

Oral and maxillofacial manifestations of systemic and generalized disease

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‘As is our pathology, so is our practice.’

Sir William Osler, Canadian-born physician, 1859–1919

The numbers are overwhelming. There are more than 8000 different diseases, with new diseases, such as AIDS, having emerged only within the last quarter of a century. An impressive list of diseases manifest in the oral and maxillofacial complex as primary disorders, many of which are unique to this location. The acquisition of this specialized knowledge base in itself is a significant challenge for the dental practitioner. However, numerous diseases originating in organ systems remote from the mouth also manifest in the head and neck area – frequently with a bewildering array of signs and symptoms. The process of clinical differential diagnosis – the taking of seemingly unrelated facts, piecing them together like jigsaw puzzle cutouts, and making a potentially life-saving diagnosis of disease that is distant from the oral cavity – represents one of the most challenging and critically important aspects of modern clinical dentistry. Such knowledge and skills are deeply rooted in medicine and pathology, and the message rings as true today as it did at the turn of the 20th century: ‘As is our pathology, so is our practice.’ It is with these thoughts in mind that the authors present a necessarily concise introduction to the topic of oral and maxillofacial manifestations of systemic and generalized disease.

Pigmentations

Mucocutaneous discolorations are stigmata of a wide variety of unrelated disorders that are not primary to

the maxillofacial complex, including inherited and acquired syndromes; disorders of the hepato-biliary, hematopoietic and endocrine organ systems; metastatic neoplastic disease; chronic drug ingestion; and heavy metal intoxications. The discolored areas reflect the pathologic accumulation of colored substances collectively referred to as pigments, which may be of endogenous or exogenous origin. The most common of the endogenous pigments are melanin, hemosiderin, bilirubin and lipofuscin. Homogentisic acid (alkaptonuric ochronosis) and porphyrins (congenital erythropoietic porphyria) are examples of more rare endogenous pigments. Head and neck mucocutaneous discolorations of exogenous origin are usually associated with chronic ingestion of an ever-lengthening list of pharmacologic drugs and, rarely today in the United States, heavy metal toxicity from occupational exposure. In general, the hyperpigmented areas are themselves innocuous; however, proper classification and diagnosis is critical to the discovery of significant and potentially life-threatening underlying disease.

Melanin-associated hyperpigmentations

Melanin is a brownish-black pigment synthesized by melanocytes as an intracellular by-product in the metabolism of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) by the enzyme tyrosinase. Melanocytes are dendritic cells that migrate from the neural crest during embryogenesis to reside ultimately in epithelia of the skin and mucous membranes of the mouth, and other sites, including the choroid plexus and ciliary body of the eye. They produce melanin when exposed to ultraviolet sunlight and melanocyte-stimulating hormone

(melanotropic hormone) produced by cells of the anterior pituitary gland. Melanin pigment granules are sequestered within membrane-bound organelles called melanosomes that are eventually transferred to neighboring keratinocytes and, less commonly, to subepithelial connective tissue macrophages, via the long dendritic processes of the melanocytes. Melanin-associated hyperpigmentation is a pathologic clinical manifestation of several unrelated disorders. The mechanisms of hyperpigmentation include an increased rate of melanin synthesis, melanocyte hyperplasia and melanin accumulation within melanocytes due to faulty transfer mechanisms. Clinically, the areas of hyperpigmentation are flat or macular, and may be generalized or localized. Discrete lesions may be focal or multifocal and range in size from small, freckle-like areas to larger patches measuring from a few millimeters in size to 20 cm or more in diameter. Colors range from bluish-

gray to varying shades of brown to black, depending on the amount and depth of location of the melanin in the affected tissues.

Peutz-Jeghers syndrome (1) is a disease complex most frequently inherited as an autosomal dominant trait. The classic clinical presentation in the majority of affected individuals is a striking pattern of brown to bluish-black macular 'freckling' of the lip vermilions and perioral skin. Similar-appearing melanotic macules may affect the skin of the hands and feet and oral mucosa (Fig. 1A-D). The hyperpigmented areas appear in early childhood and resemble freckles, but unlike freckles are not sensitive to the effects of sunlight. This presentation is virtually pathognomonic for Peutz-Jeghers syndrome. Excepting aesthetic considerations, the pigmentations themselves are of minor clinical significance. However, they serve as a mucocutaneous marker of intestinal hamartomatous polyposis, which is



Fig. 1. (A-D) Hypermelanotic 'freckling' pattern of lip vermilions, perioral skin, oral mucous membranes and skin of the digits is characteristic of Peutz-Jeghers syndrome (courtesy of Dr Mario Ramos).

a far more serious stigma of this syndrome. The polyps may cause bowel obstruction through mass effect or intussusception, bowel infarction and peritonitis. The polyps themselves are not considered to be precancerous; however, these individuals require long-term monitoring for the possibility of intestinal adenocarcinoma for which they are at slightly increased risk later in life.

Addison disease, a syndrome of endocrine origin related to chronic insufficiency of adrenal cortical hormones, is characterized by diffuse hypermelanosis of the skin ('bronzing') and patchy hyperpigmented macules of the oral mucosa (2). Primary insufficiency is caused by diseases that destroy the adrenal cortex, for example autoimmune adrenalitis (immune-mediated destruction of the adrenal gland is the most common cause of Addison disease in the United States today), infections such as disseminated tuberculosis or histoplasmosis, and metastatic neoplasms to the adrenal gland, usually breast and lung cancers. Far more serious than the pigmentations are complications resulting from decreased circulating levels of adrenal cortical hormones, especially glucocorticoids (cortisol) and mineralocorticoids (aldosterone), and to a much lesser extent, androgenic hormones. Signs and symptoms include fatigue, weight loss, nausea and vomiting, orthostatic hypotension, hypoglycemia, hyperkalemia, hyponatremia and potentially fatal acute adrenal crisis. Long-term hormone replacement therapy consisting of hydrocortisone and fludrocortisone is indicated for patients with symptomatic adrenal insufficiency; replacement of adrenal androgens may produce some beneficial effects on the perceived sense of well-being of Addisonian patients (3).

Bronzing of the skin is also a feature of hemochromatosis, a disorder of iron metabolism that is discussed in greater detail below. Although iron can accumulate in the dermis in this condition, the hyperpigmentation appears not to be due to the iron deposits but to hypermelanosis of an unknown mechanism.

Café-au-lait spots (from the French 'coffee with milk') are well-circumscribed, light to dark brown cutaneous macules ranging in size from a few millimeters to over 20 cm in greatest diameter. They are more common on the skin of the trunk and extremities, but can occur on the facial skin as well. Café-au-lait spots are stigmata of several disorders, including Jaffe-Lichtenstein syndrome, McCune-Albright syndrome and neurofibromatosis.

McCune-Albright syndrome is a symptom complex characterized by polyostotic fibrous dysplasia, endocrine abnormalities and melanotic macules (4). In contrast to neurofibromatosis, the café-au-lait spots in this syndrome have more irregular contours and tend to have a unilateral distribution overlying the affected bones (Fig. 2A). Endocrine abnormalities may be multiple and include precocious puberty, pituitary adenoma, hyperthyroidism and hypercortisolism. Skeletal abnormalities associated with the bone lesions are frequently debilitating. Affected long bones are prone to painful pathologic fracture, which may result in discrepancies in leg length, and the jawbones may be dramatically enlarged with resultant cosmetic and functional deformity (Fig. 2B and C). Osseous recontouring of the affected jawbones should be considered with the caveat that surgical manipulation may have the unwanted effect of actually stimulating bone growth.

Neurofibromatosis type I, previously known by the eponymous name von Recklinghausen disease, is typified by a variety of abnormal pigmentations, including café-au-lait spots, axillary 'freckling' and brown-pigmented spots of the iris of the eye called Lisch nodules. This is the most common form of a group of related disorders referred to as the neurofibromatoses, affecting about 1 in every 3000 births. Neurofibromatosis type I, which accounts for more than 90% of all such cases, is transmitted as an autosomal dominant trait linked to a mutation in the NF-1 gene. This mutation is the likely pathogenetic mechanism underlying the development of benign neurogenic tumors called neurofibromas. The neurofibromas are multiple, ranging from a few to hundreds, and may develop in virtually any location. The skin is the most frequently involved site (Fig. 3), including the facial skin, and with disease progression there may be considerable cosmetic disfigurement. Involvement of the jaws and oral mucosa by neurofibromas has also been reported (5). Affected individuals require close clinical follow-up for the possibility of malignant degeneration of the neurofibromas, which reportedly occurs in 2–3%.

