioners alike. ‘Thrush’ is, of course, simply a particular variant of candidosis—the pseudomembranous variant. Epidemiology The carriage of Candida spp. is almost ubiquitous in the mouths of human subjects—estimated to be present in 40 to 80% of mouths. This carriage is asymptomatic and the presence of Candida spp. isolated from a swab or oral rinse in no way implies infection and must always be interpreted alongside clinical symptoms and signs. Candida is a diverse genus of yeasts with some species growing blastospores, hyphae, or pseudohyphae. Aetiology Candidosis is often referred to as ‘a disease of the diseased’ and there is no doubt that there are often predisposing factors as the com- mensal becomes pathogenic. These factors are best considered as (1) local and (2) systemic (see Table 15.6.2). Pathogenesis C. albicans is the commonest oral species, accounting for around 50% of cases of candidosis. Other oral species include C. glabrata, krusei, tropicalis, parapsilosis, and dubliniensis. The local and systemic fac- tors exhibited by the host are compounded by the virulence factors exhibited by the yeast. Most candidosis is experienced as a superficial infection with the yeasts residing in the superficial layers of the epi- thelium and only rarely invading beyond the basement membrane (although such invasion is seen in chronic hyperplastic candidosis and seems to add to the potentially malignant nature of this particular variant). Invasion is seen in immunosuppression, notably HIV. The pseudomembranous form’s pseudomembranes are made up of desquamated keratinocytes, keratin, leucocytes (especially neu- trophils), and candida hyphae. Optimal phagocytosis and resultant death of hyphae requires anticandidal antibodies as well as complement and the

presence of CD4+ lymphocytes. Clinical features There are four main types of primary oral candidosis: • Pseudomembranous: often considered to be ‘acute’ but tips into a chronic form in the correct circumstances (e.g. poorly con- trolled or undiagnosed diabetes mellitus; prolonged use of inhaled corticosteroids). • Acute erythematous: most often seen following a course of oral antibiotics and, unlike the other types of oral candidosis, persist- ently uncomfortable or painful. Occurs at any mucosal site but most frequently on the tongue, associated with atrophy of the mucosa—hence the pain generated. • Chronic erythematous: also known as ‘denture stomatitis’ and most often seen on the palate under an upper denture (whether partial or complete). • Hyperplastic: most commonly seen at the labial commissures bilaterally and associated with smoking. Occurs in two forms— homogeneous (smooth) or nodular. These lesions (and the asso- ciated dysplasia) can regress very quickly with smoking cessation and systemic antifungal therapy. Box 15.6.5 Group III: lesions seen in HIV infection • Bacterial infections: — Actinomyces israelli — Escherichia coli — Klebsiella pneumoniae • Cat scratch disease • Drug reactions (ulcerative, erythema multiforme, lichenoid, toxic epidermolysis) • Epithelioid (bacillary) angiomatosis • Fungal infection other than candidiasis: — Cryptococcus neoformans — Geotrichum candidum — Histoplasma capsulatum — Mucoraceae (mucormycosis/zygomycosis) — Aspergillus flavus Table 15.6.2 Local and systemic factors in oral candidosis Local Systemic Wearing of a prosthetic appliance, e.g. denture or orthodontic Immature immunity (especially the young and the old) or altered immunity Decreased saliva flow, e.g. drug induced Diabetes mellitus Diet high in refined carbohydrate Cushing’s disease Use of corticosteroid inhaler for respiratory disease, e.g. chronic obstructive pulmonary disease Prescription of immunosuppressive therapy Use of antibiotics, especially long term Haematinic deficiency, especially iron

 There are also a number of secondary types of candidosis—also known as candida-associated lesions: • Angular cheilitis (also known as angular stomatitis): frequently in combination with Staphylococcus aureus and usually seen where there is a pre-established intraoral candidosis. • Median rhomboid glossitis: a diamond-shaped area of erythema- tous candidosis in the midline of the anterior two-thirds of the dorsal surface of the tongue. Oral candidosis can also be seen as part of chronic mucocutaneous candidosis with involvement of the skin, nailbeds, and mucosal sur- faces. Chronic mucocutaneous candidosis is associated with specific T-lymphocyte defects as part of a wider disease process. Chronic mucocutaneous candidosis is also seen in association with autoimmune endocrine disorders such as Addison’s disease, hypoparathyroidism, hypothyroidism, and pernicious anaemia. Differential diagnosis The diagnosis of pseudomembranous candidosis may be assisted by the gentle scraping of a lesion to remove the white patch, leaving a bleeding red area underneath. Chronic hyperplastic candida lesions may be confused with leu- coplakia and other types of white patches but their site at the an- gles of the mouth is usually confirmatory. However, confusion with hairy leucoplakia must be avoided due to the implied underlying aetiology. All lesions of suspected chronic hyperplastic candidosis must be biopsied to determine the degree of dysplasia. Clinical investigation Management of oral candidosis involves addressing potential local and systemic factors and the degree of investigation is deter- mined by an absence of clinical response to empirical treatment. See Table 15.6.3. Management Treatment is carried out in conjunction with assessing and managing the local and systemic contributory factors. Improved oral and denture hygiene is fundamental, with dentures being removed overnight and sterilized, and also stopping smoking. Topical antifungals must be used for fully 28 days as clinical resolution is evident before mycological resolution. For angular cheilitis, miconazole cream is appropriate as it is active against

both Candida spp. and Staphylococci spp. Miconazole oral gel is useful for use inside the fitting surface of dentures. A systemic antifungal is necessary for chronic hyperplastic candidosis and should be given for orally for at least 14 days, while addressing smoking cessation and referral for biopsy. Prognosis The lesions of chronic hyperplastic candidosis should be viewed as potentially malignant lesions with biopsy and close follow-up under specialist supervision mandatory. However, in reality, the develop- ment of malignancy in these circumstances is not common. Bacterial infections Tuberculosis Oral tuberculosis (TB) is rare but seems to be becoming more common, perhaps due to the emergence of multidrug-resistant TB and/or HIV-associated TB. Oral TB lesions are thought to occur in less than 1% of TB-infected patients but this is still a significant number worldwide. Aetiology/pathology The causative organism is Mycobacterium tuberculosis and oral TB may be primary or secondary with the latter more common and following on from pulmonary TB. The infected sputum seems to make contact with the dorsal surface of the tongue and this is the commonest site in the mouth for the classical oral TB ulcer. Clinical features The classical oral TB ulcer of secondary TB tends to be indurated (hard), stellate, painful, with undermined margins. While the dorsal Table 15.6.3 Local and systemic factors, and action required in managing patients with oral candidosis How to address Local factor Wearing of a prosthetic appliance, e.g. denture or orthodontic Seek assessment by dental healthcare practitioner to determine appropriateness (e.g. fit) of the denture or appliance Decreased saliva flow, e.g. drug induced Consider systemic factors, e.g. Sjögren’s syndrome Diet high in refined carbohydrate Reduce intake of refined carbohydrate especially constant use of ‘boilings’ Use of corticosteroid inhaler for respiratory disease, e.g. chronic obstructive pulmonary disease Rinse out with tap water after each actuation of corticosteroid inhaler and/or use of a spacer device Systemic factor Immature immunity (especially the young and the old) or altered immunity May require check of FBC (white cell series) HIV status, immunoglobulin levels Diabetes mellitus Check for diabetes mellitus Cushing’s disease Any other clinical signs? Prescription of immunosuppressive therapy Check patient is not oversuppressed Use of antibiotics, especially long term Check the need for antibiotics Haematinic deficiency, especially iron Check FBC (haemoglobin) and iron stores

 tongue is the usual site, there have been reports of cases in most other parts of the mouth and also disseminated lesions affecting the maxilla and mandible. The ulcer of primary oral TB tends to occur on the lateral border of the tongue. Differential diagnosis The differential diagnosis would include trauma, syphilis, deep- tissue mycosis, and squamous cell carcinoma. Clinical investigation Given the rarity of this lesions and the importance of identifying a case of TB as early as possible, as well as excluding the other im- portant differential diagnoses, a biopsy of the ulcer is important to look for classical caseating granulomatous inflammation with the bacillus identified. Once confirmed as oral TB, the primary body system affected should be identified along with underlying cause, such as HIV infection. Management Oral TB lesions tend to respond to the same treatment regimens as systemic TB (e.g. ethambutol, isoniazid, pyrazinamide, and rifam- picin), although multidrug-resistant TB is causing increasing issues worldwide. Syphilis Syphilis is caused by the spirochaete Treponema pallidum and the manifestation of the disease process may affect the mouth in each of the three established stages of infection. See Chapter 8.6.37 for fuller information on the epidemiology, clinical presentation, and treatment of syphilis. Primary stage A syphilitic chancre appears within 2 to 4 weeks of primary infec- tion. The lesion tends to appear at the site of primary exposure to the spirochaete, most commonly affecting the lip or tongue. The chancre is a painless, small nodule initially which subsequently breaks down and forms an ulcer with raised, indurated margins.

