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DEPARTMENT OF THERAPEUTIC STOMATOLOGY

Pathology of Oral Mucosa
(Lectures for the 5th year students)
Part II

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The manual is compiled in accordance with the curriculum in dentistry (Poltava, 1999) aimed at helping students in thier independent work.

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LECTURE 1

CHANGES OF ORAL MUCOSA IN ALLERGIES AND IMMUNOLOGIC DISEASES. IMMUNE-MEDIATED DISEASES.

Immune mechanisms are usually protective responses by the host to the presence of foreign substances such as bacteria and viruses. They may at the same time cause local tissue destruction by triggering several types of overreac-tion or hypersensitivity. Tissue damage (immunopathologic change) may occur in a sensitized host with subsequent exposure to the sensitizing antigen. Four types of hypersensitivity reactions have been described: I, II, III, and IV. Type I, II, and III reactions are humoral and are termed *immediate reactions* because they occur in minutes to hours. Type IV reactions are cellular or cell mediated and are termed *delayed reactions* because they occur within days.

Three of these hypersensitivity reactions are of potential importance in periodontal disease. They are anaphylaxis, or immediate hypersensitivity (type I), cytotoxic reactions (type II), and immune complex, or Arthus, reactions (type III). In addition, reactions to transfused blood are involved in immediate hypersensitivity reactions.

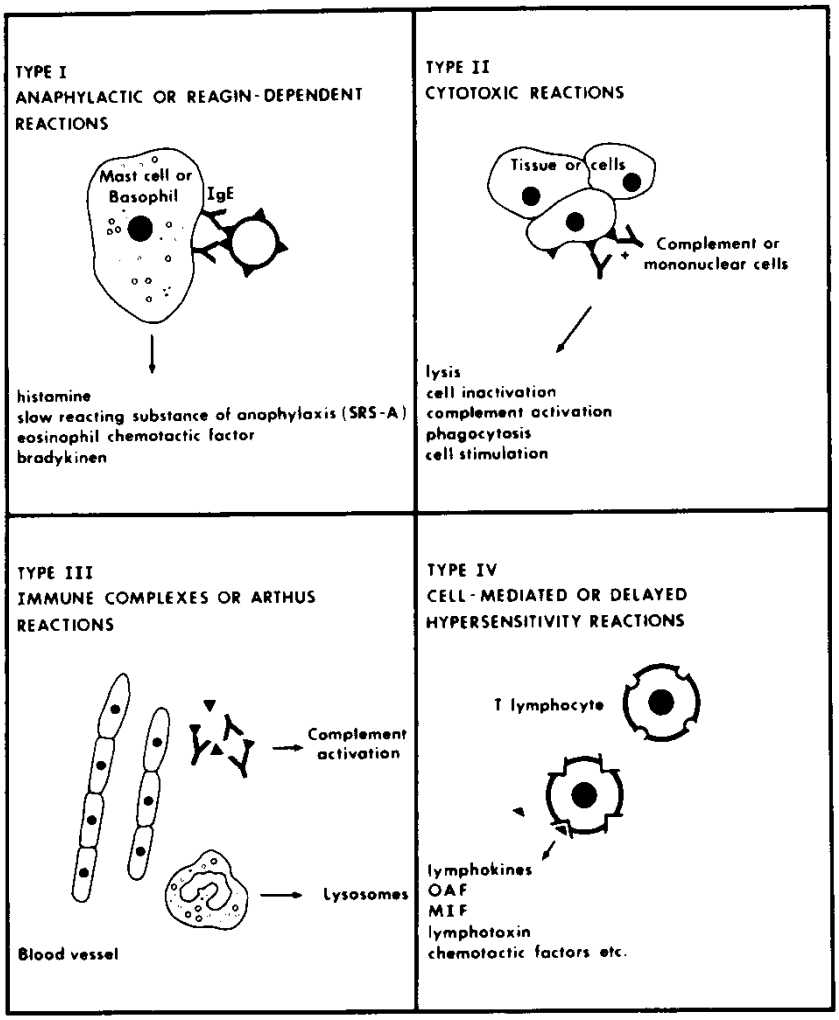
Anaphylaxis (Type I)

Two variations in anaphylactic hypersensitivity occur, depending on the route of administration of the antigen. If the antigen is injected locally into the skin, the reaction is called *cutaneous anaphylaxis.* If the antigen is injected intravenously, it is called *systemic* or *generalised anaphylaxis.* The basic mechanisms in both types of immediate hypersensitivity are the same.