Drug-related hyperpigmentations

An ever-expanding list of pharmacologic agents is associated with diffuse or focal mucocutaneous pigmentations (Table 1). The discolorations themselves



Fig. 2. (A) Large, irregular, map-like café-au-lait macules correspond to underlying bone lesions in McCune-Albright syndrome (courtesy of Dr Mark Bernstein). (B and C) The same individual pictured in Fig. 2A demonstrates dramatic, lion-like facial deformity ('leontiasis ossea') from enlargement of the mandible and maxilla (courtesy of Dr Mark Bernstein).

are innocuous and usually fade over time following discontinuation of the drug, but they require recognition and distinction from syndrome-related pigmentations. Mechanisms of hyperpigmentation include hypermelanosis, deposition of colored insoluble drug complexes and accumulation of the endogenous pigment lipofuscin (lipochrome). Lipofuscin is an intracellular, membrane-bound, yellow-brown pigment that represents the undigested residues of lipid-protein membranes derived from repair processes associated with free radical cell injury or from processes associated with cellular atrophy. Drug-related discolorations usually affect mucosa (Fig. 4) and skin and occasionally other sites such as bone or teeth.

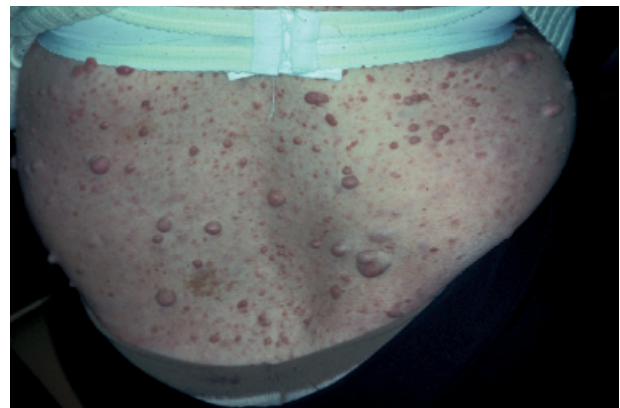


Fig. 3. Numerous neurofibromas and a few café-au-lait macules are present on the skin of the back of this individual with neurofibromatosis (courtesy of Dr Mark Bernstein).

Table 1. Drugs associated with mucocutaneous pigmentations

Antibiotics, e.g. minocycline
Antimalarials, e.g. chloroquine
Anti-AIDS drugs, e.g. zidovudine (azidothymidine, or AZT)
Cardiac drugs, e.g. amiodarone
Chemotherapeutic agents, e.g. cyclophosphamide
Laxatives, e.g. phenolphthalein
Tranquilizers, e.g. chlorpromazine
Oral contraceptives

Minocycline staining is an interesting example of drug-related pigmentation. Minocycline, an antibiotic and semisynthetic derivative of tetracycline, is commonly prescribed for a variety of inflammatory skin disorders such as rosacea and severe acne. Used with chronicity, some individuals develop grayish-blue discolorations of the facial skin, scleral conjunctiva and oral soft tissues. Colored drug complexes deposited within the bone of the palate or mandibular buccal shelf can be visualized through the overlying, somewhat translucent mucosa as areas of bluish-gray discoloration (6).

Additional pathologic complications associated with drug ingestion that may involve the head and neck include the following and are discussed in later sections: oral lichenoid eruptions, ulcerations and vesiculobullous lesions; abnormal bleeding states; and gingival enlargement.

Hemoglobin-derived pigmentations

Like melanin, hemosiderin and bilirubin are endogenous pigments that, when present in excess, can manifest as diffuse or focal areas of mucocutaneous discoloration. The nature of the pigmentations is best appreciated with some understanding of hemoglobin, the molecule from which these pigments are derived, and its metabolism. Hemoglobin is contained within red cells and uniquely serves as the oxygen transport mechanism within the blood. It is a conjugated protein having a tetrameric conformation consisting of four



Fig. 4. Grayish discoloration of the palatal mucosa appeared in an individual taking the antimalarial agent chloroquine (courtesy of Dr Mark Bernstein).

polypeptide chains (the globin moiety) that are conjugated to porphyrin molecules complexed with iron (the heme moiety). The average life span of normal circulating red cells is about 120 days. When senescent red cells are destroyed by cells of the mononuclear phagocyte system, the porphyrin rings are broken down to the non-iron-containing bile pigments biliverdin and unconjugated bilirubin. Bilirubin is then transported to the liver, where it is conjugated and becomes a component of bile. In states characterized by hyperbilirubinemia, the excess bilirubin accumulates in mucocutaneous sites, including skin, scleral conjunctiva and oral mucosa, imparting a yellowish discoloration termed jaundice. Jaundice from unconjugated hyperbilirubinemia occurs in, for example, viral or alcoholic hepatitis due to decreased hepatocyte uptake and in the hemolytic anemias when the rate of red cell destruction exceeds the processing ability of the hepatocytes (Fig. 5). Conjugated hyperbilirubinemia may be a



Fig. 5. Individual with hemolytic anemia presenting with a yellowish discoloration of the palate, characteristic of jaundice (courtesy of Dr Mark Bernstein).

consequence of bile duct obstruction due to stones or stricture, or obstruction from cancer of the liver or gall bladder. The iron molecules of catabolized hemoglobin from destroyed red cells are stored within cells of the mononuclear phagocyte system, to be mobilized for later reuse. Iron is rigidly conserved within the body and has only limited pathways of excretion through shedding of skin and mucosal epithelia. In disease states where iron stores become excessive, the iron molecules complex to protein and are visualized as intracellular yellow-brown pigment granules called hemosiderin. Pathologic accumulation of hemosiderin, termed hemosiderosis, may be localized or generalized. Petechiae, ecchymoses and hematomas, collectively referred to as purpura, are common examples of localized hemosiderosis due to bleeding into interstitial tissues. Several diseases that are discussed in greater detail below are characterized by an abnormal bleeding state and manifest clinically as oral purpura. Severe generalized iron overload, called hemochromatosis, can contribute to a diffuse bronzing of the skin. Hemochromatosis is a complication of disorders requiring long-term transfusion therapy such as for thalassemia, sickle cell anemia or aggressive chemotherapy for the treatment of cancer (7). Disorders of hemochromatosis are clinically significant because the excess iron accumulates outside the mononuclear phagocyte system within viscera such as the heart and liver, ultimately contributing to organ dysfunction.

Disorders of vascular fragility

Increased vascular fragility is a relatively common cause of abnormal small vessel bleeding and, with some

exceptions, is usually not serious. Skin and mucous membranes are frequently affected. In contrast to disorders of platelets and coagulation factors (discussed below), screening tests of hemostasis are within normal limits. The usual underlying causes are vascular injury from infection, immune-mediated mechanisms (e.g. drug-related immune complex type III hypersensitivity reactions) or nutritional deficiency (e.g. scurvy).

Hereditary hemorrhagic telangiectasia, also known by the eponymous name Osler–Weber–Rendu disease, is an inherited disorder of increased vascular fragility (8). Transmitted as an autosomal dominant trait, this bleeding disorder is characterized by developmental abnormalities of vascular structures, especially post-capillary venules located in the superficial-most areas of the skin and mucous membranes of the nose and alimentary tract. The affected vessels lack elasticity, become markedly dilated and tortuous ('telangiectasias'), and because of their superficial location are subject to rupture and external hemorrhage. Epistaxis and spontaneous bleeding from the gastrointestinal tract may be so severe as to require multiple blood transfusions. Clinically, the telangiectasias manifest as multiple, small, well-circumscribed, red papules that blanch with digital pressure.

Platelet disorders

Platelets are a critical component of vascular 'plugs' that form during hemostasis to limit blood loss secondary to vascular damage. Consequently, disorders accompanied by insufficiencies of platelet number or platelet dysfunction may contribute to pathologic bleeding states. They are characterized clinically by the development of mucocutaneous purpura (Fig. 6A and B), gingival bleeding and/or epistaxis.

