Chapter 70: Oral Manifestations of Systemic Disease

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A wide array of systemic diseases ancountered in internal medicine have manifestations in the yawning abyss that internists call the oral cavity. Most of these manifestations are nonspecific but should alert the otolaryngologist-head and neck surgeon to the possibility of concurrent systemic disease or latent systemic disease that may develop subsequently. Some diseases identified in the oral cavity may be specific, and when this is true, it is designated in the text. This chapter is not intended to be all inclusive, but it does reflect most of the oral manifestations of systemic disease encountered in a normal otolaryngology practice.

Congenital and Inherited Diseases

A great variety of congenital malformations are routinely seen in the oral cavity. This discussion of congenital and inherited disorders is confined to diseases that frequently have associated systemic components.

Bernstein (1972) has the best discussion of congenital defects in the oral cavity. A double lip, reduplication of the upper lip's vermilion, is sometimes associated with colloid goiters (Ascher's syndrome). The physician may notice that the maxillolabial sulcus is absent or shallow or that multiple frenula exist. This is often associated with a syndrome called *chondroectodermal dysplasia*, which is a congenital defect in the hair, skin, sweat glands, and cartilage characterized by hyperkeratosis, hypohydrosis, and abnormal shortening of the long bones. Total or partial anodontia frequently coexists.

The teeth may mirror several congenital conditions, including congenital syphilis, which is characterized by notched incisors (Hutchinson's teeth), dome (Moon's) molars, or mulberry molars. The teeth may be stained or mottled if the mother has ingested tetracycline or fluoride during tooth development. The teeth are often stained brownish green in congenital hemolytic anemia, caused by Rh incompatibility, and in congenital biliary atresia. This reflects staining with bilirubin and its breakdown pigments (Plate 9, A).

The bony palate may show a high palatal vault in Turner's syndrome or in congenital gonadal dysgenesis, a congenital disease of females characterized by XO chromosome karyotype, infertility, pterygium colli, coarctation of the aorta, a shield chest, and many other developmental defects. A high-arched soft palate is described in the autosomal-dominant Marfan's syndrome, a generalized disorder of connective tissue with skeletal, ocular, and cardiovascular malformations. Characteristically these patients are tall and thin with arachnodactyly and joint hypermobility. Subluxated ocular lenses and a proclivity for dissection of the aorta are other important components of this syndrome. Other marfanoid syndromes, including a high-arched palate with crowding of the teeth, have also been described by McKusick (1972) and Wyngaarden and Smith (1985). They are listed as follows:

Commonly associated marfanoid syndromes

Homocystinuria
Multiple endocrine adenomatosis III
Ehlers-Danlos syndrome

Rarely associated marfanoid syndromes

Mitral valve prolapse
Sickle cell anemia.

An autosomally recessive disorder of amino acid metabolism called *homocystinuria,* which results from a deficiency in cystathione synthetase, frequently displays the physiognomy of Marfan's syndrome, and, in addition, includes osteopenia and premature artherosclerosis as described by Stanbury et al (1983). A marfanoid habitus is also described in the section on multiple endocrine adenomatosis III.

The Ehlers-Danlos syndrome is a group of 11 inherited metabolic disorders of connective tissue, which share phenotypic expressions of Marfan's syndrome in addition to extreme laxity of the skin and joints and easy bruisability. Type VIII Ehlers-Danlos disorder is also characterized by severe periodontal disease (Wyngaarden and Smith, 1985).

Mitral valve prolapse was first described with marfanoid features, but widespread use of the two-dimensional echocardiogram has shown that this occurs in a large number of patients without the Marfan phenocopy. Similarly, patients with sickle cell anemia were first characterized by high arched palates and other Marfan's phenomena, but intensive screening for sickle cell disease has demonstrated that this is not *usually* the case.

Macroglossia with hypertrophic papillae as well as a cleft or high-arched palate may be noted in mongolism (trisomy 21), and atrophy of the fungiform papilla is frequently seen with the Riley-Day syndrome, or autosomal-recessive familial dysautonomia. A disorder of the autonomic nervous system, it is characterized by hypertension with postural hypotension and defects in temperature control.

Mucous membranes may show multiple angiomas in a neurocutaneous syndrome listed under the phacomatoses called Sturge-Weber syndrome, or encephalofacial angiomatosis. These people have port-wine staining of the skin of the face and oral mucosa in a unilateral trigeminal distribution and a proclivity for arteriovenous (AV) malformations in the brain, with resultant grand mal seizures and mental retardation.

A peculiar syndrome called phlebectasia of the jejunum, oral cavity, and scrotum has been described. It is characterized by caviar spots on the tongue, Fordyce spots on the scrotum, and a propensity for gastrointestinal bleeding caused by jejunal varicosities.

An important syndrome for the physician to recognize is Weber-Rendu-Osler syndrome, or the autosomally dominant hereditary hemorrhagic telangiectasia. It is characterized by telangiectasia of the tongue, oral cavity, and nasal mucosa, which becomes apparent at puberty and increases as the patient ages (Plate 9, B). This is also associated with

multiple telangiectasia of the gastrointestinal tract, which can cause severe blood loss, AV malformations of the liver, cirrhosis, and occasionally AV malformations of the lung with arterial desaturation resulting in cyanosis and digital clubbing.

Telangiectasia of the oral cavity may be seen in Fabry's disease (angiokeratoma corporis diffusum universale), an inborn error of glycosphingolipid catabolism characterized by telangiectatic skin lesions, hypohydrosis, corneal opacities, acral pain with paresthesia, renal failure, and cardiovascular, gastrointestinal, and central nervous system disturbances. It is caused by ceramide dihexoside deficiency as described by Standbury et al (1983).

The physician frequently encounters fibromas of the maxilla, mandible, or tongue. Five systemic syndromes associated with congenital neurofibromas and/or fibromas of the tongue and the jaws should be mentioned. One is von Recklinghausen's disease, an autosomal-dominant disease associated with multiple neurofibromas of the skin and bone with increased incidence of sarcomatous degeneration; it is also associated with hypertension caused by either bilateral pheochromocytoma or renal artery stenosis, café-au-lait spots on the skin, and oral melanosis.

A second syndrome of some interest is autosomal-dominant multiple endocrine adenomatosis type III, which is associated with neurofibromas of the tongue and lips, medullary carcinomas of the thyroid, and pheochromocytomas.

The peculiar Cowden's disease is dominantly inherited and is characterized by warty papules on the face, arms, and mucous membrane of the mouth. This syndrome has a propensity for the development of carcinomas of the breast, thyroid, endometrium, and cervix.

Tuberous sclerosis is another neurocutaneous syndrome characterized by seizures, mental retardation, and sebaceous adenomas. In this syndrome one may also see hypomelanosis, periungual fibromas, and café-au-lait spots. Intraoral fibromas are frequently observed.

The Melkersson-Rosenthal syndrome (Shklar and McCarthy, 1976) is a developmental abnormality with unilateral facial paralysis and edema of the periorbital skin, which often progresses to granuloma. The tongue is fissured and has papillary projections, which reveal fibromas at biopsy.

White lesions of the buccal mucosa and tongue are seen in dyskeratosis congenita, which features cutaneous hyperpigmentation, nail dystrophy, and severely hypoplastic bone marrow resembling Fanconi's panmyelopathy. Another interesting syndrome appears in the mouth in the form of a self-induced mutilation of the teeth, tongue, and lips. It is associated with choreoathetosis, mental retardation, and hyperuricemia (Lesch-Nyhan syndrome) and is caused by a deficiency of hypoxanthine guanine phosphoribosytransferase.

Melanosis of the gingiva may be noted as a normal variant in the black population but is also seen in the autosomal-dominant disorder of increased iron absorption from the gastrointestinal tract called *hemochromatosis.* Various melanoses of the oral cavity are listed as follows:

Hereditary melanoses

Normal variant
Hemochromatosis
Albright's disease
Peutz-Jeghers syndrome
von Recklinghausen's disease

Acquired melanosis

Addison's disease.