Although both IgE and IgG antibodies are involved in anaphylaxis, only IgE plays a direct role in its pathogenesis through its ability to sensitize the skin. This sensitizing capability is referred to as *reaginic* and the IgE antibody as *reagin.* IgG antibody combines with antigen in the circulation before it can bind to IgE in mast cells or basophils and prevents sensitization. These IgG antibodies are referred to as *blocking antibodies.* Several major features distinguish these blocking antibodies from reaginic or sensitizing antibodies.

IgE antibodies involved in anaphylactic reactions attach strongly at the Fc portion of the antibody to receptors found on mast cells and basophilic leukocytes, primarily in the skin and other connective tissues such as the gingiva. Experimentally, this binding lasts for several days. These sensitizing IgE antibodies are called *homocytotropic antibodies* because they normally bind in vivo to specific host cells, in this case both mast cells and basophilic leukocytes. In contrast, IgG-blocking antibodies bind only transiently to mast cells of other phylogenetically distinct species and are termed *heterocytotropic antibodies.* Experimentally, this binding usually lasts for only a few hours. An important component in anaphylactic hypersensitivity is that IgE antibodies normally do not fix (activate) complement.

Because plasma cells are known to produce im-munoglobulins, the finding of IgE-containing cells in peri-odontal, bronchial, and other tissues is thought to represent localized synthesis of IgE antibodies.[28] These IgE-containing cells are found primarily in the respiratory and gas-trointestinal mucosa and in regional lymph nodes. It has been suggested that IgE formed locally in tissue may then participate in local disease processes.



Immunologic mechanisms of tissue damage. The four types of hypersensitivity reactions described by Gell and Coombs and depicted by Nisengard.

Mechanisms of Anaphylactic Hypersensitivity. Ana-phylaxis occurs when two IgE antibodies that are fixed to a mast cell or basophil react with the sensitizing antigen through the Fab portion of the antibodies. This antibody-antigen reaction causes the release of pharmacologically active substances from the sensitized cells. These substances cause the response and have the potential to induce tissue damage in periodontal disease.

Of the several active pharmacologic substances released during anaphylaxis, histamine pre-exists in the cells and is promptly released by antibody-antigen complexes. Other pharmacologically active substances, such as the kinins and SRS-A, are produced only *after* the antigen-antibody complexes are formed. An α_2-macroglobulin that blocks the normally found inhibitor for collagenase is also released from challenged sensitized cells, as are prostaglandins and an eosinophil chemotactic factor.

Histamine has been the most extensively studied chemical mediator of immediate hypersensitivity. As mentioned in preceding discussion, it is widely found in mammalian tissues. Mast cells, platelets, and basophilic leukocytes contain this substance. Histamine levels in chronically inflamed gingiva are significantly higher than those in normal gin-giva. Some pharmacologic actions of histamine include increased capillary permeability, smooth muscle contraction, stimulation of the exocrine glands, and increased venule dilation and permeability. The biologic effects of histamine can be blocked with antihistamine drugs, but no apparent change in the course of periodontal disease has been demonstrated with these drugs.

Slow-reacting substances of anaphylaxis are acidic lipids that cause a sustained slow contraction of guinea pig ileum. This contraction is not inhibited by antihistamines and occurs even when histamine has been added to the point at which it can no longer cause ileum contraction. In addition to causing contraction of smooth muscle, SRS-A has some permeability-enhancing activity.