Thrombocytopenia designates a reduction below normal (a normal platelet count is 150,000–400,000 platelets/mm³) of functional, circulating platelets. Clinical manifestations of disease usually require significant depletions of platelets below 30,000–40,000 platelets/mm³. Thrombocytopenia from decreased platelet production is indicative of bone marrow failure due to, for example, infection, radiation, drug toxicity or widespread involvement of the bone marrow by malignant neoplasia. Ineffective megakaryopoiesis, as occurs in the megaloblastic anemias (vitamin B₁₂ deficiency anemia and folate deficiency anemia), is also associated with insufficient

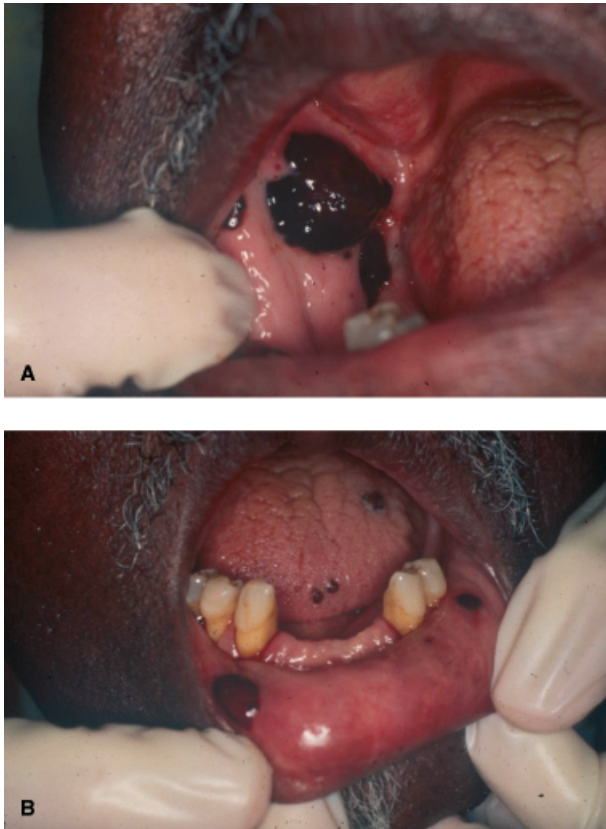


Fig. 6. (A and B) A state of thrombocytopenia was diagnosed in this individual who presented to a dental clinic with numerous oral mucosal hematomas.

platelet production (see below for additional discussion of oral manifestations of anemia). Insufficiencies of platelets may also be due to accelerated platelet destruction. This is the mechanism of thrombocytopenia in the autoimmune disorder immune thrombocytopenic purpura (9). In this disease, which affects 100 per 1 million persons each year, antiplatelet IgG autoantibodies are generated. The antibodies attach to, or opsonize, the surfaces of the platelets, thus facilitating their phagocytosis and destruction by cells of the mononuclear phagocyte system. Both children and adults, mostly adult females, are affected. Finally, in addition to bone marrow failure and accelerated platelet destruction, thrombocytopenia may be secondary to splenic sequestration of platelets in disorders characterized by hypersplenism (e.g. hereditary spherocytosis and chronic myeloid leukemia) and to dilutional effects from blood transfusions. Laboratory tests of thrombocytopenic disorders will reveal a low platelet count, prolonged bleeding time and normal tests of coagulation. Medical evaluation, diagnosis and

treatment of the specific underlying disease contributing to the platelet deficiency are necessary for a patient diagnosed with thrombocytopenia of unknown origin.

An additional category of abnormal bleeding states is characterized by dysfunction of normal numbers of circulating platelets. One of the most important causes in this category is drug toxicity, for example, chronic aspirin ingestion. Aspirin interferes with the enzyme cyclooxygenase, which normally catalyzes the conversion of arachidonic acid to a group of prostaglandins important in platelet aggregation. Tests of hemostasis in these situations will reveal an abnormal bleeding time, normal platelet count and normal tests of coagulation.

Coagulation disorders

Lastly, inherited or acquired disorders of coagulation may underlie a bleeding tendency. These disorders are important to distinguish from those previously discussed because bleeding is not typically manifest as purpura, but as potentially uncontrollable hemorrhage. Acquired disorders are the most common causes of bleeding in this category and include deficiency of vitamin K, which is essential for the synthesis of clotting factors II, VII, IX and X, and diseases of the liver, an important site for the synthesis of several of the clotting factors. Inherited disorders of coagulation are rare and include classic hemophilia (factor VIII deficiency) and von Willebrand disease (10).

Soft tissue and osseous enlargements

Soft tissue or osseous enlargements involving the maxillofacial complex are physical manifestations of several diseases, including those of the endocrine and hematopoietic systems, disorders of immune dysregulation and disseminated cancer. In general, the head and neck manifestations represent the local or regional expression of more widespread and generalized involvement of the skeletal system, subcutaneous soft tissues and viscera that are characteristic of these disorders.

Growth hormone is secreted by cells called somatotrophs that reside in the anterior pituitary gland. During normal growth and development growth hormone has generalized effects on most cells to increase metabolic rates. It also exerts a positive effect on liver cells to release somatomedins, a group of peptides that increase the proliferation of cartilage and

assist in the growth of long bones. Excesses of circulating growth hormone developing after closure of the epiphyseal growth plates in young adulthood when maximum height has been achieved results in the endocrine syndrome called acromegaly (11). A secretory somatotroph adenoma of the pituitary gland is the usual source of the excess growth hormone. Individuals with acromegaly exhibit disproportionate enlargement and thickening of osseous tissues, soft tissues, and viscera such as the heart (cardiomegaly) and thyroid gland (goiter). Impingement of the pituitary tumor on the optic nerves or optic chiasm may result in visual problems. Signs and symptoms of an enlarging intracranial mass include headache, nausea and vomiting. Maxillofacial enlargement is conspicuous, manifesting as an enlarged skull with prominent brow and nose, prognathism, coarsening of the facial features and macroglossia. Most individuals are treated by transphenoidal surgery for removal of the pituitary tumor. Alternative non-surgical therapeutic modalities include radiotherapy, and drugs that lower the serum concentrations of growth hormone including dopamine antagonists, somatostatin analogs and growth hormone receptor antagonists (12).

Thyroxine (T_4) and triiodothyronine (T_3) are the principal circulating forms of thyroid hormone secreted by follicular epithelial cells of the thyroid gland. Thyroid hormone has widespread stimulatory effects on cells and tissues, including increasing cellular metabolism and growth rates, facilitating mental processes, increasing endocrine gland activity, stimulating carbohydrate and fat metabolism, increasing heart rate and respiration, and enhancing muscle action. In adults, chronic hypothyroidism is called myxedema (13). This term reflects the tendency in this disease for the accumulation of mucopolysaccharides in soft tissue and viscera, causing thickening and enlargement. In the head and neck, the most prominent manifestations of myxedema are macroglossia and facial edema, especially the periorbital areas, due to the deposition of mucopolysaccharides in these sites. In addition, hypothyroid individuals will manifest signs and symptoms associated with a state of hypometabolism, including fatigue, listlessness, slowing of speech and mental functions, slowing of motor functions, cold intolerance and constipation. In iodine-sufficient areas such as the United States, the most common cause of myxedema is Hashimoto thyroiditis, an inflammatory autoimmune disorder characterized by the destruction of thyroid

parenchyma. Individuals with Hashimoto thyroiditis show a high incidence of other autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and Sjögren syndrome, and, importantly, are at increased risk for the development of B-cell lymphoma. Hormone replacement therapy (thyroxine) is the treatment of choice for hypothyroidism, usually resulting in successful abatement of symptoms.

Graves' disease (14) is an autoimmune disorder characterized by hyperthyroidism. Pathogenesis of disease is attributed to the production of several classes of autoantibodies directed against the receptors for thyroid stimulating hormone (thyrotropin, produced by cells of the anterior pituitary gland) that are present on the follicular epithelial cells. The binding interactions result in follicular epithelial cell hyperplasia and excessive production of thyroid hormone. Affected individuals exhibit a panoply of signs and symptoms related to a state of hypermetabolism and overstimulation of the sympathetic nervous system, including nervousness, emotional lability, heat intolerance accompanied by a warm and moist skin, weight loss in spite of a good appetite, tremor and cardiac manifestations (arrhythmias, tachycardia, palpitations). Exophthalmos is a striking stigma of Graves' disease, but not of hyperthyroidism due to other causes. Exophthalmos is characterized by proptosis of the globe of the eye secondary to weakening of the extraocular eye muscles from lymphocytic infiltrates and deposition of the mucopolysaccharide matrix into the muscle tissue that occurs in this disorder. Proptosis may be so severe as to prevent complete closure of the eyelids predisposing to dry eyes, keratoconjunctivitis and corneal ulcerations. In addition to the eye changes, Graves' patients manifest bilateral and symmetrical enlargement of the thyroid gland (goiter) due to the follicular epithelial cell hyperplasia. There is no single ideal treatment that restores thyroid function and resolves the ophthalmopathy. Current therapeutic modalities for Graves' hyperthyroidism include iodine radiotherapy (the most common treatment used in the United States), surgery and antithyroid drugs such as carbimazole (14).

Cortisol is the principal glucocorticoid secreted by cells of the zona fasciculata of the adrenal cortex. Cortisol is important in regulating the metabolism of proteins, carbohydrates and fats. Chronic hypercortisolism underlies a symptom complex referred to as Cushing syndrome (15). The most common cause of Cushing syndrome is the prolonged iatrogenic

administration of exogenous corticosteroids to induce a state of immunosuppression, for example, following organ transplantation or for the treatment of chronic inflammatory disorders such as pemphigus. Obesity is a common clinical presentation secondary to an increase in lipolysis. There is a centripetal redistribution of fat without change in total body fat as the lipid is mobilized from steroid-sensitive tissues and redistributed elsewhere such as the abdomen ('truncal obesity'), facial cheeks ('moon face') and upper back ('buffalo hump'). Hypertension, osteoporosis, diabetes and poor wound healing are more medically significant complications associated with Cushing syndrome.