Although rela- tively acute in onset, the lesion can resemble a squamous cell car- cinoma or actinic sun damage of the lip. A chancre is typically painless with the regional lymph node showing discrete nontender enlargement. This stage is highly infectious and serological tests can be deceptively negative during the initial 3 to 4 weeks of infection. The chancre itself heals within 8 to 10 weeks. Secondary stage This develops 1 to 4 months after infection and present as a general- ized maculopapular rash with lymph node enlargement. Oral lesions at this stage are usually the so-called snail-track ulcers—flat ulcers covered by a silver-coloured fibrinous membrane. These affect the tongue, tonsils, and lips and the saliva of the patient at this juncture is highly infective. The serological tests for syphilis are now positive. Tertiary stage This is delayed by up to 15 years after infection with an onset which is insidious. The oral manifestations at this stage include gummas and white patches (inappropriately termed ‘syphilitic leucoplakia’). The gummas tend to affect the palate with initial swelling and sub- sequent necrosis with a resultant painless, punched-out deep ulcer. These gummas can vary from one to several centimetres in diameter. They can also, rarely, affect the tongue and tonsils. The lesions can heal by scarring or, when affecting the palate, lead to perforation into the nasal cavity. The white patches usually affect the dorsal surface of the tongue and are irregular, diffuse, and not possible to remove by gentle scraping. The histological appearance at this stage is often nonspecific and so, once again, confirmation of the diagnosis is dependent on positive serology. Management The treatment of the oral lesions of syphilis is the same as that used for the systemic disease, with the response in the tertiary stage being correspondingly poorer. Cancrum oris Also called ‘noma’, this is rapidly spreading gangrene of the lips and cheeks, most commonly found in children in sub-Saharan Africa. It is thought to be an extension of acute ulcerative gingi- vitis as described earlier. However, there is also concomitant im- mune system hypofunction due to other disease processes, most commonly thought to be viral. Malnutrition is also thought to be a concomitant factor. Parasitic infections The ease of international travel, coupled with an increasingly large volume of migrant workers, refugees, and those seeking asylum, means that rarer tropical diseases are emerging in all countries of the world. A good example of this is the emergence of lip leishmaniasis, although other parasitic infections with orofacial manifestations are appearing in developed countries too, often with unusual clinical presentation. As with all good medicine, history-taking is the mainstay of good diagnosis with clear questioning on recent travel, country of origin, and contacts with others who have been unwell. Early biopsy of lesional tissue with an indication of possible diagnoses will assist the histopathologist with the process and differential diagnosis. Oral ulceration The oral mucosa offers a limited response to trauma or irritation with two main outcomes—white patches due to increased depos- ition of keratin associated with acanthosis (hyperplasia of the prickle cell layer), and erosion or ulceration. There are various types of oral ulcers, with a classification offered in Table 15.6.4 related to underlying aetiology. Recurrent aphthous stomatitis Recurrent aphthous stomatitis is also known as recurrent oral ul- ceration or more colloquially as ‘aphthae’. It comes in three main forms: minor, major, and herpetiform

 Epidemiology The true prevalence of recurrent aphthous stomatitis is difficult to determine due to clear differences in how the condition is defined across studies, populations, and countries. Lifetime prevalence in Western cultures is somewhere between 10 and 60%, with a 20% chance of developing the disease if neither parent has recurrent aphthous stomatitis but a 90% chance if both parents have the condition. Aetiology It is fair to say that the aetiology of recurrent aphthous stoma- titis has not been established, despite several potential aetiolo- gies being suggested including genetic and environmental factors. It is likely to

be an autoimmune or autoinflammatory disorder. There are doubtless familial and HLA-related factors. Other pos- tulated factors include mucosal trauma, food hypersensitivity, stress, hormonal changes (in women there is often a clear pat- tern of immediately premenstrual onset after puberty with the ul- cers disappearing completely during pregnancy), and the sharing of cross-reacting antigens with Gram-positive oral organisms (e.g. the 65-kDa heat shock protein in S. sanguinis) and epithelial cell structures. Several studies using molecular biological tech- niques have sought involvement of various viral and bacterial spe- cies with no consistent positive findings. It is established that stopping smoking may unmask recurrent aphthous stomatitis in a patient with no previous history of the condition, which has led to speculation that cigarette smoke in- duces some downregulation of mucosal immunity of relevance. Pathology The features are those of delayed hypersensitivity with an initial influx of lymphocytes and monocytes, followed subsequently by polymorphonuclear leucocytes. Immunohistochemical analysis has shown a significant population of CD4+ and CD8+ T lymphocytes, Langerhans' cells, and macrophages with HLA DR expression in the associated epithelial cells. Clinical features The salient clinical features of the three types of recurrent aphthous stomatitis are given in Table 15.6.5. Table 15.6.4 Classification of oral ulceration related to underlying aetiology Recurrent ulceration Recurrent aphthous ulceration (RAU): • Major • Minor • Herpetiform RAU associated with orofacial granulomatosis RAU associated with Behçet's disease RAU associated with HIV RAU associated with PFAPA syndrome Recurrent erythema multiforme HIV-related Persistent and/or recurrent ulceration Aphthous-type: • Secondary to haematinic deficiency—vitamin B12, folate or iron Aphthous-type: • Secondary to food hypersensitivity Aphthous-type: • Secondary to gastrointestinal disease: Crohn's disease Ulcerative colitis Coeliac disease Secondary to dermatological conditions: Mucous membrane pemphigoid Pemphigus Lichen planus/lichenoid tissue reaction Dermatitis herpetiformis Linear IgA disease Secondary to connective tissue disorders: • Lupus erythematosus (systemic and discoid) Single episode of ulceration Traumatic: • Physical/thermal • Chemical Infective: • Viral (but may also be recurrent) • Bacterial: syphilis, TB • Fungal: deep mycoses Drug reaction: • E.g. nicorandil (may also be recurrent) Solitary persistent, chronic ulcer Squamous cell carcinoma Table 15.6.5 Differentiating features of the three types of recurrent aphthous stomatitis Minor aphthous ulcers Major aphthous ulcers Herpetiform ulcers Sex ratio female:male 1.5:1 1:1 3:1 Age of onset (peak incidence) (years) 10–19 10–19 20–29 Number of ulcers 1–5 2–10 10–100 Size of ulcers <10 mm

> " 10 mm (some) 1–2 mm but coalesce Duration (days) 4–14 10–30 7–10 Healing with scars (%) 8 64 32 Recurrence 1–4 months <monthly <monthly Sites Lips, cheeks, sides of tongue Lips, cheeks, tongue (dorsum), pharynx, palate, gums Lips, cheeks, tongue (ventral), pharynx, floor of mouth Associated oral lesions None Erythema migrans None Treatment Corticosteroids (local) Corticosteroids, immunosuppressives Tetracycline as mouthwash