Bradykinin, a peptide formed by the enzymatic action of kallikrein on an α_2-globulin of plasma, has a number of pharmacologic activities and is considered a major pharmacologic mediator of anaphylactic hypersensitivity. These biologic activities include smooth muscle contraction, va-sodilation, increased capillary permeability, migration of leukocytes, and the stimulation of pain fibers. The action of bradykinin is not inhibited by antihistamine drugs.

Pharmacologically active mediators released by human mast cells

Mediator	**Pharmacologic Action**
Histamine	Increased capillary permeability
	Smooth muscle contraction
	Stimulation of exocrine glands
	Dilation and increased venule permeability
	Skin response: wheal and erythema
	Bone resorption?
SRS-A	Smooth muscle contraction
	Increased vascular permeability
Bradykinin	Smooth muscle contraction
	Vasodilation
	Increased capillary permeability
	Migration of leukocytes
	Stimulation of pain fibers
α_2-Macroglobulin	*Collagenase activation*

Cytotoxic Reactions (Type II)

In cytotoxic (type II) reactions, antibodies react directly with antigens tightly bound to cells. These antigens may be natural surface components of the cell, such as the cell membrane polysaccharide antigens of red blood cells. A cytotoxic reaction involving these cells may result in hemolysis. Cytotoxic antibodies may also react with antigens associated with tissue cells. These cell-associated antigens include normal cell surface antigens or those derived from bacteria, drugs, or altered tissue components.

Cytotoxic antibodies are of the IgG or the IgM class. These antibodies have the ability to fix complement, although complement fixation is not required for all types of cytotoxic antibody reactions. In addition to inducing cell lysis, cytotoxic antibodies may cause tissue damage by increasing the synthesis and release of lysosomal enzymes by cells (PMNs) coated with antigen. The tissues in the vicinity of these enzymes may then be damaged. Hemolytic transfusion reactions, hemolytic disease of the newborn, and autoallergic hemolytic anemia are examples of cytotoxic reactions induced by these antibody-antigen reactions. Cytotoxic reactions are seen in autoimmune disease in which antibodies react with a patient's own tissue components. This occurs, for example, in pemphigus, in which antibodies react with cell membranes, and in pemphigoid, in which antibodies react with the epithelial basement membrane. To date no evidence suggests an important role for cytotoxic reactions in gingivitis and periodontitis.

Immune Complex (Arthus) Reactions (Type III)

When high levels of antigen to which the host has been sensitized are present and persist without being eliminated, antigen-antibody (IgG and IgM) complexes precipitate in and around small blood vessels and, with subsequent complement activation, cause tissue damage at the site of the local reaction. Inflammation, hemorrhage, and necrosis may occur. Tissue damage appears to be due to the release of lysosomal enzymes from PMNs, mast cell activation, platelet agglutination, microthrombi formation, and neutrophil chemotaxis. This reaction is referred to as an *immune complex*, or *Arthus, reaction* and is usually mediated by IgM or IgG antibodies. These antibodies have the ability to fix complement, which is partially responsible for the chemotactic attraction of the PMNs crucial to the Arthus reaction.

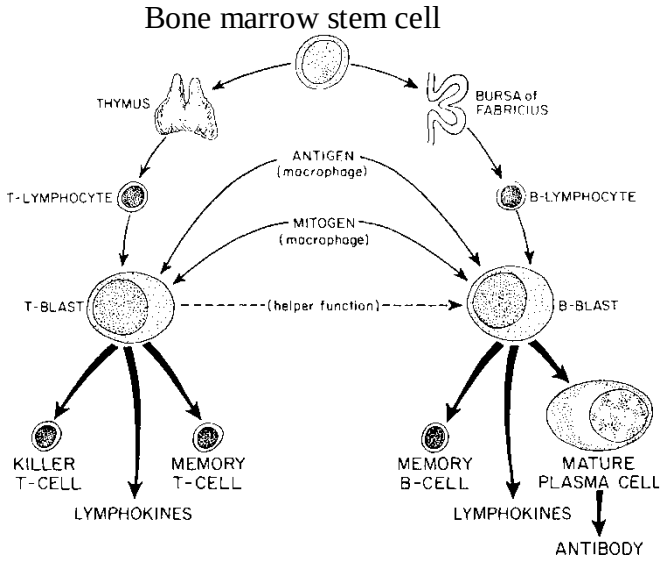
Cell-Mediated Immunity or Delayed Hypersensitivity (Type IV)