Thalassemia (16), which was discussed above in relationship to hemochromatosis, is a hemolytic anemia characterized by abnormal development of the skeletal system during childhood, leading to skeletal deformities. Abnormalities of the skull and jawbones are prominent. This is an inherited disorder in which a mutation in either of the genes encoding for the α -globin or β -globin chains of hemoglobin results in insufficient globin chain production, and thus insufficient hemoglobin and anemia. The severity of anemia is variable, depending on the number of gene alleles affected and the exact nature of the mutation. β -thalassemia major is the most devastating and severe form of the disease. In addition to the mechanism of anemia just described, β -thalassemia major is characterized by accelerated destruction of circulating, abnormal red cells by splenic macrophages and premature destruction of abnormal red cells in the bone marrow (a process referred to as ineffective erythropoiesis), both of which worsen the anemia. The marrow undergoes massive hyperplasia and expansion in a futile attempt to compensate for the anemia, with resultant skeletal abnormalities and failure of growth and development. In the craniofacial complex, an overlarge head and prognathism (the so-called 'rodent facies') are typical of affected individuals. Treatments for thalassemia are based on the severity of the anemia and include regular blood transfusions, iron-chelating therapy and bone marrow transplantation (16).

Amyloid is a pathologic, extracellular, fibrillar protein in which the aggregated protein fibrils are uniquely arranged in a β -pleated sheet pattern. In hematoxylin and eosin-stained tissue sections, amyloid appears as homogeneous, hyaline deposits that cannot be distinguished with certainty from similar-appearing proteins

such as dense, acellular collagen or compacted fibrin. Definitive diagnosis of amyloid requires the application of Congo red histochemical staining to paraffin-embedded tissue sections in conjunction with polarization microscopy yielding a characteristic apple-green fluorescence called positive birefringence (17). There are several biochemically distinct forms of amyloid that cannot be distinguished from one another on the basis of staining or birefringence characteristics, which are similar. Amyloid accumulates by different pathogenetic mechanisms in a variety of unrelated disorders. The most common of these is multiple myeloma, the most frequently occurring type of malignant plasma cell dyscrasia. In this setting, the amyloid represents immunoglobulin light chains secreted by the neoplastic clones of B cells and is designated AL amyloid for 'amyloid light chain'. Intraorally, amyloid may manifest as focal or multiple, nodular soft tissue enlargements and is one of several causes of macroglossia (18) (Fig. 7). Amyloidosis can also manifest as cervical lymphadenopathy. Skin lesions appear as waxy, pale papules frequently found in the medial canthus area.

Granulomatous inflammation is a distinctive form of chronic inflammation that microscopically identifies a limited, but important, group of disorders that may manifest as soft tissue enlargements in the head and neck (see also the discussions of Crohn's disease and tuberculosis below). Granulomas are localized collections of activated macrophages that develop as a protective host response to a variety of injurious agents, including certain bacteria (tuberculosis is the prototypical granulomatous disease), fungi, parasites,



Fig. 7. Amyloidosis in an individual with multiple myeloma manifested as multinodular macroglossia (courtesy of Dr John McMenamin).

inorganic materials or dusts, and foreign bodies such as retained suture material. These etiologic agents, unlike those that incite acute inflammatory responses, are extremely difficult for the body to kill or eliminate and, with some exceptions, are antigenic. Immune-mediated granuloma development requires a delayed type IV hypersensitivity reaction involving the secretion of interferon- γ by a population of T cells previously sensitized to the provoking antigen. Interferon- γ is the most potent mediator of delayed type IV hypersensitivity. Macrophages activated by interferon- γ are altered both morphologically and functionally. They become larger and more cytoplasmic, have greater numbers of organelles and exhibit greater activity of the plasma membrane. Functionally, they are more highly synthetic, secretory and phagocytic. All these cellular alterations augment killing and elimination of the offending agent but also serve to enhance and prolong tissue destruction and repair by fibrosis, which are hallmarks of the granulomatous diseases.

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. In the United States, black individuals are affected more frequently than white individuals and the disease typically manifests in young adults younger than 40 years of age. Many organs and tissues may be affected, especially the lungs (the majority of patients come to clinical attention because of respiratory complaints or an abnormal chest X-ray), skin, lymph nodes and salivary glands (19). A submucosal mass is the usual oral presentation and may involve any site. Jaw involvement shows areas of bone destruction, usually without expansion. Individuals may complain of xerostomia, which is secondary to marked salivary gland involvement. Skin lesions may present as discolored violaceous macules, plaques and nodules and are common on the facial skin, nose and lips (Fig. 8). The mainstay of treatment for sarcoidosis is corticosteroids.

Generalized gingival enlargement is a recognized complication of several drugs, including calcium channel blockers (e.g. nifedipine), anticonvulsants (phenytoin) and cyclosporine (20). The enlargement is due to increased amounts of collagenous fibrous connective tissue from drug-related stimulatory effects on gingival fibroblasts. Overgrowth typically begins in the interdental areas to involve progressively the entirety of the gingiva. The degree of overgrowth may be related to the level of oral hygiene. Secondary inflammation produces edematous and red gingiva in



Fig. 8. Numerous violaceous plaques and nodules are present on the facial skin in this individual diagnosed with sarcoidosis (courtesy of Dr Mark Bernstein).



Fig. 9. Gingival hyperplasia is a known complication of cyclosporine immunosuppressive therapy following organ (in this example, liver) transplantation.

contrast to firm and pink, uninflamed gingiva (Fig. 9). Cessation of growth, perhaps accompanied by some degree of resolution of the involved tissues, can be expected following discontinuation of the associated drug. Removal of remaining excess gingiva can be achieved by a number of techniques, including electrocautery, cold steel and soft tissue laser. Choosing another appropriate drug may also be useful; however, if this is not an option then meticulous home care, frequent cleanings and evaluation by a dental professional are mandatory.

Finally, metastases to the oral cavity, although uncommon, may manifest as an abnormal soft tissue enlargement (21). Their clinical presentation may mimic benign neoplastic, hyperplastic or inflammatory processes, thus necessitating the need for biopsy and subsequent pathologic examination. The most

common solid primary cancers that may disseminate to oral soft tissues are lymphoma, melanoma, and breast, kidney and lung cancers. The most common secondary locations are the gingiva, palatal mucosa and tongue (Fig. 10). Leukemia, often regarded as a liquid cancer, may also present clinically as a localized tumor mass in any site. Gingival enlargement is most characteristic of monocytic leukemias (Fig. 11). Additional oral manifestations of leukemias and cancers widely metastatic to the skeletal system include purpura from underlying thrombocytopenia, ulcerations secondary to neutropenia and predisposition to infections such as candidiasis and herpes simplex secondary to immunocompromise. Obviously, following definitive histopathologic

diagnosis, medical referral for evaluation and treatment for the specific cancer is required.

Red, white and ulcerative lesions

This category accounts for the majority of the mucosal lesions that arise in the oral cavity. Their appearance is a reflection of the underlying pathological processes occurring in the delicate tissues present in this region of the body. Oral mucosa is composed mainly of a non-keratinizing stratified squamous epithelium with a very vascular supportive connective tissue, both of which combine to give the oral cavity its red to pink color. The mucosa of the attached gingiva and hard palate is somewhat different, with a mildly keratinized epithelium and denser connective tissue tightly adherent to the periosteum of the subjacent bone (mucoperiosteum). Many red lesions of the oral mucosa are a consequence of the dilation and simultaneous engorgement of the connective tissue vasculature that occurs during inflammation. White mucosal lesions are usually caused by an excessive surface accumulation of keratin or, less often, by necrotic tissue debris admixed with microorganisms and/or fibrin. An ulcer is simply defined as a pathologic discontinuity of the surface epithelium, which could be due to trauma, infection, immune-mediated reactions or neoplasia. They are typified by a round to irregular defect that may be raised, depressed or flush with the surrounding mucosa, depending on the nature of the contributing pathologic mechanism. The adjacent tissue is almost always red and inflamed. Damage to the superficial vasculature results in serum leakage and subsequent fibrin elaboration, imparting a yellow to white surface color. The following discussion concerns systemic diseases that can produce oral lesions that are red, white, ulcerated or a combination of these features.

Wegener's granulomatosis is an idiopathic, although probably immune-mediated, disease often involving the upper and lower respiratory tracts and kidneys, although it may potentially involve virtually any region of the body. The clinical manifestations of the disease are a consequence of a necrotizing granulomatous vasculitis of the small to medium-sized arteries and veins. The resulting vascular destruction results in ischemic degradation of the tissues supplied by the affected vessels. Much of the disease targets the ears, nose, throat, paranasal sinuses and lungs. Head and



Fig. 10. Bluish, semitranslucent gingival swelling representing oral soft tissue metastasis in a patient with a known history of primary lung adenocarcinoma (courtesy of Dr Edward Marcus).