Hemochromatosis affects middle-aged men and is associated with bronzed skin, diabetes, gonadal atrophy, cirrhosis of the liver, congestive heart failure, and sometimes hypopituitarism. Pigmentation of the oral cavity in this disease is produced by melanin rather than iron. Albright's disease (the syndrome of precocious puberty, polyostotic fibrous dysplasia of bones, and "coast of Maine" café-au-lait spots) may also display melanosis of the gingiva as well as migration and mobility of teeth secondary to jaw involvement with the fibrous dysplasia. An important disorder to recognize is melanosis of particularly the skin, lips, and gums - the Peutz-Jeghers syndrome - associated with hamartomas of the small bowel and recurrent gastrointestinal bleeding (Plate 9, C). The Peutz-Jeghers syndrome is occasionally associated with malignancy *above* (not below) Treitz' ligament.

A peculiar disorder of lipoprotein metabolism, Tangier disease, is associated with pathognomonic xanthomas, particularly of the soft palate and tonsils, that appear as yellow tonsil or yellowish white to gray spots in the soft palate. Patients also appear with hepatosplenomegaly and peripheral neuropathy. This is caused by an absence of high-density lipoproteins and extremely low levels of apoproteins A1 and A2. The biopsy shows cholesterol-laden foam cells.

There is a congenital group of diseases that are lumped together as histocytosis X or as the reticuloendothelioses; they include Letterer-Siwe disease, Langerhans' cell (eosinophilic) granuloma, and Hand-Schüller-Christian disease. All of these disorders are associated with infiltrative-destructive lesions of the bone secondary to overgrowth with histiocytes and may appear as gingival epulis, loose teeth, and mucosal erosions. Systemic manifestations are produced by skin lesions, erosive lesions of a number of bones, and infiltration of the lung and liver. The etiology of these diseases continues to be obscure. Smith and Evans (1984) have the best discussion in the literature on this subject.

Gaucher's disease is an inborn error of metabolism characterized by a reduction in cerebroside breakdown with resultant accumulation of lipid-laden histiocytes in the bone marrow, liver, and spleen. This disease frequently displays radiolucent lesions in the jaw. Loose teeth with recession of the gingiva may be noted.

Hartnup disease is a congenital disorder of specific amino acid handling by the renal tubular and intestinal epithelial cells. It produces a phenocopy resembling primary pellagra. This is described more fully in the section on deficiency syndromes in the oral cavity. The pellagra-like syndrome is produced by a lowered ability to convert tryptophan to kynurenine

nicotinamide. This is attributed to deviation of tryptophan from its normal metabolic route because of the absorption defects (Stanbury et al, 1983).

Mention should be made of the oral-facial-digital syndrome, or orodigitofacial dysostosis, which is characterized by a short upper lip, hypertrophy of the frenula of the lips and tongue, and clefts of the hard and soft palates. Systemic findings include polycystic kidneys and liver and mental retardation. The unique congenital abnormality epidermolysis bullosa is characterized by bullous lesions of the skin and oral mucous membrane, caused by faulty epidermal-dermal adherence. Patients with the severe form of this disease are continually disabled with secondary infections and sepsis.

Osteopetrosis (Albers-Schönberg disease, marble bone disease) is a congenital disorder of bony osteoclastic function, which leads to bone marrow insufficiency. It can be associated with mandibular and maxillary hyperostosis, which resembles Paget's disease, fibrous dysplasia, histiocytosis X, or acromegaly. Pseudoxanthoma elasticum is another congenital defect in collagen tissue; it too may have oral manifestations related to the defects in vascular integrity that characterize this disease.

The mucopolysaccharidoses are a group of heterogeneous congenital deficiencies in enzymes that handle mucopolysaccharide breakdown and are essentially storage disease problems. Mucopolysaccharidosis type IH, or Hurler's syndrome, characteristically shows macroglossia, hypoplastic and abnormally spread teeth, corneal degeneration, and mental retardation.

Osteogenesis imperfecta (brittle bone disease) manifests itself in the mouth in the sense that the alveolar sockets and dentin participate in the generalized abnormality; the teeth are opalescent and often freely movable within the oral cavity. This disease is also associated with blue sclerae and frequent pathologic fractures of bone. Abnormalities of both the dental and skeletal systems are also seen in cleidocranial dysostosis. Abnormalities include the absence of clavicles, dolichocephaly, and supernumerary as well as malformed teeth.

The diagnosis of cystic fibrosis can be made after examination of the labial mucous glands by microscopy. This disorder in the handling of mucus stems from an unknown defect in exocrine gland function that is associated with pancreatic insufficiency, malabsorption, salt wasting, and dehydration. Patients usually die during puberty from severe lung disease with bronchiectasis and repeated pneumonia.

Acatalasemia is an autosomally recessive deficiency of catalase, an enzyme that degrades hydrogen peroxide. This disorder was discovered by Takahara in a patient with an ulcerating gangrenous lesion of the oral cavity. The application of hydrogen peroxide to the sites resulted in no characteristic foaming and caused the affected tissues to turn black.

Acquired Metabolic-Endocrine Disorders

Hyperparathyroidism, whether produced by parathyroid adenomas or parathyroid hyperplasia, can appear in the mouth in two ways. First, evidence of dehydration can exist. Most patients that are hypercalcemic for any period of time and for any reason become dehydrated because of insensitivity of the renal tubular collecting ducts to the antidiuretic

hormone. Second, hyperparathyroidism secondary to parathyroid adenomas and hyperplasia can appear as mandibular or maxillary tumors of the bone, which on biopsy display a brown tumor of von Recklinghausen, a localized area of intense osteoblastic-osteoclastic activity, and hemorrhage into a fibroangiomatous matrix. This is rare, since autoanalyzers measure serum calcium, but it is still sometimes observed.

Syndromes of low calcium can be produced by idiopathic hypoparathyroidism, pseudohypoparathyroidism, surgical hypoparathyroidism, or chronic malabsorption. This first is an acquired autoimmune disease associated with polyendocrine glandular deficiency and with orocutaneous candidiasis and pernicious anemia; the second is an inherited disorder characterized by an end-organ unresponsiveness to parathyroid hormone effects. Pseudohypoparathyroidism is also characterized by a moon face and brachymetacarpalia. All these symptoms may appear with trophic changes of the skin, nails, dryness of the mucous membranes, angular cheilitis, and enamel hypoplasia.

Both acute renal failure and chronic renal failure from diverse etiologies produce dyskeratotic changes in the eye and oral cavity, resulting in dryness of all mucous membranes to such an extent that keratoconjunctivitis and xerostomia, which resemble Sjögren's syndrome, are produced.

Disorders of the adrenal glands include adrenal insufficiency, or Addison's disease, which is most commonly caused by an immunologically mediated polyendocrine glandular failure. Bronzing of the skin and diffuse or localized hyperpigmentation of the oral mucous membranes are secondary to melanin deposits and may be the first sign of this disease. Bronzing in this disease is related to pituitary hypersecretion of adrenocorticotropic hormone, which has protein homology with melanocyte-stimulating hormone; as such it is *not* seen with adrenal insufficiency secondary to exogenous steroids or pituitary insufficiency. Cushing's disease - whether iatrogenic or produced by a disorder of the hypothalamus with adrenal hyperplasia, adrenal adenomas, or carcinomas - produces among other things an increased incidence of infectious diseases. This is most frequently manifested in the mouth as oral candidiasis. Generalized muscle weakness causing difficulties with phonation and deglutition is frequent and is part of the generalized muscle weakness in this disorder.

Hyperthyroidism, the most common cause of which is Graves' disease, is an autoimmune disease characterized by hyperplasia of all lymphoid tissue, including lymph nodes and spleen. It can be manifested in the mouth by hyperplasia of all of the lymphoid tissue-bearing areas in the oral pharynx and tonsillar regions. Hypomotility of the tongue has also been described (Shklar and McCarthy, 1976). Hypothyroidism, whether caused genetically, surgically, or as part of burned-out Hashimoto's disease (another autoimmune disease), may appear as macroglossia as well as disorders of deglutition caused by skeletal muscle weakness. Diabetes mellitus may appear orally as candidiasis of the oral mucosa for no apparent other reasons, neither known immune deficiencies nor prolonged antibiotic or steroid treatment. If diabetes is not controlled, the mouth may become dehydrated secondary to osmotic diuresis. A high incidence of chronic periodontal disease exists in diabetes.