The phenomenon of delayed hypersensitivity belongs to the class of immune responses known as *cell-mediated immunity*. These reactions are referred to as *type IV*.

Cellular immunity does not involve circulating antibodies but is based on the interaction of antigens with the surface of T lymphocytes. There are actually two populations of lymphocytes. Lymphocytes that can develop into plasma cells that produce antibodies are designated as B cells because they were found to proliferate in the bursa of Fabricius in birds and the bone marrow of mammals. These cells circulate from the blood or the thoracic duct to the lymphatic tissues, the cortical germinal centers of lymph nodes, and the red pulp of the spleen, where they differentiate into plasma cells. These differentiated cells can then produce antibodies. B lymphocytes have been shown to produce biologically active lymphokines (see following discussion).

In contrast, the T cells migrate from the bone marrow to the thymus, where they divide and become immunocompetent. From the thymus they migrate to the peri-cortical areas of lymph nodes and the white pulp of the spleen. The relationship between T and B lymphocytes and cellular and humoral immunity is complex, with frequent interactions between B and T cells.

T lymphocytes or B lymphocytes sensitized to an immunizing antigen can be stimulated to undergo blastogenesis or transformation in vitro and presumably in vivo. This consists of morphologic enlargement and synthesis of proteins, RNA, and DNA and results, ultimately, in mitotic di vision. This increases the number of immunocompetent lymphoid cells that are specific for a particular antigen. Some oral bacteria, including *Actinomyces* and some strains of *Streptococcus*, produce extracellular substances that inhibit blast transformation of normal peripheral lymphocytes. Similar substances from some bacteria also inhibit fibroblast growth.



Schematic diagram illustrating the derivation and response of B and T lymphocytes. Antigen- and mitogen-induced responses result from the presence of macrophages.

Anaphylactic hypersensitivity.

Two variations in anaphylactic hypersensitivity occur depending on the route of administration of antigen. If the antigen is injected locally into the skin, the reaction is called cutaneous anaphylaxis. If the antigen is injected intravenously, it is called systemic or generalized anaphylaxis. The basic mechanisms in both types of immediate hypersensitivity are the same.

Angioneurotic oedema, oedema angioneuroticum Quincke. Acute disease characterized by the swelling of the subcutaneous tissue usually affecting the lips, mouth, eyes and genitalia. The name is misleading since the nerves and vessels are not involved. A rapid appearance of erythematous weals around the mouth should be regarded as a medical emergency; in this situation the patient should be monitored carefully for any signs of **respiratory obstruction.** The causes are multifactorial as in other

urticarias. The hereditary variety is an autosomal dominant disorder and is characterized by life-threatening laryngeal oedema and acute abdominal pains caused by oedema of the bowel wall. During the acute episodes, the facial features are grossly distorted and there is usually no itching.

Urticaria is an intensely *itchy* condition with swelling of the dermis that raises the epidermis into weals. Acute rashes are often IgE-dependent in patients with an atopic background. In chronic cases the aetiology is mostly unknown. There are special varieties of **cold, solar** and **cholinergic urticaria** induced by cold, sunshine (action spectra 290-500 nm) and excessive sweating, respectively.