Fig. 11. A patient with chronic myeloid leukemia presented with marked gingival enlargement (leukemic gingivitis) (courtesy of Dr Mark Bernstein).



Fig. 12. Striking example of 'strawberry gingiva' in an individual with Wegener's granulomatosis (courtesy of Dr Mark Bernstein).

neck manifestations are many, but consist partially of nasal and sinus congestion, skin rash and epistaxis (22). Additionally, necrotizing glomerulonephritis may compromise kidney function through chronic destruction of the renal filtering apparatus. A striking feature of the disease is the development of strawberry gingivitis, a deeply red, irregular, granular and occasionally ulcerated gingival hyperplasia (23) (Fig. 12). There are numerous additional oral complications that include, in part, alveolar bone destruction with loss of tooth support, palatal perforations due to severe necrosis of the nasal cavity floor, and non-specific ulcerations. The disease is diagnosed histologically in conjunction with laboratory detection of serum anti-neutrophil cytoplasm antibodies (c-ANCA). Untreated, Wegener's granulomatosis is rapidly fatal, with most individuals expiring within 1 year due to organ compromise. However, early diagnosis and prompt treatment, usually with corticosteroids and cyclophosphamide, often result in prolonged remission or cure.

Inflammatory bowel disease

There are two types of idiopathic inflammatory bowel disease that are associated with oral lesions: Crohn's disease and ulcerative colitis (24).

Crohn's disease is a chronic condition that can affect any portion of the alimentary tract and may undergo varying periods of remission. The disease, however, most frequently affects the small and large intestines, originating within the bowel wall as localized, granulomatous inflammation that leads to aphthous-like or

linear ulcerations of the intestinal mucosa, which increase in size and leave intervening zones of unaffected mucosa. These 'skip lesions' are characteristic of the disease. Symptomatic individuals complain of abrupt, severe abdominal pain, sometimes mimicking appendicitis, and diarrhea. Malabsorption syndromes may occur due to the progressive destruction of large segments of intestinal epithelium. Oral involvement in Crohn's disease often arises independent of bowel symptoms and consists largely of aphthous-like ulcers or ulcerated nodules, cheilitis and a cobblestone appearance to the mucosa (25) (Fig. 13). Also, superficial punctate and serpiginous ulcerations, a condition known as pyostomatitis vegetans, may be noted. Significant complications are associated with Crohn's disease. Ulcerations may penetrate through the bowel wall to form peritoneal or perianal fistulas, or peritoneal abscesses. Bowel strictures may develop in response to fibrosis secondary to healing. Of concern is the increased risk for gastrointestinal carcinoma in individuals with Crohn's disease. The treatment of Crohn's disease is multifactorial and often includes multiple medications, such as sulfa drugs, corticosteroids and immunosuppressives. Surgery may be required to correct severe intestinal complications. The biologic behavior of the oral lesions is somewhat unpredictable, with some regressing after resolution of bowel symptoms and others necessitating a separate course of treatment.

In contrast to Crohn's disease, ulcerative colitis is restricted to the colon and is not characterized by



Fig. 13. Patient with a history of Crohn's disease presenting with recurrent ulcerated nodules of the oral mucosa, including the dorsum of the tongue (courtesy of Dr Paul Barabas).

granulomatous inflammation. The disease initially arises in the distal large intestine, with regional inflammation and abscess formation within the colonic crypts of Leiberkühn. As the condition evolves, progressive mucosal destruction contributes to a retrograde advancement to involve larger segments of the bowel. The ulceration of the bowel epithelium exposes the mural vasculature, allowing blood to seep into the intestinal lumen. Additionally, the absence of large portions of the mucosa creates a disturbance in water absorption – a significant function of the colon. The result is that patients experience intermittent bouts of bloody mucoid diarrhea with severe abdominal pain that can persist for days to months. The intervening asymptomatic periods may last for years. Ulcerative colitis is, like Crohn's disease, associated with intra- and extraintestinal complications, including bowel strictures, perianal abscesses and oral pyostomatitis vegetans (Fig. 14). In extreme cases, the bowel ulcerations erode deeply enough into the supporting wall to destroy the portions of the neural plexus that control peristalsis, resulting in cessation of movement, gangrene, and possible perforation and death. The majority of individuals, however, have relatively mild disease, although approximately one-third will have symptoms severe enough to undergo colectomy. Pharmacologic treatment of ulcerative colitis is structured according to the severity and anatomic extent of the disease, and incorporates 5-aminosalicylic acid formulations, corticosteroids and immunosuppressives (24). Over

the long term, there is an increased chance of developing colon carcinoma.

Vesiculobullous diseases

The etiology of vesicle formation in the oral cavity is complex and encompasses a wide range of conditions, such as viral infection, immune-mediated reactions and trauma. This discussion concerns the mucocutaneous autoimmune vesiculobullous diseases, a group of conditions that often initially manifest within the mouth and may have significant oral and extraoral complications (26). Generally, these diseases afflict individuals in the sixth to seventh decades of life, although people of any age may be affected. There tends to be a female gender predilection. Vesiculobullous lesions can potentially involve any oral site and cases with substantial gingival involvement have been described as 'desquamative gingivitis'. The non-specificity of this term is due to the common clinical picture that characterizes this set of diseases. In addition to sharing clinical features, many of these diseases share histologic features as well. This may necessitate adjunct diagnostic procedures in order to establish a specific diagnosis. The most commonly utilized laboratory procedure for this purpose is direct immunofluorescence (DIF) testing (26). DIF requires the tissue adjacent to the vesicle or ulcer (perilesional tissue) to be sampled and placed into a transport medium, known as Michel's solution, rather than in formalin. Sections of the patient's biopsy are then incubated with a series of fluorescein-labelled antihuman antibodies that will bind to specific pathologic immunoglobulins within the tissue. The resulting complex when viewed under a fluorescent microscope will emit a pattern corresponding to the site of antibody deposition, thereby enhancing the ability to make a diagnosis of a specific disease. A chairside method by which the clinician induces a vesicle on seemingly uninvolved mucosa by applying a firm lateral or rotational pressure, known as the Nikolsky test, can help narrow a clinical differential diagnosis down to the autoimmune vesiculobullous diseases. In addition, it must be stressed that the following diseases may also be induced by a number of pharmacologic agents, including penicillin.

Pemphigus vulgaris is a chronic disease resulting from autoantibodies directed against constituents of the intercellular bridges that hold neighboring epithelial cells together (27). The consequence of this attack is



Fig. 14. Patient with non-specific 'gastrointestinal symptoms' presented to the dentist with yellowish-white pustules of the gingiva and vestibular mucosa characteristic of pyostomatitis vegetans. Medical referral and evaluation following biopsy revealed inflammatory bowel disease (courtesy of Dr Mark Bernstein).

degradation of the desmosomal complex followed by loss of epithelial cell adherence and the development of delicate fluid-filled vesicles and/or bullae that readily burst. Cutaneous lesions are multiple and consist of flaccid blisters that may exhibit a lateral expansion when compressed. Oral lesions precede skin lesions in up to 60% of cases. In the oral cavity, the buccal mucosa, gingiva, tongue and soft palate are most commonly involved with multiple, painful ulcers of varying size and shape. Involved gingiva frequently manifests as a desquamative gingivitis (Fig. 15). A positive Nikolsky sign is characteristic of the disease. DIF shows an intercellular distribution of immunoreactants, reflecting the desmosomal site of immune system activity. Pemphigus is treated with systemic corticosteroids and sometimes with additional immunosuppressants to partially alleviate the side effects of corticosteroid therapy. Prior to the development of effective therapy, this disease was usually fatal, since individuals with extensive desquamation were predisposed to infection and dehydration. With modern therapeutics, the prognosis has significantly improved, with the fatality rate declining to approximately 10%, due in large part to the side effects of steroids.

Paraneoplastic pemphigus is a rare condition that occurs in conjunction with an existing malignancy, usually a lymphoma or leukemia, or much more rarely with a benign lymphoid lesion (28). The exact pathogenesis of the disease has yet to be elucidated, but it is thought to result from the reaction of patient antitumor antibodies with components of the epithelial attachment complexes. The clinical manifestations of

paraneoplastic pemphigus are variable and often resemble other vesiculobullous diseases such as lichen planus, erythema multiforme or pemphigus vulgaris. These manifestations include ocular, oropharyngeal and labial mucosal ulcerations, and targetoid, lichenoid and bullous cutaneous lesions (28). The affected individuals are treated with palliative systemic corticosteroids and/or immunosuppressive medications, but usually succumb to the underlying malignancy (27).