 Minor recurrent aphthous stomatitis About 80% of recurrent aphthous stomatitis is of this type, often presenting around puberty and extending into middle age. They are found more frequently in females than males. A burning or tin- gling sensation is often experienced by the patient 1 to 2 days before the onset of ulceration. The ulcers are round or oval with a classical erythematous halo and yellow or white fibrinous floor. They occur singly or up to five in number and can cause significant discomfort and pain, the most common

sites of involvement of the oral mucosa are the inner aspect of the lips and cheeks and the lateral margins of the tongue (Fig. 15.6.12). The ulcers last 4 to 14 days with rates of recurrence varying from 1 to 4 months in an irregular pattern. For some women, ulcers occur consistently in the premenstrual phase, leading up to menstruation. Major recurrent aphthous stomatitis Around 10% of patients with recurrent aphthous stomatitis have this form of ulceration. Once again a prodromal phase is evident with ulcers larger than 1 cm in diameter becoming evident over the next few days. These ulcers are often sited around the soft palate and fauceal complex, causing the swallowing of food and liquid to be- come quite troublesome. These ulcers are most commonly single but can occur multiply. The margins are more irregular and the ulcers more cratered than the minor variant and so, to the unsuspecting, oral cancer may be mistakenly diagnosed (Fig. 15.6.13). This puta- tive diagnosis is further compounded by the duration of these ulcers since they can stay around for several months. In addition to the soft palate and fauces, the lips, cheeks, and tongue can also be involved. Scarring is a common finding in the healing phase. Herpetiform recurrent aphthous stomatitis These are recurrent crops of tiny ulcers up to 100 in number af- fecting any part of the mouth including the gums, palate, and tongue (Fig. 15.6.14). These are the least common type of recurrent aph- thous ulcers but present more commonly in women than men. They can be very persistent and chronically recurrent, with new ulcers appearing before the previous crop has healed. Differential diagnosis It is important to differentiate genuine recurrent aphthous stomatitis from similar types of ulceration found in patients with haematinic deficiency (seen in up to 20% of patients with recurrent aphthous stomatitis) and those with food hypersensitivity reactions. Similarly, it is important to exclude underlying local and systemic disease such as orofacial granulomatosis, Crohn’s disease, ulcerative cheilitis, and coeliac disease. It is also important to exclude, by way of blood test, any leuco- penic state, particularly that of cyclic neutropenia and drug-induced neutropenia. (a) (b) Fig. 15.6.12 Minor aphthous ulceration of (a) the buccal mucosa and (b) the lower lip. Note the normal appearance of the mucosa away from the ulcers. (a) (b) Fig. 15.6.13 Major aphthous ulcers, which are more than 10 mm in diameter on (a) the tongue, with several smaller ulcers, and (b) the left buccal mucosa.

 Clinical investigation It is important to exclude local trauma in the initiation or promul- gation of recurrent aphthous stomatitis, this requiring examination by a dental healthcare practitioner. Inadequate dentures or broken down fillings may cause the development of recurrent mucosal ul- ceration. Similarly, by eliciting a full history from each patient, underlying contributory systemic disease can be excluded—such as gastrointestinal disorders and the immunobullous disorders. A plan for investigation is shown in Table 15.6.6. Management The mainstay of treatment for recurrent aphthous stomatitis re- mains topical corticosteroids. These come in various preparations including pellets (hydrocortisone hemisuccinate), mouth rinse (betamethasone valerate), sprays (beclomethasone dipropionate), and creams (clobetasol propionate). Topical tetracycline can be useful in treating the herpetiform variant of recurrent aphthous stomatitis. Benzydamine hydro- chloride as a spray or mouth rinse, and chlorhexidine gluconate as a mouth rinse, can also be used to facilitate symptom relief and faster remission of ulceration. Not infrequently, recurrent aphthous stomatitis is sufficiently se- vere to merit the use of systemic prednisolone and, in the longer term, immunomodulation in the form of azathioprine. HIV-related ulceration often responds well to thalidomide. Recent studies have shown that TNFα inhibitors may be helpful in treating patients with severe and complex recurrent aphthous sto- matitis which otherwise do not respond to standard topical and sys- temic therapy. Prognosis Recurrent aphthous stomatitis may occur from childhood and around puberty

long into adulthood. Unfortunately, most patients simply accept their recurrent ulceration as a fact of life, frequently reinforced by the attitude of healthcare professionals. Recurrent aphthous ulceration can be a significantly debilitating disorder which demands appropriate investigation and management. Special circumstances A relatively new syndrome has emerged, known as PFAPA syn- drome, comprising periodic fever, aphthous ulceration of the oral mucosa, pharyngitis, and adenitis (inflammation and enlargement of the cervical lymph nodes). This condition appears to be com- moner than once thought and responds promptly to oral prednis- olone and, where there are significant recurrences, tonsillectomy has been shown to be beneficial. Recently, there has been some interest around low levels of vitamin D in patient with PFAPA syndrome with vitamin D supplementation claimed to reduce the number and severity of episodes. This will require further clinical investigation. Behçet's disease Behçet's disease or syndrome is described in Chapter 19.11.10 but it is important to highlight that recurrent aphthous stoma- titis remains the salient diagnostic feature of the disease. Although reported as a relatively uncommon disorder, it is probably sig- nificantly underdiagnosed and it is most important that patients with recurrent aphthous stomatitis are asked about genital ulcer- ation and episodes of red eye. Colchicine has been found useful in managing the mucosal ulceration associated with Behçet's disease. Oral manifestations of dermatological and multisystem disorders Oral lichen planus and oral lichenoid tissue reactions Lichen planus may affect the skin, the genital mucosa, and/or the oral mucosa. The dermatological aspects are dealt with in Chapter 23.5. Epidemiology Oral lichen planus (OLP) is a common disorder and most often found as a coincidental finding in asymptomatic individuals. It is said to affect around 2% of the adult population, predominantly middle-age to older women. Aetiology OLP is increasingly considered to be an autoimmune disorder with a cell-mediated response being initiated against, as yet, unidentified antigens in the basement membrane zone. An associated genetic pre- disposition linked to type 1 T-helper cell cytokine polymorphisms
Fig. 15.6.14 Herpetiform ulceration: there are many coalescing ulcers on the ventral surface of the tongue. Table 15.6.6 Investigation plan for patients with recurrent aphthous stomatitis Local Remove trauma, e.g. dentures Change to a sodium lauryl sulphate-free toothpaste Check if patient has reduced or stopped smoking recently Systemic Blood tests: • FBC • Vitamin B12, folate, iron stores • Coeliac disease screen (e.g. tissue transglutaminase) Exclude systemic disease on systems questioning and examination Check current medication, e.g. nicorandil Check diet for intake of benzoates, cinnamaldehyde, chocolate, and sorbic acid

 may augment the antigenic challenge, although the overall aetiology is still something of a mystery. An association between hepatitis C virus antibody positivity and lichen planus of the skin has been reported, particularly in the Mediterranean basin, although whether this is a causal relationship or an involvement of hepatitis C virus directly (or indirectly) in the pathogenesis of lichen planus has yet to be established. Evidence that OLP and hepatitis C virus may be linked is frequently contradictory but there is increasing opinion that patients with OLP should be screened for hepatitis C virus in 'high-risk' patients, while accepting that many patients with asymptomatic hepatitis C virus have no ob- vious risk factors. Emotional stress has been shown to be a risk factor for OLP and it is likely that other 'environmental' factors are identified in due course as the autoimmune aspects of this condition are elucidated further. Toothpastes containing sodium lauryl sulphate may irritate (rather than initiate) the condition and a trial of a sodium lauryl sulphate-free toothpaste is sensible. Pathology The histopathological picture of OLP is that of a well-defined in- filtrate of predominantly T lymphocytes just under the rete-pegs within the lamina propria. The so-called saw-tooth pattern of rete- pegs often seen in