Acromegaly, caused by acidophilic tumors of the pituitary gland (secondary to a hypothalamic defect), may appear with prognathism and teeth spacing secondary to mandibular bony overgrowth as well as macroglossia and diffuse enlargement of the bones

of the maxilla and the mandible. Prepubertal hypopituitarism appears with oral manifestations; the teeth are not responsive to growth hormone, unlike the bone of the jaws. Since the teeth are normal in size and the jaws are small, difficulties with tooth eruption and proper alignment occur (Shklar and McCarthy, 1976).

Paget's disease is an acquired disorder of excessive bone resorption with variable attempts at repair. The skull and maxilla are frequently involved. There may be extensive enlargement and deformation of the maxilla, with spacing and mobility of the teeth. This produces the syndrome of leontiasis ossea (lionlike facies).

Pregnancy may produce an inlammatory gingival hyperplasia caused by increased gingival reactivity to local irritants. This usually develops in the patient's first trimester and is maintained throughout the pregnancy. It may evolve into a "pregnancy tumor" of the gingiva, which the biopsy shows to be a pyogenic granuloma. Menopause may be associated with a number of oral manifestations, the most common being desquamative gingivitis and generalized atrophic alterations of the oral mucosa.

Acanthosis nigricans is usually an acquired disorder. It appears as dark, velvety skin lesions in the intertriginous areas of the skin and is also seen at the corners of the mouth and the edge of the tongue. The malignant type is commonly associated with gastric adenocarcinomas, and the benign type with endocrine disturbances of the pancreas and adrenal glands.

Malignant Diseases

Any discussion of malignant diseases of the oral cavity must be divided into primary and secondary. Primary tumors are usually squamous cell carcinomas of the oral cavity and are discussed in Chapter 72. This chapter focuses on other malignant diseases that manifest themselves in the oral cavity on the oral effects of therapy for malignant diseases, including chemotherapy and radiation.

Nonhematologic malignant diseases of other organ systems occasionally appear as metastatic diseases in the oral cavity. Rusthoven et al (1984) described two cases of metastatic adenocarcinoma of the rectum presenting in the oral cavity. One patient had paresthesias and pain; the other patient developed a growth at the site adjacent to a tooth extraction and had erosion of the mucosa. The metastatic spread of solid tumors from distant primary sites to the oral mucosa, mandible, or maxilla is rare. Probably less than 1% of oral malignancies are truly metastatic tumors; at least 70% of these are adenocarcinomas. The most common primary sites involved, in decreasing order of frequency, are breast, lung, kidneys (hypernephroma), colon, rectum, thyroid, prostate, and melanoma. Metastatic lesions of the oral cavity may clinically resemble benign tumors such as fibromas, giant cell granulomas, pyogenic granulomas, or periodontal abscesses, or may present with teeth loosening. Differential diagnosis would include granulomatous diseases, Paget's disease, histiocytosis X, hyperparathyroidism, and benign bone tumors.

Carcinoids are tumors of neuroectodermal origin and primarily arise in the gastrointestinal tract. If they are metastatic to the liver, they can produce the carcinoid syndrome by manufacturing a number of autocoids; the oral mucous membrane participates

in the characteristic flushing seen in this syndrome. What is less well appreciated is that the diversion of tryptophan metabolism from kynurenine nicotinamide formation caused by overproduction of autocoids in aggressive carcinoids may lead to an acquired pellagra syndrmoe, with consequent oral manifestations of angular cheilitis and hyperkeratosis of the oral cavity similat to what is seen in primary (nutritional deficiency) pellagra.

It is well known that non-Hodgkin's lymphoma of various histologic types, including Burkitt's lymphoma and chronic lymphocytic leukemia (diffuse well-differentiated lymphocytic lymphoma), frequently appears in the oral cavity's soft tissues, including the sot palate and Waldeyer's ring. A review of this subject by Eisenbud et al (1983) revealed that in 31 cases of initial oral presentations of non-Hodgkin's lymphoma, 75% were diffuse non-Hodgkin's lymphoma, and 13 out of 31 (on subsequent staging) were either stage III or IV. Chronic lymphatic leukemia (diffuse well-differentiated lymphocytic lymphoma) particularly has the proclivity to involve the tonsillar tissues as well as other lymphoid-bearing tumors in the oral mucosa. Only diffuse histiocytic (large cell) lymphoma and Burkitt's lymphoma display any major predilection for symptomatic involvement of the bony maxilla or mandible.

Mycosis fungoides is a form of cutaneous T-cell lymphoma in which the skin is involved initially with a psoriaform or eczematous lesions that progress to plaque with tumor formation. It may remain localized to the skin for many years, with only late involvement of the internal organs. The oral mucosa is rarely involved, but the lips are frequently affected.

Hodgkin's lymphoma can occur in the oral cavity - particularly in the palate, floor of the mouth, and gums. It appears clinically as a primary oral squamous cell carcinoma until the full nature of the disease is recognized.

Multiple myeloma and its counterpart, amyloidosis, are both caused by malignant proliferation of plasma cells (differentiated B cells). They can produce oral effects in a number of ways (Epstein et al, 1984). Patients may have jaw pain, usually related to radiolucent areas of myeloma in the mandible or maxilla. Patients may complain of paresthesias secondary to nerve compression by bony masses, amyloid nodules, or extramedullary plasmacytomas. They may also appear as soft tissue masses caused by extramedullary plasmacytomas and resembling epulis. Involvement of bone can produce mobility and migration of the teeth. Amyloid may appear as macroglossia with smooth atrophic tongue or, more commonly, as pearly papules on the tongue and oral mucosa.

Effects of the myeloma proteins on coagulation factors and platelet aggregation, thrombocytopenia secondary to myelophthisic involvement of the bone marrow by plasmacytosis, and the effects of chemotherapy can all produce oral petechiae or hemorrhagic bullae; the results resemble either immunologic thrombocytopenic purpura or hemophilia. A subvariant of the plasma cell dyscrasias, a disease called heavy chain (Franklin's) disease, is a monoclonal production of an IgG heavy chain fragment, which clinically resembles a lymphoma. It may appear in the mouth. Patients with heavy chain disease have a peculiar edematous violaceous uvula, which sometimes suggests the diagnosis.

A monoclonal production of the IgA heavy chain fragment is called alpha-heavy chain disease. It usually appears with malabsorption caused by extensive small intestine involvement with lymphoma. Hence the oral mucosa changes of folate and vitamin A deficiency may be

a prominent sign.

Ewing's sarcoma is a rare tumor of bone arising in pluripotent mesenchymal tissue. It occasionally involves the mandible and presents with chin and lip paresthesias. It may be confused with granulomatous disease, Paget's disease, histiocytosis X, or hyperparathyroidism.

The acute leukemias may appear with oral manifestations but usually demonstrate oral signs only later in the course of the illness. Acute myelogenic leukemia, particularly the monocytic or myelomonocytic variants, frequently appears with hyperplastic gingiva secondary to involvement of the gums with immature myeloid elements. Acute lymphoblastic leukemia may involve the lymphoid-bearing tissue of the oral mucosa, including the tonsils. Later in the course of the illness, thrombocytopenia may produce hemorrhagic lesions of the gums or oral mucosa and petechiae. Agranulocytosis secondary to bone marrow involvement may produce the syndrome of agranulocytic angina described later. The other effects are described in the next paragraphs.

The effects of radiation and chemotherapy in the oral cavity are well known and extremely common. They are well described by Carl (1983). Radiation delivered to the head and neck region for either primary or secondary malignancies may produce mucositis as well as atrophy of the salivary glands, usually with the serous acinar glands being more affected than the mucous acinar glands and leading to a syndrome of xerostomia similar to Sjögren's syndrome. Patients receiving radiation to the head and neck have a high incidence of radiation caries secondary to a change in the pH of the oral cavity, increasing cariogenic organisms (*Lactobacillus* and *Streptococcus mutans*), and a definite breakdown of the periodontal membrane. Radiation caries may be significantly prevented by the use of pretreatment fluoride gels. Chronic changes caused by radiation therapy can include radioosteonecrosis of the mandible or maxilla, a particularly distressing problem.