Mucous membrane (cicatricial) pemphigoid differs from pemphigus vulgaris in that the targets of autoimmune attack are components of the attachment complexes that anchor the epithelium to the basement membrane, resulting in the development of subepithelial vesicles (29). As the name implies, lesions arise primarily on the mucosa, affecting oral, ocular, anogenital, esophageal and respiratory sites, with the skin involved to a lesser degree. Over the course of the disease, multiple vesicles form and ulcerate, eventually healing with scarring (except within the oral cavity). This leads to the particularly debilitating complications of mucous membrane pemphigoid, such as strictures in hollow anatomic structures, and fusion of the eyelids to each other and/or to the globe, predisposing patients to ocular infection and eventual blindness. A positive Nikolsky sign is typical. DIF testing will show antibody deposition along the basement membrane zone corresponding to the involved hemidesmosomes. The treatment of mucous membrane pemphigoid is dependent on the anatomic extent and severity of the lesions. If the oral cavity is the sole area of involvement, treatment is comprised of oral hygiene instruction and advocacy of a soft diet, which minimizes inflammation and trauma to the tissues, and topical corticosteroids. Systemic corticosteroids and immunosuppressants are incorporated into the treatment plan if extraoral sites are involved. Because of the potentially severe ocular sequelae, referral to an ophthalmologist is essential if this disease is suspected.

Lichen planus is an immune-mediated mucocutaneous disease of unknown etiology that often exhibits ulcer formation. The oral mucosa is commonly involved, but lesions may also arise on the skin, usually the flexor surfaces of the extremities, as well as on the anogenital mucosae. There are several subtypes of oral lichen planus, but the two most frequently encountered are the reticular and erosive forms (30). Reticular lichen planus is characterized by red mucosal patches with an overlying white, lace-like hyperkeratosis ('Wickham's



Fig. 15. Biopsy of this individual presenting with desquamative gingivitis revealed pemphigus vulgaris (courtesy of Dr Surendra Singh).

striae'). Lesions tend to be asymptomatic and bilateral, often presenting on the posterior buccal and labial mucosae. Such lesions can eventually ulcerate, a symptomatic subtype that is designated as erosive lichen planus (Fig. 16A and B). Cutaneous lesions manifest as deep, red to purple papules with faint overlying striae. Lichen planus tends to be a chronic, relapsing condition, necessitating long-term follow-up. The treatment of oral lichen planus is dependent on the severity of the lesions. Asymptomatic reticular lesions require only periodic evaluation, once or twice per year. Symptomatic reticular or erosive lesions can be treated with topical or systemic corticosteroids, and patients should be evaluated three to four times per year. There is some dispute regarding the potential for oral lichen planus to undergo transformation to squamous cell carcinoma. Such events have been documented (31) but are rare, and may actually represent a separate malignant event occurring in a site coincidentally involving lichen planus.

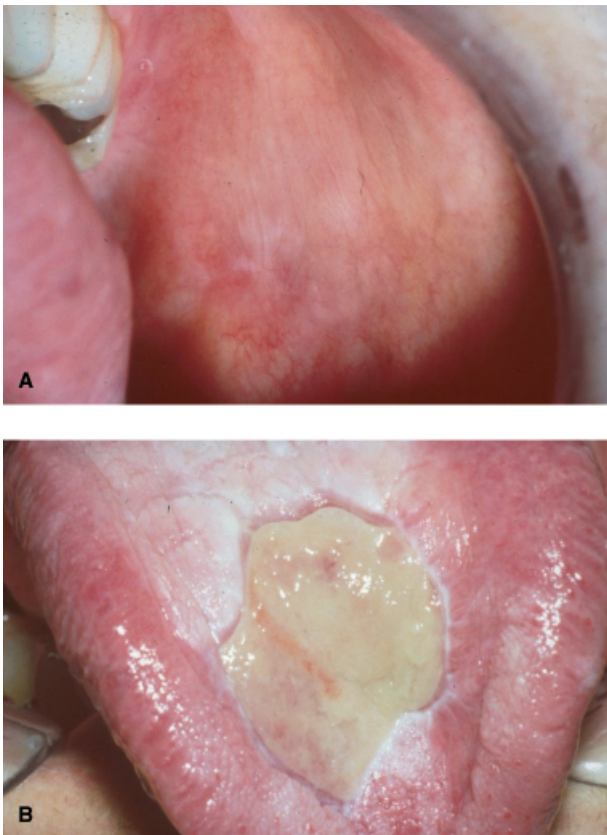


Fig. 16. (A and B) Biopsy of these painful, multifocal, persistent and recurrent red, white and ulcerated lesions of the buccal mucosa and tongue dorsum revealed lichen planus (courtesy of Dr. Mitchell Stern).

Lupus erythematosus is an autoimmune disease that shows a wide range of clinical presentation, anatomic involvement and severity due to the production of autoantibodies to a variety of tissue antigens (32). SLE is the most severe expression of the disease and frequently affects the head and neck. Individuals with SLE are most often initially diagnosed in the third decade of life and there is an overwhelmingly female predilection. The onset of disease is heralded by vague constitutional complaints, skin eruptions, photosensitivity and arthritis, with the condition then evolving to affect multiple organ systems. Up to 50% of patients have renal involvement from glomerular immune complex deposition, contributing to eventual kidney failure and accounting for the most frequent cause of death in these individuals. The cutaneous manifestations of SLE consist of the often striking butterfly rash of the malar processes and bridge of the nose, and discoid lesions. As many as 25% of patients with SLE show oral involvement, commonly on the palate, buccal mucosa and gingiva. Oral manifestations include non-specific ulcerations, cheilitis and lichenoid lesions. A milder subtype of lupus, chronic cutaneous (discoid) lupus erythematosus (CCLE) occurs in the absence of systemic involvement, usually in middle age. The skin manifestations of CCLE are characterized by discoid lesions that are roughly circular or ovoid, erythematous, scaly plaques. As the discoid lesion expands radially, it leaves behind central zones of atrophy, scarring, alopecia and hypopigmentation. Within the oral cavity, CCLE presents as an erythematous, sometimes ulcerated, lesion surrounded by white peripherally radiating striae, a clinical picture similar to erosive lichen planus. The appropriate treatment for SLE is dictated by the extent and severity of the disease. Combinations of corticosteroid, immunosuppressive, antimalarial and non-steroidal anti-inflammatory drugs are often used. The treatment for CCLE reflects the milder course of the disease and is usually comprised of systemic and topical corticosteroids, occasionally supplemented with antimalarials.

Drug-related oral diseases

As previously mentioned, pemphigus and pemphigoid may be associated with certain pharmacologic agents. However, other diseases of varying severity can be associated with drug intake. Additionally, drugs may be associated with oral pigmentations and

soft tissue enlargements, which were considered in earlier sections.

Many drugs, as well as certain dental materials such as composite resins and amalgam, can induce lichen planus-like lesions (30). In general, lichenoid mucositis displays many of the clinical and histologic characteristics of lichen planus, but differs from true lichen planus in minor ways. A significant point of departure is anatomic involvement. Whereas lichen planus almost always displays a bilateral distribution of oral lesions, lichenoid mucositis tends to be unifocal, although the lesions themselves are clinically indistinguishable from those of true lichen planus (Fig. 17). Lichenoid lesions associated with dental materials represent a type of contact hypersensitivity and will often be found on mucosal surfaces that touch the offending materials when at rest. Resolution of the condition necessitates the identification and removal of the causative agent.

The etiology of the immune-mediated disease erythema multiforme is unknown, but approximately half of the cases can be associated with recent infection, usually with a bacteria or virus, or drug intake. Erythema multiforme commonly occurs in males, usually arising in the third to fourth decades of life. Approximately 1 week prior to onset, individuals



Fig. 17. Individual taking the drug tamoxifen for breast cancer and subsequently developing this desquamated and erythematous area of the maxillary vestibular mucosa and gingiva. Biopsy revealed histopathologic features characteristic of lichenoid mucositis (courtesy of Dr Paul Barabas).

experience a series of non-specific symptoms, such as fatigue, fever, headache and sore throat, followed abruptly by the development of mucocutaneous lesions (33). The skin lesions are polymorphous, often initially forming on the extremities. Some start out as erythematous macules with subsequent vesiculation, while others manifest as the classic target lesion of the disease. Oral involvement is generalized, consisting of transient red patches that erode to form irregular and painful oral ulcerations. Lesions involving the vermilion of the lips will show dramatic crusting. Erythema multiforme is self-limiting, usually resolving within 2–6 weeks, although recurrences are possible. Two variants of erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis, show more extensive anatomic involvement. The former is characterized by oral, ocular and genital lesions, with the conjunctival ulcerations potentially leading to scarring and blindness similar to that of pemphigoid. In the latter form, in addition to the mucosal involvement, large areas of the skin are desquamated, resulting in a high mortality rate. Conventional erythema multiforme is treated with either topical or systemic corticosteroids and palliative care, depending on the severity of symptoms. Topical anesthetics may be given to patients whose nutrition is compromised by lesional discomfort. Discontinuation of any drug should be considered if a causal relationship can be established.