lichen planus of the skin is not so marked in OLP but there is often a prominent degeneration of the basal cell layer with apoptosis, and also acanthosis of the prickle-cell layer. Surface changes are determined by the clinical variant and may be keratotic, hyperkeratotic, or erosive. Clinical features OLP comes in seven variants (Box 15.6.6), three types of which are shown in Fig. 15.6.15. Oral lesions most commonly present in isolation, but they can also present in association with skin lesions and/or genital lesions. In these circumstances, the oral lesions tend to significantly outlast the skin or genital lesions, with a mean duration of around 7 years. Around 10% of patients with OLP have skin lesions—notably a popular red or purple rash on the flexor surfaces of the wrists, with a superimposed network of Wickham's striae ('spider-web' appearance). OLP is considered to be a potentially malignant condition, and this risk is thought to be significantly greater in smokers and in those with the erosive or atrophic variants. Vulvovaginal-gingival syndrome (with a similar entity affecting the glans penis in men) is a particularly distressing variant of OLP with symptomatic lichen planus affecting the gingivae (widespread erythema and sloughing of the gums with pain and bleeding) alongside symptomatic genital lichen planus. This subtype of lichen planus is thought to have an increased risk of both oral and genital malignancy. Differential diagnosis There are a number of conditions which present with a similar clinical and/or histological appearance—the so-called lichenoid-spectrum disorders. These include graft-versus-host disease which may occur after bone marrow transplantation and, indeed, after various types of organ transplantation. The appearance of a lichenoid-like lesion (a) (b) (c) Fig. 15.6.15 Oral lichen planus: (a) reticular, (b) ulcerative, and (c) atrophic forms. Box 15.6.6 Variants of OLP • Reticular • Erosive (also called ulcerative) • Papular • Atrophic • Plaque • Bullous • Desquamative gingivitis (this is more a description than a type as it can occur with any of the above-listed variants but is essentially an atro- phic variant; can also occur with some of the vesiculobullous disorders such as mucous membrane pemphigoid)

 at any time after organ transplantation should be viewed with sus- picion but particularly at times of reducing antirejection immuno- suppressive drug therapy. A biopsy is required along with early notification to the transplant team about possible rejection. Oral lichenoid tissue reactions—also called oral lichenoid lesions—have a similar clinical presentation and similar histology (although some authors would suggest that plasma cells are more evident in lichenoid tissue reactions) but in circumstances where a likely aetiological factor has been identified (e.g. amalgam restor- ation or drug therapy). There is some evidence to support the removal of amalgam res- torations where an lichenoid tissue reaction has occurred locally to a restoration, with replacement by a nonmercury-containing restora- tive material. However, where the lesions of OLP are widespread in the mouth (particularly in association with desquamative gingivitis) and/or associated with skin/genital lesions, amalgam replacement is unlikely to be of any value, particularly in the context of this being a condition of exacerbation–remission anyway. Where doubt exists, cutaneous patch-testing should be performed as this also allows al- ternative dental materials to be identified since there is increasing evidence that mucosal reactions to gold and other dental materials is commoner than once thought. However, it should also be under- stood that cutaneous patch-testing may not always replicate the re- sponse of the oral immunological mechanisms. There is a growing list of drugs implicated in lichenoid tissue re- actions of the oral mucosa, including β-blockers, diuretics, and oral hypoglycaemic drugs. Such putative associations offer greater cred- ibility where the reaction has occurred in short order after commen- cing therapy with the drug. In these circumstances, stopping the drug may prove helpful but is by no means always curative. Clinical investigation

Asymptomatic reticular lesions do not require biopsy (unless the pa- tient is a smoker) but all other lesions should be biopsied, particularly in smokers. This will allow the formal diagnosis to be established but also any degree of dysplasia and any presence of fungal hyphae, since superimposed candidosis in OLP can worsen symptoms. Management The mainstay of treatment remains topical corticosteroids although there is still a paucity of randomized controlled trials to compare these preparations with placebo. Topical corticosteroid application can be in the form of tablets to dissolve in the mouth (e.g. hydro- cortisone hemisuccinate 2.5 mg), mouthwash (e.g. betamethasone 0.5-mg tablets to be dissolved in water), sprays (e.g. beclomethasone dipropionate) and creams/pastes (e.g. clobetasol in mucoadhesive paste). Topical therapy with tacrolimus or pimecrolimus has gained momentum although there are some contradictory study results regarding the efficacy of these preparations and their use remains ‘off-licence’. Systemic therapies in common use for recalcitrant cases include prednisolone, azathioprine, and mycophenolate, although random- ized controlled trials are few and far between. Use of the biologicals, such as adalimumab and infliximab will doubtless gain momentum for the most severe cases but outcome measures are awaited. Importantly, all patients with OLP should be advised to stop smoking, given the increased risk of oral cancer. Areas of dysplasia should be followed up with repeat biopsies over time with a decision on early intervention by way of surgical or laser excision. There is little in the literature to determine whether or not topical or sys- temic immunosuppressive therapies decrease or increase the risk of malignant transformation in OLP and this should be a focus of future study. Prognosis Although there is an increased risk of malignant transformation in OLP, the main problem with this condition is its chronicity and lack of response to topical therapies. Much debate remains in the literature about whether patients with OLP require follow-up and, if so, where that follow-up should be—primary or secondary care. Regardless, patients with OLP should be informed of the need for self-monitoring of their oral mucosa with the requirement to report any changes to their dentist for assessment. Lupus erythematosus (systemic and chronic discoid) Both the systemic and chronic discoid variants of lupus erythematosus can manifest in the mouth, affecting the palatal and buccal mucosae predominantly. These are considered as ‘lichenoid spectrum’ disorders and so are often confused clinically with OLP. The oral lesions tend to be red and white—an atrophic or erosive centre with a white, keratotic border. Histologically, the lesions have varying degrees of keratosis with areas of hyperplasia and atrophy affecting the lesions in equal measure. Submucosal collections of lymphocytes are evident and these are often focal (as opposed to the wide band in OLP) and around blood vessels—the so-called peri- vascular infiltrate. Chronic discoid lupus erythematosus is now considered to be po- tentially malignant and so it is important to differentiate this con- dition from other mucosal disorders by way of biopsy. Otherwise treatment is similar to that described for OLP previously. The lesions of systemic lupus erythematosus tend to respond to the systemic therapies instituted to treat the wider disease. Bullous lesions Mucous membrane pemphigoid Mucous membrane pemphigoid is not one disease but rather a group of blistering disorders of autoimmune origin manifesting with subepithelial splitting to form blood-filled bullae. The bullae are primarily on the mucous membranes but skin involvement is also possible (bullous pemphigoid). The bullae tend to heal with scarring when they affect sites other than the mouth (and especially the eyes)—hence the historic term of ‘cicatricial’ pemphigoid. Oral scarring is unusual and should not be used as a diagnostic feature. Epidemiology Mucous membrane pemphigoid is rare but its true epidemiology re- mains elusive. It is known to be significantly less common than OLP. It affects women more than men and appears in the 30 to 50 years age group, or older. Aetiology and pathogenesis The identification of a causative or triggering factor for this auto- immune blistering disorder has not been forthcoming, but this is not