Chemotherapy for systemic malignancies can produce a variety of changes in the oral cavity - ranging from stomatitis to gangrene - often with little surrounding secondary inflammation. Stomatitis is an inflammatory and rather painful reaction that is seen with a variety of chemotherapeutic agents, most often with cytosine arabinoside, methotrexate, cyclophosphamide, anthracycline derivatives, 5-fluorouracil, and bleomycin. Chemotherapy can also produce changes of the salivary glands similar to those attributed to radiation therapy, with intense xerostomia. The effects of chemotherapy are also manifested through myelosuppression and immunosuppression. With decrements in the white blood count, patients may develop a syndrome called agranulocytic angina, in which extreme pain exists in the mouth but usually little is seen except mucosal atrophy with a striking absence of inflammation; this may progress to variable deep ulcers with a necrotic base. The immunosuppressive effects of chemotherapy, especially prednisone, can result in chronic opportunistic infectious diseases in the oral mucosa, particularly *Candida albicans* and herpes simplex (Plate 10, A). These should be rapidly diagnosed and treated with fluconazole, acyclovir tablets, or both.

Mention should be made about oral mucositis in bone marrow transplants since both (1) autologous bone marrow transplants for refractory lymphomas and even high-risk solid tumors such as breast cancer with poor prognostic features and (2) allogeneic bone marrow transplants for aplastic anemia, as early treatment in chonic myelogenic leukemia, and for

relapsed acute nonlymphatic and acute lymphatic leukemia are being increasingly practiced. The otolaryngologist will frequently be called on to treat this type of oral mucositis.

Virtually all patients who have received bone marrow transplants develop mucositis. The mucositis range from mild oral mucosal ulceration to gangrene. Severity of the mucositis in bone marrow transplants is often determined by the conditioning regimen, the regimen of chemotherapy or total body radiation used to ablate the bone marrow before transplant. There is a high incidence ni some series of herpes simplex as at least a partial cause of the mucositis. This can be treated by oral or intravenous acyclovir and is frequently used prophylactically in herpes simplex antibody-positive patients before transplant.

Oral candidiasis is also frequent and can be treated with fluconazole as well as chlorhexidine (Peridex). Chlorhexidine is particularly effective in some series because of its antibacterial properties.

There are a number of mouthwashes that can produce symptomatic relief. Stomatitis Mixture, which is a compounded prescription of Maalox, Benylin, and Xylocaine Viscous, is frequently effective; so too is so-called Stomafate, which is Carafate slurry, Benylin syrup, and Maalox suspension. Another favorite regimen, somewhat facetiously termed *Magic Mouthwash,* includes tetracycline, nystatin (Mycostatin), and a steroid preparation. These may all, as emphasized, produce only symptomatic relief.

Much attention has been given to the acquired immunodeficiency syndrome (AIDS) in the last 10 years. This is a symptom complex that was virtually limited to homosexuals, IV drug abusers, and recipients of large numbers of blood transfusions over a long period of time, such as hemophiliacs; now, however, it has become a threat to the population at large. The symptom complex is characterized by peripheral lymphopenia, a decrease in cellular immunity as assayed by skin testing, and a decrease in blastogenic transormation of lymphocytes to a number of B-cell stimulants such as pokeweed mitogen. It is also characterized by polyclonal hypergammaglobulinemia often with paraproteins on serum protein electrophoresis. Analysis of the subpopulation of the T-cell lymphocytes in this syndrome invariably discloses a reduced T-helper:suppressor cell (T4:T8) ratio that is related to reduction in helper cells and initial proliferation of the suppressor cell population. These patients also manifest high titers of antibodies to Epstein-Barr virus, cytomegalovirus, toxoplasmosis, and hepatitis. More recently they have been found to have antibodies to human T-cell leukemia virus, subset III (HTLV III), in their serum. This is an RNA retrovirus that infects T4 lymphocytes and leads to T4 elimination and nondiscrete immunoproliferation.

People with AIDS usually pursue one of several courses, although considerable overlap exists. They manifest a great proclivity for opportunistic infections, the number of which is legion. Opportunistic infections of the mouth are frequently causes by *Candida* stomatitis involving the tongue and oral mucosa. This is frequently associated with *Candida* esophagitis and not infrequently with systemic candidiasis. This should be treated with systemic amphotericin when possible rather than local treatments such as nystatin (Mycostatin) or fluconazole (Diflucan). Another frequent oral infection is herpetic gingivostomatitis, which frequently disseminates and should be treated with acyclovir.

Recently, we have learned much about oral manifestations of HTLV infection and AIDS. Some of these oral lesions are reflections of reduced immune function and as such are oral opportunistic infections. Their significance is that they are usually diagnosable early and are highly predictive of the development of the full syndrome. Many of these lesions represent oral manifestations of full-blown AIDS itself.

Certainly, candidiasis is a most common and first described oral opportunistic infection. It can take several forms: *pseudomembranous candidiasis,* or so-called thrush, presents as plaques that can be easily removed, leaving an erythematous surface. There is a less common atrophic form of candidiasis seen as patches on the palate, mucosa, or tongue; this form is much more difficult to diagnose. The least common form of oral candidiasis in AIDS presents as hyperkeratosis, so-called *Candida* leukoplakia. These lesions cannot be removed mechanically, but they do regress with treatment. Obviously, *Candida* leukoplakia can be confused with other forms of leukoplakia.

Candida infection of the mouth can also produce angular cheilitis producing erythematous fissures of the corner of the mouth. Localized oral candidiasis usually responds to topical antifungal agents.

Other fungal infections that have been seen in AIDS patients include histoplasmosis, which must be diagnosed by biopsy and requires systemic therapy; geotrichosis, which can be diagnosed by culture or potassium hydroxide preparation and requires amphotericin, and *Cryptococcus,* which can be cultured or biopsied and, again, requires amphotericin therapy.

Herpes simplex is a very common viral syndroem in AIDS patients. It can usually be diagnosed by clinical appearance or in smears and usually can be readily controlled by oral acyclovir. Herpes zoster is also seen and usually requires intravenous acyclovir.

Hairy leukoplakia is usually grouped with viral infections and is described in all risk groups for AIDS. The differential diagnosis of hairy leukoplakia includes *Candida* leukoplakia, epithelial dysplasia (oral cancer), which is common in these patients, and the white sponge nevus, a plaque form of lichen planus. The biopsy is not particularly revealing, it shows epithelial hyperplasia and very little inflammation. Epstein-Barr virus can be identified in superficial layers of the epithelium using cytochemistry and Souther-Blot techniques. At present it is felt that hairy leukoplakia is an Epstein-Bar virus-induced benign epithelial hyperplasia. If this is diagnosed, high doses of oral acyclovir appear to reduce the lesion clinically.

It has only recently been recognized that unusual forms of gingivitis and periodontitis can be seen frequently in patients with AIDS. The periodontal disease seen in these individuals resembles acute necrotizing ulcerative gingivitis. This disease is usually rapidly progressive with loss of periodontal soft tissue and rapid destruction of supporting bone with loss of teeth. The disease may be so fulminating as to resemble noma seen in severely malnourished patients in developing countries. There is no currently effective treatment for this condition; regimens include thorough debridement and curettage and topical antiseptics such as povidone-iodine and chlorhexidine mouth rinses. Some authorities recommend short courses of metronidazole in severe cases.

It should also be mentioned that *Mycobacterium avium intracellulare* can appear in the mouths of these individuals, is diagnosed by culture and biopsy, and requires multiple systemic therapy. Consultation with a specialist in infectious diseases or a hematologist skilled in AIDS treatment is recommended in this situation.

The course of recurrent opportunistic infections is usually inexorably downward, and death follows from one or more systemic opportunistic infections. The physician should observe strict universal precautions as detailed by the Centers for Disease Control (CDC) when any questions of this syndrome is suggested.

Patients with AIDS can develop Kaposi's sarcoma. Kaposi's hemorrhagic sarcoma, the cell of origin being the endothelial cell, was once a very rare disease. It is closely linked with AIDS and involves plaquelike lesions of the skin, which on biopsy are often diagnosed as sclerosing hemangiomas until the true nature of the disease is recognized. Kaposi's sarcoma may disseminate viscerally, often to the gastrointestinal tract, bone, lymph nodes, lung, and spleen. Kaposi's sarcoma often first appears as oral hemorrhagic lesions, with eventual development of necrosis and ulceration. This should be considered a forerunner of visceral involvement, and these patients should be referred for endoscopy and colonoscopy to determine the extent of these lesions.