Traditionally known as scleroderma, systemic sclerosis is a chronic, immune-mediated condition characterized by inflammatory and fibrotic changes that compromise the function of multiple organ systems (34). The disease typically arises in middle-aged adults and often occurs in conjunction with other autoimmune diseases, such as SLE, rheumatoid arthritis and Sjögren's syndrome. Symptoms tend to originate in the skin, which becomes edematous and subsequently hardened and smooth, tightening the facial skin and degrading the nasal ala into what has been described as a 'mouse-like' facies. Radiating perioral fissures may be noted. This process also contributes to flexion contractures of the hands and resorption of the terminal phalanges. Vascular compromise results in ulceration of the fingertips and the development of Raynaud's phenomenon. This extensive fibrosis may cause particularly severe organ dysfunction, leading to loss of gastrointestinal motility, glomerulosclerosis and pulmonary fibrosis, with eventual heart failure. Continuous perioral collagen deposition causes a significant microstomia, and fibrosis of the tongue and esophagus results in limited mobility and dysphagia.

Gingival recession is also common, and salivary gland fibrosis leads to frequently severe xerostomia and cervical caries. Radiographic changes include an increased width of the periodontal ligament spaces in all quadrants, and mandibular resorption that tends to be more pronounced in the posterior regions. Systemic sclerosis is a chronic, progressive disease with a poor prognosis. Patients may be prescribed D-penicillamine to reign in collagen production; otherwise, treatment must be tailored to the affected organ systems. Frequent dental recall is imperative, due to both the predisposition to caries and periodontal disease, as well as the difficulty in oral hygiene maintenance resulting from microstomia and flexion contractures.

Infectious diseases

The oral cavity is subject to innumerable bacterial, fungal, viral and parasitic infections, some of which are indicative of profound underlying immune dysfunction. The following discussion concerns several significant systemic infections that can involve the head and neck.

Candidiasis is a common fungal infection that is established in a wide range of settings, from denture wearing to severe immunosuppression. The causative organism is usually *Candida albicans*, a natural resident of the oral cavity, although overgrowth by other species may also cause disease. Candidiasis has been associated with poor denture hygiene and fit, broad-spectrum antibiotic treatment, diabetes mellitus, and an immunocompromised state due to anticancer therapy or AIDS (35). There are three major forms of oral candidiasis: pseudomembranous, atrophic and hyperplastic. Pseudomembranous candidiasis, known colloquially as 'thrush', appears clinically as numerous, widely distributed, white, curd-like plaques, and is often linked to antibiotic therapy and immunosuppression (Fig. 18). These plaques can be easily wiped away with a gauze pad, leaving behind an erythematous surface that may show pinpoint bleeding areas. The atrophic subtype is associated with denture stomatitis, the use of steroid-containing inhalers and immunosuppression (Fig. 19). It is characterized by deeply erythematous patches that are often painful and/or impart a burning sensation. Another variant of atrophic candidiasis is angular cheilitis, which manifests as symptomatic red patches at the labial commissures (Fig. 20). This variant results from decreased vertical

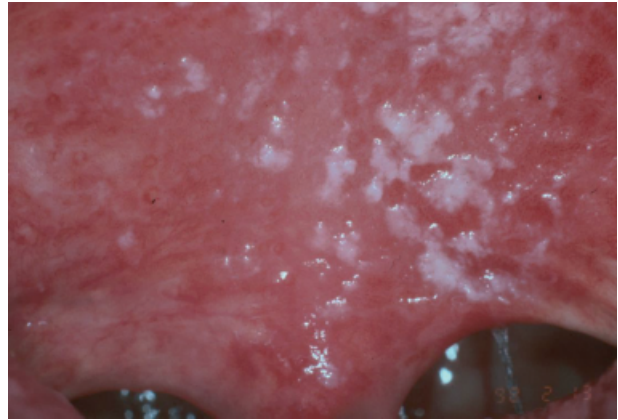


Fig. 18. Removable white plaques resembling cottage cheese or curdled milk are typical of pseudomembranous candidiasis (courtesy of Dr Thomas Scorziello).



Fig. 19. Velvety-appearing area of patchy erythema of the palatal mucosa in an immune compromised patient representing atrophic, or erythematous, candidiasis (courtesy of Dr Michael Glick).



Fig. 20. White, removable fungal colonies at the oral commissure in an immune compromised patient represented angular cheilitis (courtesy of Dr Michael Glick).

dimension and subsequent saliva leakage in denture wearers. Hyperplastic candidiasis appears as a white to yellow raised leukoplakia, which consists of accumulations of keratin admixed with fungal organisms. These lesions cannot be wiped off because they are a consequence of an underlying epithelial lesion, often a benign hyperkeratosis or epithelial hyperplasia (although dysplasia has been associated with this type of candidiasis). Whether these lesions are induced by the fungus or merely represent ensuing colonization of existing keratin is disputed. Oral candidiasis can be successfully treated with topical and systemic antifungal medications (35). Topical medications are available in several forms and can be tailored to the preferences of the patient. However, it is essential that the patient with oral candidiasis be evaluated for any underlying predisposing factors since treatment is likely to fail should they persist.

Syphilis is a bacterial disease caused by the spirochete *Treponema pallidum*. It is typically transmitted through sexual activity, but may also be spread to an infant by an infected mother. The spirochetes gain entry into the body through breaks in the skin or mucosa, and then travel to the regional lymphatics before disseminating throughout the body. The clinical expression of the disease has been divided into three occasionally overlapping stages (36). The first stage of acquired syphilis, designated primary syphilis, occurs after an incubation period that may last from a few days to as much as 3 months. It is characterized by the presence of an indurated, well-circumscribed ulcer known as a chancre at the site of bacterial introduction, with or without regional lymph node enlargement. Progression to secondary syphilis follows resolution of the chancre, usually after a period of up to 6 months. During this stage, there is greater systemic involvement with an expanded complex of frequently non-specific signs and symptoms. Individuals may develop a diffuse, cutaneous maculopapular rash that may eventually heal with altered pigmentation and scarring. Some will develop oral mucous patches, irregular raised lesions with shallow ulceration, and condyloma lata. Following resolution of the lesions of secondary syphilis, individuals enter a latent stage that could, in the absence of cure, progress to tertiary syphilis after 10–30 years. The manifestations of this stage of the disease are varied and consist mainly of cardiovascular and neurologic signs and symptoms, such as aortic aneurysm, meningitis, ataxia and dementia. Pregnant females with active

infection can pass the disease to their offspring. Congenital syphilis, in keeping with the acquired infection, presents with an abundance of clinical findings. Head and neck sequelae include molar teeth with a highly convoluted occlusal table ('mulberry' molars) and Hutchinson's triad: incisors with a constricted horizontal aspect ('screwdriver' incisors), interstitial keratitis leading to visual difficulty, and eighth nerve deafness. Other oral manifestations include altered maxillary and mandibular dimensions, palatal arching and perioral fissuring (36). Penicillin is the preferred treatment for syphilis uncomplicated by HIV infection.

Tuberculosis is a widespread disease that currently infects approximately one-third of the world population. Transmission is through the inhalation of airborne droplets generated by the sneezing, coughing or talking of someone with active disease. These droplets, which contain the causative organism *Mycobacterium tuberculosis*, reach the bronchioles and alveoli, thereby exposing the bacilli to the lung parenchyma. The resulting granulomatous inflammatory response may halt disease progression, but often there is only partial control with resultant localized tissue necrosis. Unmolested bacilli can migrate to the lymphatic and blood vascular system, resulting in dissemination to all parts of the body. Individuals with tuberculosis experience fever, night sweats, fatigue, anorexia, dyspnea and coughing, sometimes with hemoptysis (37). The disease may then enter into a state of latency. Because of the ability of mycobacteria to achieve extensive systemic distribution, the clinical manifestations of the disease are many. Head and neck involvement is uncommon, but when present consists of cervical lymphadenopathy, tuberculous osteomyelitis, macroglossia, salivary gland enlargement and oral ulcerations often having a deep, fungating appearance and irregular outline. The management of the dental patient with suspected or active tuberculosis is complex (38–41). Although there has yet to be a documented patient-to-dentist transmission of tuberculosis in a dental setting, the aerosolization of oral fluids that occurs during dental procedures provides a theoretical risk of infection. To minimize this risk, patients with active disease should only be treated on an emergent basis, with all other dental treatment deferred until non-infectivity can be demonstrated. Should a dental procedure be necessary, universal precautions must be meticulously followed, and aerosol-generating equipment such as

Table 2. Selected diseases associated with AIDS*Opportunistic infections*

Candidiasis

Aspergillosis

Zygomycosis

Cryptococcosis

Histoplasmosis

Tuberculosis

Herpes simplex virus

Human papillomavirus

Cytomegalovirus

Epstein-Barr virus

Pneumocystis carinii pneumonia

Toxoplasmosis

Neoplasms

Non-Hodgkin's lymphoma

Kaposi's sarcoma

Squamous cell carcinoma

Carcinoma of the uterine cervix

Other

Aphthous-like ulcers

Periodontal disease

Necrotizing ulcerative gingivitis/stomatitis

Salivary gland lymphoepithelial cysts

Thrombocytopenia

Pharmacologic melanosis

Other head and neck manifestations

The parathyroid glands are endocrine organs, usually 4–6 in number and approximately the size of a pea, located behind the lobes of the thyroid gland. They are partially responsible for the regulation of serum calcium. Decreased extracellular calcium concentration stimulates the glands to release parathyroid hormone (PTH), which enters the bloodstream and acts upon bone and the epithelium of the ascending loop of Henle (42). In bone, PTH ultimately induces an increase in osteoclast activity and number, resulting in the liberation of calcium from the bone matrix into the bloodstream. In the kidneys, the hormone acts to help resorb calcium from the urine and stimulate the production of active vitamin D, which will then cause calcium to be absorbed by the intestine.