surprising given the heterogeneity of identified antigens in mucous

15.6 The mouth and salivary glands 2819 membrane pemphigoid. Many antigens have been identified; all components of the epithelial basement membrane hemidesmosome and its anchoring filaments, including BP180, laminin-331 and -332, alpha-6 integrin, and beta-4 integrin. The antibodies generated may be of the IgG, IgA, or IgM classes and there is often associated complement deposition. Circulating autoantibodies may be detected in serum, but not as frequently as in pemphigus. Clinical features The salient feature is blood-filled blistering and, with oral mucous membrane pemphigoid, desquamative gingivitis (Fig. 15.6.16). Oral mucosal involvement is the commonest site followed by the eyes, nose, and oesophagus. The bullae tend to rupture within hours to leave a raw, uncomfortable area of mucosal erosion or ulceration. Antigenic epitopes are increasingly being identified as unique for each site of mucosal involvement. Differential diagnosis Differential diagnosis includes the other immunobullous disorders, such as pemphigus, linear IgA disease, and dermatitis herpetiformis; and the other dermatoses, such as bullous lichen planus. There is growing evidence that Linear IgA disease may simply be a subset of mucous membrane pemphigoid. An important differential diagnosis is that of angina bullosa haemorrhagica, a blood-filled blistering disorder of unknown aetiology although the blisters are though to occur following minor trauma. They are also commoner in patients using inhaled corticosteroids for pulmonary disorders. It is imperative to ex- clude an underlying blood dyscrasia and coagulopathy. It is important that patients with this condition are encouraged to have the confidence to burst the blister, particularly when it affects the soft palate as an enlarging blister at this site can induce panic about compromising the airway. Early deroofing of the blister also reduces the tension therein and the reduced likelihood of prom- ulgation of the blister. Clinical investigation Clinical investigations include two biopsies—one for routine histo- pathology and the other for direct immunofluorescence. Linear de- position of immunoglobulin and/or complement at the basement membrane zone, in conjunction with the clinical findings, will es- tablish the diagnosis. Indirect immunofluorescence, by way of a blood test, may also be helpful. Management As is frequently the case with oral mucosal disorders, good quality randomized controlled trials are largely lacking when it comes to establishing the best therapeutic regimen to treat patients with mu- cous membrane pemphigoid. Topical corticosteroids are the main- stay of treatment with the gingival variant frequently helped by the use of occlusive corticosteroid therapy administered in gingival ven- eers or soft occlusal splints. Systemic therapies known to be worthwhile include dapsone, azathioprine, and mycophenolate mofetil. Cyclophosphamide may be added when ocular disease is associated and particularly troublesome. Regarding the biologicals, rituximab (a monoclonal anti-CD20 antibody) is deemed to be most effective although optimal regi- mens have yet to be established and whether its use should be in conjunction with other immunosuppressive agents. The use of intra- venous immunoglobulin is gaining some ground in the literature as an effective treatment for otherwise recalcitrant mucous membrane pemphigoid. Where a diagnosis of oral mucous membrane pemphigoid is es- tablished, it is important to have the patient seen by an ophthal- mologist to ensure there are no features of ocular pemphigoid, given the propensity for conjunctival scarring and possible deteri- oration in vision. Prognosis Spontaneous remission from mucous membrane pemphigoid has been recorded in several studies but the more likely outcome is local and/or systemic therapies over many years. Pemphigus vulgaris Pemphigus vulgaris (PV) is a potentially fatal immunobullous dis- order which commonly affects the oral mucosa and, indeed, may first present with oral involvement. Epidemiology and aetiology PV is commoner in women than men with women tending to pre- sent earlier by age, around 50 years. Around a quarter of

patients have an existing autoimmune disease at the time of presenting with PV, but its aetiology or triggering factors are unknown. (a) (b) Fig. 15.6.16 Mucous membrane pemphigoid showing irregular and persistent ulceration of (a) the palate and (b) the buccal mucosa.

SECTION 15 Gastroenterological disorders 2820 Pathogenesis The two major types of PV are mucocutaneous and mucosa-alone. The autoantibodies target the keratinocyte adhesion proteins asso- ciated with desmosomes at the intercellular junctions, in particular desmoglein. Antidesmoglein-3 antibodies are associated with the mucosa-alone variant of the disease. It is thought that the develop- ment of antidesmoglein-1 heralds the transition from mucosa-alone PV to mucocutaneous PV. The predominant autoantibody is of the IgG class. The deposition of autoantibodies causes destruction of intercellular adhesion within the prickle-cell layer with resultant acantholysis and bulla formation, above the basement membrane. Clinical features Around 40% of patients with PV only ever have the mucosa-alone variant. The bullae tend to be superficial within the mucosa and filled with clear fluid as opposed to blood. They are fragile and rup- ture readily and quickly—often within minutes of forming—to leave a shallow ulcer which may persist for months (Fig. 15.6.17). The involvement of multiple oral sites is associated with a poorer prog- nosis with a more prolonged course of disease, often recalcitrant to multiple therapies. Historically, the use of Nikolsky's sign has been used, whereby rub- bing the oral mucosa can induce bulla formation, but this sign is not reproducible and attempts to demonstrate it should not be performed. Differential diagnosis The initial phase of bulla formation in PV means that confusion be- tween PV and aphthous ulceration should not occur, albeit that they are both chronic ulcerating disorders. Other types of pemphigus (e.g. vegetans and foliaceus) only rarely affect the oral mucosa and can normally be differenti- ated from PV on the basis of clinical presentation and histology. However, the association of PV with underlying malignancy, and in particular lymphoproliferative disease, is worthy of mention. So- called paraneoplastic pemphigus may be the sole manifestation of an underlying malignant process. The antigens in this case are the plakins and indirect immunofluorescence is often most helpful. Familial benign chronic pemphigus, also called Hailey–Hailey disease, is a rare genetic disorder which should be part of a differen- tial diagnosis of blistering conditions in children and young adults. It brings a poor quality of life and is often very challenging to treat. Clinical investigation Two biopsies of the oral mucosa are required—one of an intact blister, if possible, for routine histopathology, and one of perilesional tissue for direct immunofluorescence. The histology shows a suprabasal split in the epithelium with an intraepithelial bulla and acantholytic cells evident within the cleft. Indirect immunofluorescence is also frequently positive, and can also be used to assess response to treat- ment, but patients can also give that information directly! Management Treatment is similar to that for pemphigoid with topical cor- ticosteroid therapy for mild disease confined to the oral cavity. Thereafter, with recalcitrant disease, prednisolone at high dose can be changed relatively quickly to combination therapy with an immu- nomodulating drug such as azathioprine or mycophenolate mofetil. Rituximab is emerging as the biological agent of choice. Prognosis The course of PV is that of exacerbations and remissions over a long period of time. The death rate from PV is around 5% over the lifetime of the patient with, nowadays, mortality more likely to be from the side effects of drug therapy rather than from the disease itself. (a) (b) (c) Fig. 15.6.17 Pemphigus vulgaris: erosions affecting (a) the palate and (b) the tongue. Direct immunofluorescence (c) on oral mucosa reveals intercellular IgG autoantibodies to desmoglein 3 (green staining).

 Where response to therapy is slow or not evident at all, consider again the possibility of paraneoplastic pemphigus. Erythema multiforme EM is a potentially fatal mucocutaneous bullous disorder, thought to be hypersensitivity driven. It is subdivided into EM minor, EM major, and Stevens–Johnson syndrome. Epidemiology and aetiology The prevalence rate of EM in its various forms is about 1%, affecting predominantly young adults aged 18 to 30 years, women more than men. Certain HLA types have been associated with EM, but not con- sistently. The role of HSV as a triggering factor is well documented but poorly understood. HSV DNA is detected by polymerase chain reaction in the skin biopsies and lesional scrapings from more than 50% of patients with the condition. Other triggers include Mycoplasma pneumoniae infection and drugs, such as nonsteroidal anti-inflammatory drugs and anticonvulsants (e.g. carbamazepine). Recurrent EM is a recognized clinical entity, with HSV playing a role as well as hypersensitivity reaction to the food additive group the benzoates (E210–E219). Pathogenesis T lymphocytes are predominant in the biopsy specimens of lesional tissue. These autoreactive T cells are recruited to the skin and mu- cous membranes with resultant tissue lysis and keratinocyte death, often with bulla formation. One difference between EM induced by HSV and that induced by drugs is that drug-induced EM is negative for HSV DNA but positive for the production of TNFα. Separation of the basement membrane zone leads to the classic blood-filled blis- ters which appear readily around the lips; otherwise small intraepi- thelial vesicles occur. Clinical features History taking may reveal the prescription of a new drug. EM minor affects one mucosal area with associated skin lesions, whereas EM major involves two or more mucosal areas and skin. Stevens–Johnson syndrome is a severe variant of EM major and is potentially fatal. There are associated systemic symptoms, such as malaise, fever, and cough. Skin features are ‘target’ lesions (also called ‘iris’ lesions) which are present over the limbs symmetric- ally. Oral lesions occur in up to two-thirds of cases of EM and include bullae and erosions (Fig. 15.6.18). Healing can take up to 5 to 6 weeks. Differential diagnosis The differential diagnosis includes primary herpetic gingivostomatitis as well as the immunobullous disorders and fixed drug eruptions. Clinical investigation There are none to clinch a diagnosis although other investigations might be appropriate, including white cell count and renal and liver function tests. HIV testing should be considered. Management Treatment is decided on the basis of severity of the illness, including the requirement for hospitalization. For milder cases, rest and copious oral fluids are required: severe cases need hospital admission, intravenous fluids, and corticosteroids, either orally or parenterally. Prognosis Most episodes of EM are entirely self-limiting and nonrecurrent. However, a few patients with EM have recurrent disease. Such pa- tients should be considered for patch-testing against the benzo- ates. A 6-month trial of aciclovir, famciclovir, or valaciclovir should be tried at an appropriate prophylactic dose. Patients with severe, recurrent EM should be considered for immunomodulation. Thalidomide may be a useful drug, and a number of biologicals have also been used successfully. Oral manifestations of gastrointestinal disorders Given that the mouth is part of the gastrointestinal tract, it should come as no surprise that the gastrointestinal disorders can have primary manifestations (a direct extension of the disease) and sec- ondary manifestations (e.g. due to malabsorption or chronic blood loss) within the mouth. Crohn’s disease and orofacial granulomatosis Crohn’s disease is discussed in Chapter 15.11 but it is important to understand about the oral (and orofacial) manifestations of Crohn’s (a) (b) Fig. 15.6.18 Erythema multiforme: (a) haemorrhagic crusted upper lip; (b) diffuse erosions of the palate.