Patients with the AIDS syndrome can develop aggressive B-cell non-Hodgkin's lymphoma with some regularity, the oral manifestations of which have already been described. They also can develop a strange wasting syndrome characterized by intense polyneuritis, transverse myelitis, or central nervous system abnormalities with dementia. These neurologic abnormalities can be caused by herpes toxoplasmosis, the retrovirus itself, and by progressive multifocal leukoencephalopathy. There are no known specific oral manifestations of the wasting syndrome.

Hematologic Diseases

Hematologic diseases with oral manifestations are described here in the order of disturbances of the erythron, myeloid, or megakaryocytic-platelet compartment of the bone marrow.

The Plummer-Vinson syndrome (DeWeese and Saunders, 1982), sometimes called the Patterson-Brown-Kelly syndrome or sideropenic dysphagia, is a symptom complex caused by iron deficiency. It produces atrophic glossitis caused by the atrophy of the filiform papillae, angular cheilitis, and occasionally hyperkeratotic lesions in the oral mucosa. It is also associated with koilonychia (or spoon nails), pagophagia, and esophageal webs that can be premalignant if they are hyperkeratotic.

Megaloblastic anemias, whether caused by a vitamin B12 deficiency (commonly coming from pernicious anemia, surgical resection of the ileum, or small intestinal diverticula) or by a folic-acid deficiency (most commonly coming from malnutrition), manifest themselves in the oral cavity as a part of megaloblastic changes in the entire gastrointestinal tract, which are so well demonstrated morphologically in the bone marrow. Clinically, patients with megaloblatic anemias have painful atrophy of the entire oral mucous membranes and tongue as well as recurrent aphthous ulcers. "Magenta tongue", which is said to be rather

characteristic, may herald a B12 deficiency.

Polycythemia (or erythrocytosis), which is either primary (caused by malignant involvement of the bone marrow and a part of the myeloproliferative syndromes) or secondary (caused by hypoxemia of various etiologies), can often appear with engorged reddish-purple discoloration of the gingiva and tongue. Thalassemia, a congenital disorder of production of the globin chain of hemoglobin, is a chronic anemia and may appear in the oral cavity as a mass (caused by extramedullary hematopoiesis) or as a prominent maxilla with severe malocclusion. This is produced by secondary bony overgrowth consequent to chronic bone marrow expansion. Myelofibrosis is a disease that is in the myeloproliferative category, either secondary to the spent phase of polycythemia rubra vera or as a primary process. It is a chronic anemia, which after many years may also present with masses in the mandible and maxilla. A biopsy reveals extramedullary hematopoiesis.

The porphyrias are a strange and rare group of disorders that are characterized by defects in the metabolic assembly of the hemoglobin molecule. Congenital erythropoietic porphyria is characterized by erythrodontia secondary to porphyrin deposits in the gums and teeth. Porphyria cutanea tarda, an acquired form of porphyria, is associated with photosensitive vesicles of the skin and oral mucous membranes and is frequently seen in, but not limited to, acloholics with chronic liver disease.

Thrombocytopenia secondary to collagen vascular disease, disseminated intravascular coagulation, a number of drugs, or a primary immunologic disorder often appears with oral hemorrhagic bullae in the mucous membrane and petechiae. Occasionally it is a harbinger of systemic disease (James et al, 1984).

Agranulocytosis can be produced by a number of immunologic diseases and drugs (including chemotherapeutic agents); it produces the syndrome of agranulocytic angina, which has been described in the section discussing effects of chemotherapy and radiation. Agranulocytosis may also appear as oral necrotic and ulcerative lesions. A necrotizing gingivitis produced by the fusospirochetal organisms of Vincent's angina may also be seen.

Hemophilia is a congenital disorder in the production of worthy factor VIII molecules. Factor VIII is important in the intrinsic phase of blood coagulation. Its deficiency is characterized by bleeding from multiple sites, frequently manifested in the mouth as well as in joints and skin.

The most common hereditary coagulation abnormality is von Willebrand's disease. It is dominantly inherited. The diagnosis is established by finding a prolonged bleeding time, a low level of factor VIII procoagulant activity, and abnormally low levels of factor VIII - von Willebrand protein by immunologic assay and diminished platelet aggregation in response to ristocetin. The clinical bleeding symptoms of this disorder are notoriously heterogeneous and may range from virtually no symptoms to a disease resembling factor VIII deficiency. If the history suggests von Willebrand's disease and surgery is contemplated, hematologic consultation should be obtained and the patient's blood typed. Certain types of von Willebrand's disease will respond to DDAVP (arginine vasopressin) and obviate the need for blood component therapy. DDAVP is *contraindicated* in other types of von Willebrand's disease.

Mention should be made of two qualitative defects in granulocytes that are associated with oral manifestations. The first of these is chronic granulomatous disease, an inherited metabolic defect in the oxidative killing of organisms by normal-appearing granulocytes having the ability to phagocytize but not to kill. These patients are afflicted with recurrent bacterial infections with chronic suppurative cervical lymphadenitis; they can present with recurrent aphthous-like ulcers in the mouth. Recent research has shown that recombinant gamma interferon is strikingly effective in treating this entity.

The second disorder is Chédiak-Higashi disease, which is an inherited disease of the lysosomal membrane of granulocytes, characterized by large blue lysosomal particles in white cells demonstrated with Wright's stain. Partial cutaneous albinism and defects in platelet and coagulation function are other features. Patients with this disease also suffer from recurrent bacterial infections and can present with periodontal disease and mouth ulcerations. They also may develop non-Hodgkin's lymphoma if they survive the recurrent infections.

Collagen vascular diseases

The collagen vascular diseases are intimately associated with a number of oral manifestations; the best review of the subject is by Campbell et al (1983). The first disoder is Sjögren's syndrome. Sjögren's syndrome has been a source of controversy and misunderstanding in the literature for years. In reality it is a symptom complex consisting of keratoconjunctivities with xerostomia and arthritis. The triad alone established the diagnosis of Sjögren's (or sicca) syndrome. The sicca syndrome is sometimes associated with lacrimal, parotid, and submandibular gland enlargement caused by benign lymphocytic involvement; it is then referred to as Mikulicz's disease. These patients complain of dry eyes, salivary insufficiency, atrophy, and fissures and ulcers of the tongue, buccal membranes, and lips, particularly at the corners of the mouth. An increased incidence of caries is often seen. A large number of patients with the sicca syndrome have antibodies reactive with nuclear antigens SS-B and SS-A. They frequently display polyclonal hypergammaglobulinemia on serum-protein electrophoresis. Labial biopsy specimens show an intense infiltration of lymphocytes and destruction of most of the acinar tissue along with islands of epimyoepithelial cells.

Sjögren's syndrome can be divided into two clinical groups. If Sjögren's syndrome is not associated with another known autoimmune diorder, it is called primary Sjögren's syndrome. A minority of these patients develop collagen vascular disease during the follow-up period. If Sjögren's syndrome is associated with other autoimmune diseases - particularly lupus, rheumatoid arthritis, scleroderma, and occasionally dermatomyositis - it is called secondary Sjögren's syndrome. Causes of xerostomia are listed as follows:

1. Acute or chronic renal failure

2. Radiation

3. Chemotherapy

4. Sjögren's syndrome, primary and secondary

5. Mikulicz's disease

6. Sarcoidosis

7. Lymphoma

8. Drugs with anticholinergic properties

9. Opiate derivatives

10. Graft-versus-host disease.

Systemic lupus erythematosus (SLE) is an inflammatory condition of small blood vessels that predominantly affects women and is associated with a variety of pronounced autoimmune phenomena, producing a wide spectrum of symptomatology, including skin ulcers and rashes, arthritis, inflammation of serosal surfaces, and involvement of the kidney, heart, lung, and brain. Of patients with SLE, 25% have associated oral lesions, which are usually superficial ulcers with surrounding erythema. Direct and indirect immunofluorescence of these lesions shows granular staining of the basement membrane of the dermal-epidermal junction with immunoglobulins and complement. This is similar to what is seen in the skin lesions. If a patient with lupus develops immunologic thrombocytopenia, the mouth may display petechiae and the characteristic hemorrhagic bullae of immunologic thrombocytopenia. Chronic discoid lupus, which is confined to the skin and mucous membranes and rarely progresses to SLE, can present as ulcerative, vesicular, and white keratotic lesions of the tongue and oral mucosa and as the sicca syndrome.