Primary hyperparathyroidism results from oversecretion of PTH in the setting of a parathyroid gland neoplasm or hyperplasia, resulting in hypercalcemia and destructive bone lesions, which, if severe enough, can contribute to pathologic fractures and vertebral body collapse. Changes that the dentist may see early in the disease are a consequence of a disturbance of the trabecular structures of the jaws, appearing radiographically as a dissolution of the lamina dura and a loss of trabecular definition. This frequently results in a ground-glass osseous pattern. With untreated primary hyperparathyroidism, individuals may develop jaw radiolucencies consisting of one or more locules. These lesions, known as 'brown tumors' from their gross appearance, histologically represent central giant cell granulomas (it must be noted that they are not related to granulomatous inflammation). Primary hyperparathyroidism necessitates surgery to remove either the parathyroid neoplasm or all but one of the hyperplastic parathyroid glands.

Excessive PTH secretion is also characteristic of individuals in chronic renal failure. The associated bone abnormalities, which are similar to but generally less severe than those of primary hyperparathyroidism, are known as renal osteodystrophy. The pathogenetic mechanism is speculative (43), but it is thought that the clinical picture derives in part from the inability of the kidneys to produce the active form of vitamin D, which in turn results in diminished intestinal calcium absorption. Dysregulation in serum calcium/phosphorus balance is another proposed mechanism. The end result is a low serum calcium level that stimulates a

high-speed handpieces and air syringes should be used as little as possible. Tuberculosis can be effectively treated in most patients through an extensive and long-term multi-drug antibiotic regimen.

A comprehensive discussion of AIDS is beyond the scope of this article. The dental practitioner should, however, be aware of the range of disorders that may arise in the setting of human immunodeficiency virus infection (Table 2).

compensatory PTH release (secondary hyperparathyroidism) and subsequent osteoclastic bone degradation. Individuals with renal osteodystrophy sometimes exhibit expansion of the mandible and maxilla with giant cell lesions and a radiographic ground-glass appearance (Fig. 21A and B).

Anemia is a general term that refers to a condition wherein the patient suffers from a net decrease in the number of normal red blood cells and/or hemoglobin per unit of blood volume. This occurs either through decreased production or increased destruction of erythrocytes, or by having a high proportion of structurally or functionally abnormal cells. The result of this process is low blood oxygen content and, in some cases, a predisposition to organ ischemia.

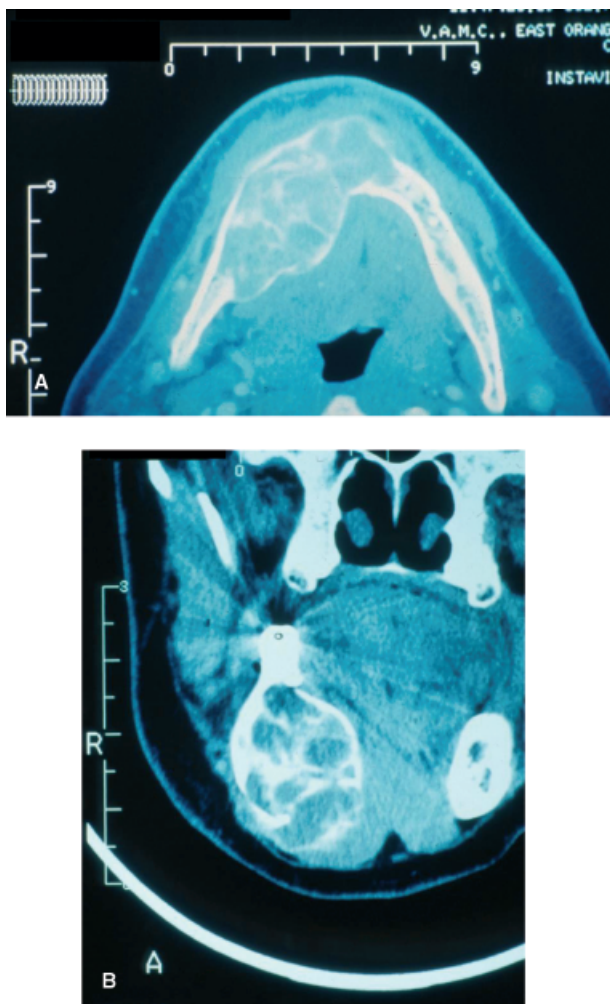


Fig. 21. (A and B) Transverse and coronal CT scans demonstrate a multilocular radiolucency ('brown tumor') of the mandible in a patient with hyperparathyroidism (courtesy of Dr Ian McDonald and Dr Bernard McGivern).

Symptoms of pallor, fatigue, dyspnea, tachycardia, vertigo and weakness relate to a diminished hemoglobin concentration and insufficient blood and tissue oxygenation.

Iron is an essential nutrient necessary for many biologic processes, including the production of hemoglobin and erythrocyte development. A deficit of this element may result from low dietary content, malabsorption or myriad underlying conditions leading to decreased cellular uptake of iron, increased need or continuous loss of blood. Iron deficiency anemia is the most common form of anemia. It tends to occur in females, often during adolescence and childbearing age, and is associated with pronounced menstrual flow and increased need during normal somatic growth and pregnancy. Peripheral blood smears show erythrocytes that are decreased in size (microcytic), and pale (hypochromic) due to deficient hemoglobin. Intraoral examination of individuals with iron deficiency anemia often reveals angular cheilitis and atrophic glossitis. Atrophic glossitis is a commonly painful condition characterized by loss of lingual filiform papillae resulting in a red, shiny ('bald') tongue (Fig. 22). Affected individuals will show cutaneous and mucosal pallor, and brittle, concave fingernails (koilonychia). Iron deficiency anemia is a component of Plummer-Vinson syndrome, in which patients also present with angular cheilitis and atrophic glossitis, and also dysphagia due to the development of membranous structures called 'esophageal webs' that span the lumen of the esophagus. Carcinogenesis of the oral cavity, hypopharynx and esophagus is linked to this syndrome and is an added concern. Individuals diagnosed with iron deficiency



Fig. 22. Atrophic glossitis is an oral manifestation of iron deficiency anemia and (as in this individual) the megaloblastic anemias (courtesy of Dr Mark Bernstein).

anemia should be examined and treated for any contributing underlying medical conditions and given dietary iron supplements (44).

Pernicious anemia is a condition that may have an autoimmune basis, and is ultimately responsible for the development of vitamin B₁₂ deficiency in affected individuals. It is a consequence of inflammatory and degenerative changes that occur within the stomach mucosa leading to the destruction of gastric parietal cells. These cells serve many important functions, including the secretion of intrinsic factor that is necessary for the transport of vitamin B₁₂ across the membrane of intestinal epithelial cells. Pernicious anemia is described as a 'megaloblastic anemia', a term that reflects the large size attained by all the hematopoietic cells and their marrow precursors, including erythrocytes. The disease is most commonly encountered in the elderly. In addition to the usual non-specific systemic complaints associated with anemia, clinical manifestations include paresthesia, gastrointestinal disturbances, oral mucosal erythema, atrophic glossitis, dysphagia, and pain and burning of the oral tissues (44). Pernicious anemia can be successfully treated with vitamin B₁₂ injections; however, neurologic complications may persist. This disease has been associated with a slightly higher risk of gastric carcinoma.

Conclusion

The maxillofacial complex is a dynamic group of inter-related structures that often reflects the presence of various underlying systemic and generalized disease processes, including innumerable infectious, metabolic and immune-mediated disorders. All these process may profoundly alter the appearance and function of the mouth and contiguous tissues. Because dental professionals are the only members of their communities to perform routine oral surveillance, they have a unique opportunity to recognize underlying disease before it is detected by either the patient or their physician. It is in this capacity that the dental professional can have the greatest impact on his or her patient's health.

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