 disease as they may be the only manifestation of the underlying dis- ease process in the wider gastrointestinal tract and/or their appear- ance in a

patient with known underlying Crohn’s disease may herald a worsening of the systemic disease. Orofacial granulomatosis is a condition manifesting clinic- ally with chronic lymphoedema of the mouth and/or face, notably swelling of the lips and oral mucosa, a full-thickness, erythematous gingivitis, and mucosal ulceration of various clinical types. Biopsy of affected tissue shows lymphoedema with or without granuloma- tous inflammation. It is a condition which frequently responds to the exclusion of certain food-related chemicals from the diet and, as such, is distinct from gastrointestinal Crohn’s disease (albeit that some patients followed-up over time may be reclassified as having gastrointestinal Crohn’s disease), although the entity of Crohn’s dis- ease may have a similar clinical presentation and histology in the orofacial region. The exact relationship between Crohn’s disease and orofacial granulomatosis is currently unknown, although recently published immunogenetic studies have added further weight to these being discrete entities. Epidemiology It is estimated that up to 30% of patients with Crohn’s disease have orofacial signs of the disease, particularly oral ulceration and other mucosal changes, often asymptomatic. In various studies, clinical evidence of Crohn’s disease was found in around 20 to 50% of patients with orofacial granulomatosis, with an estimate of 15 to 20% of patients with this condition developing Crohn’s disease over a 10- to 15-year follow-up period. Some studies have also identified that most people with orofacial granulomatosis have underlying signs of ileocolonic inflammation, but in a different pattern to that found in Crohn’s disease. Aetiology The aetiology of Crohn’s disease is complex—a combination of genetic, environmental, and mucosal regulatory factors. Food hypersensitivity reactions have long been implicated in orofacial granulomatosis, but compelling evidence has emerged linking al- lergy with orofacial granulomatosis and Crohn’s disease. Pathogenesis/pathology Crohn’s disease is a chronic granulomatous disorder with the incon- sistent finding of noncaseating granulomas deep in biopsies—often in the underlying muscle—hence the need for deeper than usual biopsies of the oral mucosa. The commonest feature on biopsies is lymphoedema, although this is not diagnostic. T lymphocytes are the predominant cells in the histology of Crohn’s disease and orofacial granulomatosis, alongside multinucleated giant cells originating from macrophages. More recently, the array of dendritic cells of the mucosa has been identified alongside the IgE- expressing B lymphocytes and mast cells, thus highlighting the link with food allergy. There has been interest over several years in the systemic response of IgA to Saccharomyces cerevisiae in Crohn’s dis- ease as well as the local secretory IgA response in several subclasses in orofacial granulomatosis. The potential role of Mycobacterium paratuberculosis in Crohn’s disease is still being investigated, but this organism has been effectively excluded in orofacial granulomatosis using polymerase chain reaction technology. Clinical features Clinical features include upper and lower lip swelling, which is con- stant, rather than intermittent in nature (Fig. 15.6.19). That said, there can be fluctuations in episodes of lip swelling. Other features are oral ulceration of the aphthous type but also linear ulcers of the lower buccal sulci. These liner ulcers, as well as ‘staghorning’ of the sublingual folds are virtually pathognomonic of underlying gut Crohn’s disease. There is also cobblestoning of the buccal mucosae, papillary hyperplasia of the hard palate, mucosal tagging, angular cheilitis, and full-thickness gingivitis (redness extending from the papillae between the teeth to the reflected gingivae in the buccal and labial sulci). Differential diagnosis The differential diagnosis includes other noncaseating granuloma- tous disorders such as sarcoidosis. Occasionally, with an acute ex-acerbation of lip or facial swelling, a dental abscess or angio-oedema may have to be excluded, albeit that dental abscesses are painful and the swellings of Crohn’s disease are not. The historic entities of cheilitis granulomatosa of Miescher and Melkersson–Rosenthal syndrome (with associated lip swelling, fis- sured tongue, and lower motor neuron palsy of the facial nerve) are

now considered by many simply to be variants of orofacial granulomatosis. (b) (a) Fig. 15.6.19 Orofacial granulomatosis in a 15-year-old boy showing (a) enlarged lips and (b) hyperplastic gingivae.

15.6 The mouth and salivary glands 2823 Clinical investigation Orofacial granulomatosis is essentially a clinical diagnosis, based on the constellation of clinical features. However, biopsy may also prove helpful. It is important to exclude underlying inflammatory bowel disease in all patients with orofacial granulomatosis, using inflam- matory markers, faecal calprotectin levels, and direct imaging of the gut if required. Management In light of recent studies, diet avoidance of benzoates, cinnamon, and sorbates should be advised on an empirical basis with patch- testing being reserved for nonresponders. Thereafter, management is often difficult with prednisolone and azathioprine being the mainstay of systemic treatment. For lip swelling, a positive response is often seen with combination therapy of intralesional triamcinolone and topical tacrolimus or pimecrolimus. Recalcitrant disease may respond to biological agents such as infliximab or adalimumab. Prognosis Orofacial granulomatosis and orofacial Crohn's disease remain dif- ficult diseases to treat, with patients best referred to oral medicine clinics for management. Liaising with gastroenterology colleagues is essential. Ulcerative colitis Oral manifestations of ulcerative colitis are almost always accom- panied by a flare-up of the gut disease activity. The main manifestation is recurrent aphthous stomatitis, but other oral mucosal conditions include pyostomatitis vegetans and stomatitis gangrenosum. Coeliac disease The presentation and management of coeliac disease are dealt with in Chapter 15.10.3. The oral manifestation of coeliac diseases is pre- dominantly aphthous-type oral ulceration with this reported in 25 to 40% of patients with coeliac disease. Where iron or folate defi- ciency results from malabsorption, signs of such deficiencies may also manifest (e.g. angular cheilitis and mucosal atrophy). Such defi- ciency manifestations are much rarer now with many societies aug- menting manufactured food with folic acid. Current guidance would support the screening of patients with prolonged, severe, or atypical oral ulceration for coeliac dis- ease with serological tests including total IgA and IgA antitissue transglutaminase antibodies. Paediatric patients with widespread enamel defects should also be screened. Several studies report prompt resolution of oral ulceration and other oral signs with the exclusion of gluten from the diet of con- firmed cases. Where haematinic deficiency has been identified, im- provement may only begin with the initiation of replacement therapy. Oral manifestations of haematological disorders Haematinic and other deficiencies Deficiencies in iron, folate, or vitamin B12 frequently cause oral manifestations including glossitis, oral ulceration, nonspecific sto- matitis, and red patches of the mucosa. Often such deficiencies are latent and so a full blood count will not necessarily reveal a problem as the haemoglobin concentration may be normal, if low, within the reference range. Assays of iron, folate, and vitamin B12 should be specifically requested. Such deficiencies or anaemia may cause glossitis (Fig. 15.6.20), soreness of the tongue or mouth more generally, angular cheilitis, or recurrent oral ulceration. Deficiencies in folate and/or vitamin B12 may cause macroglossia. Iron deficiency is known to predispose to oral candidosis. At the other end of the scale, iron overload in haemochromatosis can present with oral ulceration, angular cheilitis, and sensory nerve deficit. Pain and discomfort are often associated with geographic tongue (also called benign migratory glossitis; Fig. 15.6.21)—a condi- tion with histology very similar to that of psoriasis of the skin and thought to be commoner in patients with psoriasis although by no means always associated. Geographic tongue has been associated with zinc deficiency in one study but this has never been replicated. The lesions of geographic tongue may, however, be zinc responsive, whether topical or systemic. Fig. 15.6.20 Tongue showing