Scleroderma is frequently associated with Sjögren's syndrome. It is a disorder of unknown etiology, characterized by arthritis, calcinosis cutis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia. Fibrosis may involve the entire gastrointestinal tract, leading to malabsorption; it can also produce cardiorespiratory symptoms caused by fibrosis of the lung and heart. One of the most frequent manifestations is Raynaud's phenomenon, particularly of the upper extremities on exposure to cold. Nielsen et al (1984) described Raynaud's phenomenon of the tongue, which is associated with peripheral Raynaud's phenomenon and appears as a white tongue associated with dysarthria. Scleroderma victims frequently display a marked inability to open the mouth, the so-called purse-string contractures secondary to fibrosis. Immobility of the tongue and disorders in deglutition have been described frequently, as have abnormalities of the periodontal membrane with gingivitis (Alexandridis and White, 1984; Eversole et al, 1984).

Polyarteritis nodosa is a disease of middle-aged men associated with inflammatory skip lesions in the medium-sized arteries. It is characterized by chronic skin ulcerations and frequent involvement of the kidney and nerve roots without involvement of the lung; few immunologic markers exist in the blood. Ulcerations of a vasculitic nature can be found in the buccal mucosa and soft palate, which on biopsy show a characteristic inflammatory reaction around the adventitia and the media of blood vessels.

Takayasu's, or pulseless, disease predominates in young females with granulomatous involvement of the aortic arch. It can present as difficulty i swallowing and ischemic pain of

the mouth during talking and swallowing.

Dermatomyositis-polymyositis is an immunologic disease of muscle usually characterized by the absence of a rash or periungual erythema in adults (but with proximal muscle weakness, elevated creatine phosphokinase levels, and myopathic EMGs) and by interstitial fibrosis of the lung. It can also present as secondary Sjögren's syndrome. The muscle involvement may involve the tongue and upper portion of the esophagus, with difficulties in phonation and deglutition. Stomatitis is not uncommon, and aspiration pneumonia is frequent.

Rheumatoid arthritis usually does not involve the oral cavity except for in Sjögren's syndrome, unless the disease evolves into an uncommon subvariant called rheumatoid vasculitis. In that situation, mouth ulcers similar to those in polyarteritis nodosa may be seen. Occasionally arthritis of the temporomandibular joint may intefere with mouth opening.

Diseases of Uncertain Etiology

Granulomatous diseases

Sarcoidosis, or Mortimer's malady, is a systemic granulomatous disease of unclear cause that predominantly affects blacks. It is characterized by the presence of noncaseating granulomas virtually throughout the body but with frequent involvement in the skin, lymph nodes, lung, and liver. It usually pursues a benign, insidious course, but it can have considerable clinical activity and resemble other granulomatous diseases, such as infectious granuloma. Wegener's granulomatosis, lethal midline granuloma, or even lymphoma. Occasionally sarcoidosis appears with masses on the tongue, lips, mandible, and maxilla. A biopsy demonstrates characteristic noncaseating granulomas. The diagnosis can be confused not only with Wegener's granulomatosis and lethal midline granuloma but also with infectious granulomatous diseases, such as histoplasmosis and blastomycosis.

A peculiar symtom-complex syndrome in sarcoidosis is Heerfordt's disease (or uveoparotid fever), which is characterized by the acute onset of uveitis, iritis, parotid enlargement, and fever; it is associated with Bell's palsy, and frequently Sjögren's syndrome occurs. The course of this disease is decisively benign and usually resolves without specific treatment.

Wegener's granulomatosis is a rare disorder, histologically characterized by granulomatous inflammation and vasculitis. The destructive granulomatous inflammation most commonly involves the paranasal sinus mucosa, lungs, synovia, skin, and kidneys. This is usually a chronic progressive disease with no treatment, but cytotoxic agents, particularly cyclophosphamide, have greatly improved the prognosis. Recently the development of serum antineutrophil cytoplasmic antibodies (ANCAs) has added immeasurably to the early diagnosis of this syndrome.

Handlers et al (1985) reviewed 10 cases of Wegener's granulomatosis manifesting in the oral cavity. The most common early oral lesion is a hyperplastic gingiva, which is red to purple and has many petechiae (Plate 10, B). Tooth mobility, loss of teeth, and failure of the wound to heal are common manifestations. The disease may remain localized to the oral

cavity for unusually long periods of time before multiorgan involvement occurs. It is important to bear in mind that oral biopsy tissue may not exhibit the characteristic eature of granulomatous vasculitis seen elsewhere. Diagnostic histologic pattern consistently present include pseudoepitheliomatous hyperplasia, epithelial histiocytes, giant cells, and eosinophils. Failure to recognize these diagnostic and clinical features delayes diagnosis and treatment of this progressive disease.

Lethal midline granuloma is a very rare disease characterized by destructive granulomas, often leading to mutilation of the upper respiratory tract and the face. This disease resembles Wegener's granulomatosis, except that it does not involve the lungs, kidneys, or skin. Histologically, lethal midline granulomas display no vasculitis. Cultures for mycobacteria and fungi are negative. Untreated, the disease can lead to massive destruction and deformation of the face and upper respiratory tract. Early radiation therapy is the treatment of choice and requires early recognition. Lethal midline granuloma must be carefully separated from lymphomatoid granulomatosis and prognosis differ. Hematologic consultation is suggested.

Nongranulomatous diseases

Dermatitis herpetiformis is a dermatologic condition associated with malabsorption and characterized by a recurrent eruption of closely cropped vesicles with erythematous haloes, resembling herpes, on the skin of the extremities and buttocks; they do not form the characteristic dermatome pattern commonly seen in herpes. Occasionally the oral mucosa is involved, with erythematous macules and papules, purpura, and superficial erosions. These are all nonspecfic; direct immunofluorescence may demonstrate IgA in the basement membrane area of the bullous lesions.

Psoriasis is a little-understood dermatologic condition characterized by scaly, silver plaques on an erythematous base that produce bleeding when stripped off. Biopsy of these lesions shows parakeratosis, acanthosis, and intra-epithelial microabscesses. Rarely psoriasis appears in the mouth with white, crusted, hyperkeratotis lesions on the oropharynx; the surrounding buccal mucosa is usually brightly erythematous.

Behçet's syndrome is a strange condition of unknown cause that consists of recurrent oral and genital ulcers, arthritis, and inflammatory disease of the eyes and gastrointestinal tract. It has been observed that the skin, central nervous system, and coronary blood vessels may be involved. Often Behçet's syndrome appears as recurrent aphthous ulcers, which may also be found in the genital area and skin. Eye lesions consist of iritis, retinal vasculitis, optic neuritis, conjunctivitis, and keratitis. Involvement of the central nervous system with meningitis is a particularly distressing complication.

Inflammatory bowel disease, both regional enteritis (Crohn's disease) and ulcerative colitis, may present with recurrent aphthous ulcers, part of the extraintestinal manifestations of inflammatory bowel disease. With ulcerative colitis the aphthous ulcers are frequently associated with other mucous membrane involvement, iritis, arthritis, and erythema nodosum. Regional enteritis is a noncaseating granulomatous disease of the gastrointestinal tract from the mouth through the anus. Occasionally masses resembling granulomas can be seen in the mouth; a biopsy displays noncaseating granulomas. Ramsdell et al (1984) have described, in

addition to the aphthous ulcerations in regional enteritis, oral ulcerations that may be deep and extensive. Additional manifestation include thickened, edematous buccal mucosa, producing a cobblestone appearance similar to that found in the gut, swelling of the lips, and granulomatous cheilitis. Ulcerative colitis may also manifest pyostomatitis, which is a particularly distressing progressive necrotic and inflammatory involvement of the entire oral mucous membranes. Causes of aphthous ulcers are listed as follows:

1. Primary causes

2. B12 deficiency

3. Folate deficiency

4. Gluten-sensitive enteropathy

5. Chronic granulomatous disease

6. Behçet's syndrome

7. Inflammatory bowel disease.

Reiter's syndrome is a recurrent arthritis condition characterized by conjunctivitis, asymmetric oligoarticular arthritis, urethritis, circinate balanitis, and keratoderma blenorrhagia, particularly seen on the soles of the feet. Reiter's syndrome can follow *Yersinia* enterocolitic infections, or it can be seen in the absence of this infection. It is closely associated with the HLA-B-27 phenotype. Painless oral ulcers as well as gingival lesions with hemorrhagic crusts and exudates can be seen in this syndrome. In this situation it may be confused with disseminated gonococcemia or infectious enteroarthropathy most commonly seen with *Salmonella* or *Shigella* infections.

Kawasaki disease (mucocutaneous lymph node syndrome) is an acute multisystem illness that predominantly affects children but has been described in adults. It is characterized by a triphasic course. The initial phase of acute illness is marked by high fever, conjunctival injection, and oral changes producing a strawberry tongue and desquamative rash (Plate 11, A). The second phase begins with a decline in the acute findings and includes cardiac disease and joint manifestations. The third phase is usually asymptomatic (Soman et al, 1983).

Immunologic Diseases

Idiopathic polychondritis is a strange disease. The cartilage is felt to be the autoimmune target tissue because antibodies against chondroitin sulfate have been found in the blood. It is characterized by progressive destruction of the cartilage of the ears, nose, and upper respiratory tract. Arthritis and aortic insufficiency may occur. The patient may have extensive difficulty with breathing and talking, yet nothing will be seen on examination of the oral cavity.

Sex-linked recessive (Bruton's) agammaglobulinemia is a congenital defect in the production of all classes of serum immunoglobulins and is associated with atrophy of

lymphoid tissue of the mouth, soft palate, tonsils, and lips.

Chronic mucocutaneous candidiasis (1) is a recurrent disorder occasionally associated with idiopathic hypoparathyroidism and pernicious anemia, (2) probably has an autoimmune basis, and (3) is characterized by depressed cellular immunity and recurrent candidiasis in the mouth, esophagus, and skin. Treatment with fluconazole is very effective. The candidiasis rarely disseminates.

Some mucositis in bone marrow transplants is mediated by the graft-versus-host reaction or the treatment for same, which often includes methotrexate. Methotrexate stomatitis can be ameliorated in some cases with leucovorin mouthwash. Acute mucosal graft-versus-host reaction usually runs its course, whereas chronic graft-versus-host reactions can last for years and are characterized by erythematous atrophy of the mucosa as well as lichenoid changes in the mucosa. There is no known treatment for this problem. It is often symptomatic and resembles Sjögren's syndrome.

Graft-versus-host (GVH) disease is an acute and chronic disorder seen after bone marrow transplantation and blood transfusion presumably with immunocompetent lymphocytes in patients with severe combined immunodeficiency syndrome (Swiss agammaglobulinemia). Oral manifestations have recently been well described by Schubert et al (1982) and Barrett and Bilous (1984). They are very frequently seen after allogeneic bone marrow transplantations, may occur very early, and are characterized by painful mucosal atrophy, erythema, and licheniform lesions in the buccal and labial mucosa. Biopsy may show the pathologic findings described previously in the sicca syndrome. Other manifestations of GVH disease resemble scleroderma, primary biliary cirrhosis, rheumatoid arthritis, systemic lupus erythematosus, and lichen planus with erythematous skin lesions and later atrophy. These changes are not associated with congenital or acquired immunosuppression alone but must be caused by the injection of immunocompetent cells into an immunosuppressed patient.

The Wiskott-Aldrich syndrome is an X-linked recessive inherited disease characterized by eczema, chronic thrombocytopenia with purpura of the skin and oral mucous membranes, low IgM concentrations with later development of cellular immunodeficiency, and a propensity to develop infections. Non-Hodgkin's lymphoma develops later in the course.

Pemphigus vulgaris and pemphigus vegetans are serious bullous skin disorders that affect the oral cavity in about two thirds of cases (Pedersen and Klausen, 1984). In about half of the cases the mouth is initially affected, with later involvement of the skin. The immunology of this disease has been well described. On biopsy the lesions show bullae in the suprabasal layer of the epithelium. Direct immunofluorescence displays intracellular deposits of immunoglobulin in the affected area, and indirect immunofluorescence shows autoantibodies in the serum and bullae fluid against the epithelial intracellular substance. Many feel that this antibody is directly involved in the reaction against epithelial cellular material, with the release of proteolytic enzymes leading to bullae formation. This disease also involves all areas of the gastrointestinal tract and is a source of sepsis - the usual mode of death. Systemic steroids are the treatment of choice in pemphigus.

There are two pemphigoid diseases: bullous pemphigoid and benign mucous membrane pemphigoid. In the latter the lesions are virtually confined to the eye and oral cavity. Oral

lesions are seen in about one third of the cases with bullous pemphigoid. In these two diseases a biopsy displays subepithelial bullae, and direct immunofluorescence demonstrates autoantibodies against the basement membrane of the surface epithelia. Anti-basement membrane antibodies are detected in the serum and fluid of the lesions. It is felt that the lesions in bullous pemphigoid and benign mucous membrane pemphigoid are caused by an autoimmune reaction against the basement membrane of surface epithelial cells. The treatment of these diseases is much more satisfactory than that for pemphigus and can usually be controlled by intermittent systemic steroid therapy. A reaction similar to pemphigoid can be seen when penicillamine is used in the treatment of primary biliary cirrhosis or systemic rheumatoid vasculitis.

Erythema multiforme (Bean and Quezada, 1983) is a heterogeneous symptom complex characterized by pleomorphic skin lesions that are often symmetric. The most characteristic skin lesion is an iris, or target, lesion; this consists of concentric lines of erythema interspersed with normal skin, the center of which is usually a papule. This is frequently associated with a systemic symptomatology such as fever, malaise, and arthritis; when it involves the mucous membranes it is frequently called the Stevens-Johnson syndrome (Plate 11, B).

The etiology of this disease is multifactorial. It can be seen after streptococcal illness and infections such as herpes and mycoplasma. Penicillin and sulfa are the most common drugs implicated in its etiology. Occasionally patients with a splenectomy develop recurrent erythema multiforme, but it has an unknown cause in 50% of the patients.

Oral manifestations of erythema multiforme are frequently estimated at around 50% and consist of bullae, ulcerations, and hemorrhagic crusts, particularly around the lips. Histologically, oral lesions exhibit degenerative changes of the epithelium, with epithelial vacuolation of the basal layer and inflammation mostly with mononuclear cells. Associated with such changes are deposits of immunoglobulin and complement, which have been found in subepithelial vessels. Systemic steroids are indicated for very symptomatic cases.

Lichen planus (Pedersen and Klausen, 1984) is a dermatologic condition that affects the mucous membranes of the lips, tongue, and tonsils as the sole manifestation in one third of the cases, dual involvement of the mucous membranes and skin in another third, and the skin alone in another third. The mucous membrane lesions are asymptomatic papules that range in color from white to blue to gray and whose morphology may be reticular, linear, annular, or even plaquelike (Plate 12, A). Occasionally, bullous lesions are seen that seem to indicate mucous membrane pemphigoid. The skin lesions are violaceous papules on the extensor surface of the forearms and neck, which are chronic and heal with some atrophy. The pathogenesis of this disease is far from clear but is thought to be an immunologic disease because of reports of fibrin and complement deposition in the basement membrane zone with an infiltration of inflammatory cells just below the dermis. That this disease can be seen after bone marrow transplantation and in association with SLE supports this hypothesis. Findings indicate that a combined type IV (delayed) and III (antigen-antibody) hypersensitivity reaction takes place in the lesions in response to locally produced or released epidermal/mucosal antigens.

Urticaria is an eruption of common skin wheal, or hives, and is familiar to any layperson. When the edema extends into the deep portions of the dermis and the subcutaneous or submucosal tissues, it is called *angioedema.* In addition to the skin and mucous membranes, angioedema may involve the lung, gastrointestinal tract, and cardiovascular system. Angioedema frequently occurs in the mouth, tongue, uvula, and soft palate and may seriously impair breathing. It is classified as follows:

IgE-dependent activation of mast cells

Atopy
Specific antigen sensitivity (food, drugs)
Physical stimuli (cold)

Complement mediated

Hereditary and acquired C1 esterase inhibitor deficiency
Serum sickness
Hypersensitivity vasculitis
Reaction to blood products

Agents with direct action on mast cells

Radiation contrast media

Agent altering arachidonic acid pathways of inflamamtion

Aspirin.