depapillation due to iron deficiency. Fig. 15.6.21 Geographic tongue: a common benign lesion frequently misdiagnosed as candida infection or anaemia.

SECTION 15 Gastroenterological disorders 2824 Vitamin C deficiency appears to be becoming more common in industrialized societies despite the increasing availability of fruit and vegetables. Diets overwhelmed by convenience foods may be responsible. Oral manifestations include spontaneous haemorrhage of the gingivae and mucosa with enlargement and erythema of the interdental papillae. This is frequently followed by destruction of periodontal tissues and loosening of the teeth, perhaps due the need for vitamin C in the cross-linking of collagen fibres. Where there is marked, sudden, and unexpected periodontitis, vitamin C levels should be checked by blood test. Blood malignancies Acute leukaemia, particularly of the myelomonocytic form, may present in young people with sore, bleeding gums with vari- able swelling of the gingivae—particularly the interdental pa- pillae (Fig. 15.6.22). This can be confused with primary herpetic gingivostomatitis. Frequently, there will be no particular lack of good oral hygiene measures to explain the gingivitis—a feature most often picked up by dental surgeons or dental hygienists. Myelodysplasias may present with peripheral sensory changes af- fecting the trigeminal nerve. Spontaneous gingival or prolonged oral bleeding after dental ex- traction may alert the clinician to an undiagnosed coagulopathy or acquired thrombocytopenia (e.g. due to drug therapy). Leucopenia and agranulocytosis may manifest in the mouth with ulceration which is often atypical. This is most commonly drug related. Oral purpura and blood-blister formation following minimal trauma may be seen in thrombocytopenia from varying causes, including drug therapy. Orofacial pain syndromes Temporomandibular disorders Temporomandibular disorders should be considered an ‘umbrella term’ for the various types of disorders that affect the temporoman- dibular joint and investing musculature. The commonest condition, and one with increasing prevalence worldwide, is temporomandibular joint dysfunction syndrome—seen so commonly in young women in many countries as to be considered almost a ‘rite of passage’. This presents variably with pain in the joint(s), muscular tenderness, limitation of jaw movement, and ‘clicking’ in the joint(s). The symptoms are often worse on wakening and are thought to be related to nocturnal clenching or grinding of the teeth—habits that are believed to be stress related. Chewing gum is also thought to worsen the symptoms and this habit should be stopped. Simple analgesia with the fabrication of an occlusal appliance by a dentist may prove helpful, although systematic reviews have failed to identify any particular treatment of value. Where the above-mentioned symptoms are accompanied by ‘locking’ open or closed of the jaw, then internal derangement of the temporomandibular joint should be considered and this will require referral to an appropriate specialist for management. Inflammatory and degenerative arthropathies should be con- sidered in the context of patients with an appropriate underlying disease process. Oral dysaesthesias The oral dysaesthesias are a diverse group of disorders, often pre- senting with oral burning or dryness (in the context of normal saliva flow). They are commoner in women by a ratio of around 9:1. They rarely occur under the age of 40 years. Where examination of the mouth reveals no abnormality, then a diagnosis of primary burning mouth syndrome may be considered. Burning may also be a symptom secondary to haematinic deficiency, oral candidosis, or elevated blood sugar. Occasionally, burning mouth may be seen as a reaction to drug therapy, such as angiotensin-converting enzyme inhibitors and statins. The oral dysaesthesias are seen most commonly in women around the age of the menopause and are thought to be hormo- nally related, at least in part. Hormone replacement therapy does not tend to improve symptoms although treatment with oral α- lipoic acid in conjunction with gabapentin or pregabalin, cognitive behavioural therapy, and topical clonazepam

have been shown in studies to be of some benefit. Treatment outcomes are frequently disappointing. Trigeminal neuralgia Trigeminal neuralgia classically presents with a sharp, shooting pain affecting one or more divisions of the trigeminal nerve, most com- monly the maxillary division, followed by the mandibular division and only very rarely the ophthalmic division. It tends to affect older patients with focal demyelination of the peripheral nerve being a common finding in affected patients on autopsy. The paroxysms of pain can be very debilitating, even though they last only for seconds. Patients under the age of 60 years and those unresponsive to drug therapy should undergo MRI scanning to exclude space-occupying lesion and demyelination. MRI scan- ning with contrast will also identify those patients in whom there is an associated microvascular compressive loop. Such patients may benefit from a microvascular decompression procedure with long- term success, in term of pain relief, being claimed in 70% or more of patients. Otherwise, drug therapy is the mainstay of treatment— carbamazepine, oxcarbazepine, lamotrigine, and gabapentin being some of the drugs showing efficacy in studies. Fig. 15.6.22 Hyperaemic swollen gingivitis in a patient with leukaemia.

 Other oral conditions Halitosis Halitosis seems to be being reported more often, which may be due to the relentless advertising of oral healthcare products and the desire to reach perfection in health. ‘Bad breath’ is a subjective standard, often worsened by fear of working in close proximity to colleagues, or fixation on sexual problems, fear of intimacy, or other psycho- logical problems. However, there can also be some physical causes, and increasing the oral intake of clear fluids daily, as well as the use of a triclosan-containing toothpaste may help, as may gently brushing the dorsal surface of the tongue. Patients with halitosis should be checked out by a dentist to ensure that active gum disease is not a contributory factor, alongside other forms of oral sepsis. Assessment of the throat should be carried out to ensure that there is no focal sepsis related to chronic tonsillitis or, rarely, a pharyngeal pouch. Other diseases such as diabetes, gastro-oesophageal reflux, and (rarely) trimethylaminuria can cause halitosis and should be ex- cluded if symptoms fail to settle with local interventions. Patients suspected of having ‘delusional’ halitosis should be referred for psy- chiatric assessment. Oral manifestations of drug therapy Drugs are increasingly being reported to have oral side effects, not least of all a reduction in salivary flow (see following section). Other side effects include oral ulceration (e.g. nicorandil), taste disturb- ance (e.g. angiotensin-converting enzyme inhibitors), and tongue swelling (e.g. angiotensin-converting enzyme inhibitors). Drugs should always be considered as possible causes for oral symptoms and signs and the corresponding literature checked. Salivary gland disorders Disorders affecting the salivary glands can be classified as intrinsic salivary gland diseases (e.g. Sjögren’s syndrome) and extrinsic sal- ivary gland diseases (e.g. drug-induced dry mouth). Dry mouth (xerostomia) Dry mouth may be reported by a patient as a symptom but, simi- larly, reduction in salivary flow may be seen by a dental healthcare worker and reported as a clinical sign. Salivary gland hypofunction is common, and a major side effect of much drug therapy (e.g. anti- depressants, diuretics, and antihistamines). It is also seen in Sjögren’s syndrome (both primary and secondary variants) as well as other systemic diseases such as diabetes mellitus where the degree of dry- ness is related to the level of glycaemic control as well as the carriage of candidal organisms. Epidemiology The true prevalence of dry mouth is unknown but, with such a vast number of potential aetiologies, it is undoubtedly common and underreported by patients. The prevalence of primary Sjögren’s syndrome clearly depends on the population surveyed but is up to 2.5% and commoner in white women around the age of 30 to 40 years. The prevalence of secondary Sjögren’s syndrome again depends on the population