Toxic and Drug Effects on Oral Cavity

Diphenylhydantoin (Dilantin), a drug used in the treatment of epilepsy and various types of neuralgia, is associated on prolonged use with occurrence of gingival hyperplasia of both the maxillary and mandibular areas. This is seen only at the sites of teeth formation and probably is related to less-than-adequate oral hygiene (Plate 12, B). Staining of the teeth during ingestion of tetracycline and fluoride during tooth development has already been described in the section on congenital lesions. Mercury, bismuth, lead, and arsenic can produce dark gray or black pigment at gingival margins; the latter two metals may also produce changes in the nails and deobfuscate obscure hematologic, gastrointestinal, or neurologic illness. Iodides and bromides may produce idiosyncratic granulomas in the oral cavity. There are a variety of drugs that have anticholinergic activity; some are listed as follows:

1. Atropine

2. Dicyclomine (Bentyl)

3. Propantheline (Pro-Banthine)

4. Antiarrhythmics

5. Phenothiazine tranquilizers

6. Tricyclic antidepressants

7. Antiparkinsonian drugs.

These are predominantly antiarrhythmic drugs, tricyclic antidepressants, and anticholinergic drugs, and they are used in a variety of gastrointestinal disturbances. They produce mouth and eye dryness and can be treated locally with 0.25% ophthalmic pilocarpine, which stimulates the minor salivary glands. The most common allergic reaction to drugs in the oral mucosa is the vesicular bullous reaction, which was discussed in the section on erythema multiforme.

Botulism, a toxic disease produced by ingestion of the toxin of *Clostridium botulinum*, makes acetylcholine transmission at the neuromuscular junction difficult. The first signs of this disease - besides difficulty with eyesight and dilated, fixed pupils - may be dry mouth, inability to swallow, and poor phonation caused by involvement of the bulbar musculature.

Neurologic Disorders

Parkinson's disease and Shy-Drager syndrome (idiopathic orthostatic hypotension) are currently thought to be similar if not the same disease. Besides having extrapyramidal symptoms, both are associated with idiopathic atrophy of the autonomic nervous system, which produces hypohydrosis, orthostatic hypotension without compensatory tachycardia, and dry mouth and eyes. The tremor of parkinsonism can involve the lips and tongue. Bradykinesis may affect the masticatory muscles. Esophageal motility disturbances may affect deglutition and frequently lead to aspiration pneumonia.

Myasthenia gravis is an autoimmune disease with antibodies directed against the actylcholine receptors of the neuromuscular junction. It may present with difficult swallowing and phonation, with resultant muscular atrophy. The recent development of clinically available serum acetylcholine receptor antibodies has greatly facilitated the early diagnosis of this condition. Similarly, amyotrophic lateral sclerosis, a degeneration of the pyramidal tract involving the bulbar motor neurons, may produce difficulty with deglutition, mastication, and phonation. Fasciculations of the tongue with later atrophy are characteristic.

Syringobulbia is a developmental cavitary defect in the cervical spine cord, often extending into the medulla. It is manifested by weakness of the tongue, palatal paralysis, and unilateral vocal cord involvement.

Wallenberg's lateral medullary plate syndrome is produced by thrombosis of the posterior inferior cerebellar artery. Dysphagia and palatal paralysis are seen and are caused by involvement of the glossopharyngeal and vagus nerves. Involvement of the solitary tract produces a loss of taste.

Bell's palsy (unilateral facial nerve paralysis) may be idiopathic or postviral; it may be associated with diabetes mellitus, sarcoidosis, non-Hodgkin's lymphoma, or leptomeningeal carcinomatosis. It appears as a peripheral facial paralysis with disorders in phonation and mastication. If the chorda tympani nerve is involved, taste on the anterior two thirds of the tongue is lost.

Multiple sclerosis (MS) is an idiopathic demyelinating disorder characterized by optic neuritis, nystagmus, ataxia, tremor, peripheral neuropathy, and transverse myelitis. Dysarthria ("scanning speech") secondary to cerebellar dysfunction is extremely common, as is difficult with breathing and swallowing.

Myotonic dystrophy is an autosomally dominant disease characterized by distal myotonia (difficulty in muscular relaxation). It is frequently associated with ocular and oropharyngeal muscle involvement, producing facial weakness, dysarthria, and difficulties with phonation and mastication. Cataracts, hypogonadism, baldness, atrophy of the sternocleidomastoid muscles, and cardiac disease are common accompaniments.

A variant of the pickwickian syndrome, sometimes called the Alfred Hitchcock syndrome, is idiopathic alveolar hyperventilation. It is seen in patients who are moderately obese (Burock, 1984). This syndrome is associated with sleep apnea changes on the electroencephalogram, idiopathic alveolar hypoventilation with chronic PCO_2 retention, snoring, and a history of sleep apnea and daytime sleepiness. These patients may have headaches, secondary polycythemia, and often digital clubbing and pulmonary hypertension. They frequently exhibit cardiac arrhythmias and syncope. The site of upper airway obstruction is in the oropharynx and the velopharyngeal sphincter. If the patients do not respond to progesterone, tricyclic antidepressants, and aminophylline, an otolaryngology consultation is frequently obtained, since removal of excess adenoids and tonsils and a uvulopalatopharyngoplasty is often helpful. A tracheostomy is sometimes indicated. The diagnosis of sleep apnea - idiopathic hypoventilation syndromes has become so complex that initial consultation with a neurologist specializing in sleep disorders is recommended *before* therapeutic or surgical intervention in these conditions.

Deficiency States

Deficiency states in the USA are virtually limited to alcoholics, food faddists, and patients with malabsorption. Malabsorption produces deficiencies of vitamins A, D, E, and K, as well as calcium and folate. The oral manifestations of hypocalcemia are detailed in the section on acquired endocrine-metabolic diseases; and folate deficiencies are discussed in the hematology section. Common causes of malabsorption are listed as follows:

Maldigestion

1. Exocrine pancreatic insufficiency

2. Biliary tract disorders

3. Bacterial overgrowth with deconjugation of bile salts

a. Blind loops

b. Jejunal diverticulae

c. Scleroderma and intestinal motility disorders

Malabsorption

1. Congenital

a. Hartnup disease

b. Abetalipoproteinemia

2. Gluten-sensitive enteropathy (celiac disease)

3. Whipple's disease

4. Amyloidosis

5. Crohn's disease

6. Tropical sprue

7. Non-Hodgkin's lymphoma

8. Agammaglobulinemia (usually with *Giardia lamblia* infestation).

A deficiency of vitamin K leads to a deficient assembly of worthy procoagulants of the prothrombin complex (factors II, VII, IX, and X), leading to a hemorrhagic diathesis that often presents with oral hemorrhagic bullae. This may also be produced with warfarin (Coumadin) anticoagulation.

Besides the oral manifestations produced by the lack of vitamin B12 and folate (mentioned in the section on hematology), these two deficiencies may produce recurrent aphthous ulcers. Recurrent aphthous ulcers can also be seen in gluten sensitivity with malabsorption (celiac disease).

Vitamin A deficiency produces nyctalopia and dyskeratotic changes of the skin and mucous membranes as well as angular cheilitis and defects in the dentin and enamel of developing teeth. A biopsy reveals pseudoepitheliomatous hyperplasia and even carcinoma in situ. These problems revert with the administration of vitamin A.

Vitamin B2 (or riboflavin) deficiency is associated with angular cheilitis as well as burning pain in the lips, mouth, and tongue. Later changes include atrophy of the mucous membranes of the mouth. Scurvy, or vitamin C deficiency, is associated with perifollicular hemorrhages and petechiae in the mouth caused by vascular integrity compromise, gingival hyperplasia, and stomatitis.

Pellagra, an acquired disorder caused by dietary niacin (nicotinic acid or nicotinamide) deficiency, is associated with hyperkeratotic dermatitis (a bronze rash), diarrhea, and dementia. It can also present with oral mucous membrane atrophy and painful erythematous, edematous angular cheilitis. Deficiencies of vitamins B and C, niacin, and folate frequently occur concomitantly.

A peculiar disease named acrodermatitis enteropathica is characterized by psoriaform lesions, especially about the mouth, candidiasis of the oral cavity, and diarrhea. It is caused by a zinc deficiency (often caused by a congenital deficiency in zinc ligand, a prostaglanding necessary for its absorption). Secondary causes include prolonged hyperalimentation with zinc supplementation. Symptoms can be completely reversed with zinc supplementation.