surveyed but also on the commonality of the asso- ciated autoimmune disease, for example, up to 30% of patients with rheumatoid arthritis, and up to 15% of patients with systemic lupus erythematosus. Aetiology and pathogenesis Sjögren's syndrome is a chronic autoimmune disorder which oc- curs in a stand-alone form (primary) and in a form secondary to an underlying systemic autoimmune disorder such as rheumatoid arthritis and lupus. The lacrimal and salivary glands, along with all the exocrine glands, have a classical inflammatory infiltration with B lymphocytes. The associated marked inflammatory reaction causes scarring of glandular tissue with loss of acini and their replacement with fibrous tissue. See Chapter 19.11.4 for further discussion. Clinical features The classical presentation of Sjögren's syndrome involves dryness of the mouth and/or eyes. Primary Sjögren's syndrome is often associ- ated with other features such as tiredness, arthralgia, and myalgia. Differential diagnosis The differential diagnosis of dry mouth includes sarcoidosis and, increasingly, the obstructive sleep apnoea–hypopnoea syndrome. It has been suggested that a group of patients with generalized nodal osteoarthritis and sialadenitis also have xerostomia, but with no evi- dence of autoantibodies—the so-called SOX syndrome (sialadenitis, osteoarthritis, and xerostomia). The sialadenitis is nonspecific as op- posed to the lymphocytic infiltrate seen in Sjögren's syndrome. This putative disorder requires further investigation. Clinical investigations Most current diagnostic criteria include the need for objective evi- dence of salivary gland and/or lacrimal gland involvement, in add- ition to symptoms reported by the patient. Objective assessment includes the presence of autoantibodies in serum and/or the pres- ence of focal lymphocytic sialadenitis on minor labial salivary gland biopsy. The use of noninvasive salivary gland ultrasound scanning is gaining popularity in diagnosis, rather than parotid salivary gland sialography, but requires ratification. Management The loss of saliva function is most debilitating and distressing, af- fecting taste, speech, chewing, swallowing, sexual intimacy, and leading to worsening dental caries, gum diseases, loss of teeth, and poor denture retention. It may also lead to recurrent oral infections with candidal or staphylococcal species. Treatment focuses on increasing salivary flow by the use of oral pilocarpine. Where there is no residual functioning salivary tissue, patients may benefit from using sips of water and a saliva substitute. In dentate patients, high-concentration fluoride toothpaste should be used to avoid caries and tooth surface loss. Oral and dental hy- giene should be maximized. Regular dental and oral review by a dental professional will assist in identifying early any infections with candida or staphylococcal species. Where systemic involvement in primary Sjögren's syndrome is marked, immunosuppressive drugs are often tried, including

 hydroxychloroquine and azathioprine. Given the pathophysiology of Sjögren's syndrome, biological agents such as rituximab are showing promise. Prognosis Sjögren's syndrome is a progressive disease characterized by worsening symptoms over time. There is an increased lifetime risk of the development of lymphoma, mostly non-Hodgkin B-cell type, predominantly of the marginal zone histological form, particularly in the primary variant of Sjögren's syndrome, although various studies have failed to agree the specific increased risk. Such lympho- mas are frequently extranodal and originate in mucosa-associated lymphoid tissue—so-called MALT lymphomas. It is known that the risk of developing lymphoma is higher in pa- tients with persistent unilateral or bilateral major salivary gland en- largement, persistent lymphadenopathy, evidence of vasculitis, and/ or low complement levels and the presence of cryoglobulins. Where minor salivary gland biopsy has been carried out, histological evi- dence of germinal centres also appears to increase the risk of subse- quently developing lymphoma. Where persistent enlargement of the major salivary glands is pre- sent, these should be subject to regular

review by way of ultrasound scanning, MRI scanning, and/or fine needle aspiration biopsy to determine the development of focal lymphoma. Sialadenitis (acute and chronic) Bacterial or viral infections and rarely allergic reactions may cause inflammation of the salivary glands. These agents may give rise to acute, chronic, and allergic sialadenitis, and recurrent parotitis. One particular variant, of unknown aetiology, is recurrent parotitis of childhood which appears to resolve spontaneously after puberty. Aetiology Ascending infection of the parotid gland may occur due to obstruc- tion of the ductal system by a calculus (stone), stricture, or mucus plug. Acute parotitis may also follow the use of a drug causing xerostomia. The most common microorganisms involved are Staphylococcus aureus, Streptococcus milleri group, and other mem- bers of the oral flora. The most common acute viral parotitis was historically mumps but routine vaccination against this has seen the incidence drop dramatically in many countries. Salivary glands are sometimes affected by HIV infection, with an enlargement of the parotid glands giving a Sjögren's-like picture. Chronic sialadenitis is usually associated with duct obstruction. Pathology Acute sialadenitis shows an acute inflammatory reaction of the sal- ivary tissue, with a predominantly neutrophil infiltration, except in mumps, which shows an infiltration by mononuclear cells. In both chronic and recurrent sialadenitis there is a marked periductal and acinar infiltration by mononuclear cells, with some duct epithelial hyperplasia, accompanied by acinar atrophy and fibrosis. Clinical features The presenting symptom of acute sialadenitis is a painful swelling in one of the major salivary glands. Commonly the patient has a low-grade fever, oedema and erythema of the cheek, trismus, and a purulent discharge may be evident at the duct opening. In chronic sialadenitis there are usually clinical features of duct obstruction of the affected glands. With involvement of the sub- mandibular salivary gland, there is pain and swelling in the sub-mandibular or retromandibular region, with a reddened duct orifice discharging pus. Differential diagnosis There is little clinical difficulty in the differential diagnosis between acute sialadenitis of the parotid or submandibular gland due to as- cending infection and mumps in hitherto healthy young patients. Any discharging pus should be sampled for organisms with anti- biotic sensitivity determined. Empirical prescribing is warranted with a drug such as amoxicillin. In chronic sialadenitis, there is usually clinical or radiological evi- dence of a calculus and ultrasound scanning may show duct dilatation. Management In acute, chronic, or recurrent bacterial sialadenitis the appropriate antibiotics should be used to control the infection, but occasionally surgical drainage may also be necessary. Careful oral hygiene meas- ures are important in all types of sialadenitis. There is no special treatment for mumps, but rest and isolation for about a week are indicated. In chronic sialadenitis, the cause of obstruction, such as a calculus, should be removed. Course and prognosis Acute sialadenitis will resolve with the aid of antibiotics and gen- eral management of the patient. Mumps will resolve spontaneously and second attacks are very rare. Chronic sialadenitis may persist for many years and may lead to destruction of the gland, unless the cause of duct obstruction is removed early. Recurrent parotitis in childhood may show spontaneous recovery after puberty. Salivary gland neoplasms The salivary gland neoplasms are a complex and diverse group which can affect the major and the minor salivary glands. Most are slow growing and benign, but some are malignant and aggressive with manifestations such as lower motor neuron palsy of the facial nerve as it passes through the parotid gland. FURTHER READING Arduino PG, Porter SR (2008). Herpes simplex virus type 1 infec- tion: overview on relevant clinic-pathological features. J Oral Pathol Med, 37, 107–21. Armitage GC (2004). Periodontal diagnosis and classification of peri- odontal diseases. Periodontol 2000, 34, 9–21. Armitage GC, Cullinan MP (2010). Comparison of the clinical features of chronic and aggressive periodontitis. Periodontol 2000, 53, 12–27. Atout RN, Todescan S (2013). Managing patients with necrotizing ul- cerative

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