Treatment
Antihistamine medications:
dimedrolum 0,05g 1 tablet twice a day or 1%solution 1ml as intramuscular injection;
diprazinum 0,025g 1 tablet twice a day or 2,5%solution 1ml as intramuscular injection;
suprastinum 0,025g 1 tablet twice a day or 2%solution 1ml as intramuscular injection;
ketotifenum 0,001g 1 tablet twice a day ;
All of the above-mentioned medications have a somnolent effect, can not be prescribed to drivers.
Diazolinum 0,05-0,1g 1 tablet twice a day, has not a somnolent effect.
Acidum ascorbinicum (vitamin C) 0,05g two tablets twice a day, rutinum 0,02-0,05g two tablets twice a day or syrup from Rosae fruits to lower small vessels permeability.
In the signs of respiratory obstruction intramuscular injection of prednisolonhemisuccinattis 25mg is recommended, patient has to be hospitalized.

Anaphylactic shock.

Anaphylactic shock is a reaction of the immediate hypersensitivity. It can occur in the previously sensitized organism. The role of the antigen can play every of the medications that contacts the organism with any way, for example anesthetic taken orally or injected or applied on the skin or oral mucous or taken as aerosoleum.

Patient complaints are usually as follows: weakness, headache, acute pain in the chest, abdominal pain. In heavy stages of the shock patient can lose consciousness. Oedema and bronchoobstruction are one of the most serious manifestations of the anaphylactic shock. Patient is anxious, has a skin rash. Blood pressure is lowered from 90/50 mm Hg (in light cases of the anaphylactic shock) to 50/10 mm Hg (in heavy forms of the disease).

Forms of the anaphylactic shock.

Very quick (lightning) form. It starts in 1-2sec after the contact with allergen. Patient looses consciousness, has convulsions and pupils do not reflect to the light. In 8-10 minutes the patient can die.

Heavy form of the anaphylactic shock begins in 5-7 minutes after the contact with allergen. Heart failure, cerebral oedema, acute insufficiency of the kidneys, hemorrhages into the organs of vital importance (cerebrum, adrenal glands) are the main reasons of mortality in the anaphylactic shock.

Moderate form of the anaphylactic shock takes place in 30 minutes after the contact with allergen. Patients complaints are weakness, headache, fingers and toes become dumb, breathing is difficult. This condition lasts from 15-20 minutes to an hour or more.

In all three cases mentioned above after being rendered first aid patient needs hospitalization.

In light cases of the anaphylactic shock patient complaints in weakness, headache, feeling creepy all over or in hands and feet. But patients condition in this case is normalized in 10-20 minutes. Patient has to be strongly recommended to contact therapeutist or allergologist in the nearest future.

The anaphylactic shock can proceed in different variations:

1. Cardiogenic;
2. Bronchospasmatic with bronchoobstruction, larynx oedema and spasm;
3. Cerebral form with convulsions and unconsciousness;
4. Abdominal form with acute abdominal pain.

Scheme of emergency actions in the anaphylactic shock.

Stop the contact with the allergen. Wash oral cavity with water, aspirate with the syringe the allergen solution, infiltrate the skin around the place of injection with 0,1% solution of adrenalinum.

Simultaneously:

adrenalinum 0,3-0,5 mg percutaneous;

gluco-corticoids (hydroccortison hemisuccinas 25-100mg or prednizolon hemisuccinas 30-100mg or dexametazoni 4-20mg) intravenously or in the base of the tongue.

In the case of bronchospasm: euphillini 5-10 ml of the 2,4% solution in 10-20ml of 5% glucose solution intravenously or 1-1,5 ml of the 24% solution intramuscular. In heavy cases patient has to be intubated.

In the case of convulsions 10-20 mg (2-4 ml of 0,5%) seduxeni intramuscular, in heavy cases 10-30 mg of the medication intravenously.

DISEASES OF THE ORAL MUCOSA: NON-INFECTIVE STOMATITIS

RECURRENT APHTHAE (APHTHOUS STOMATITIS)

Recurrent aphthae constitute the most common oral mucosal disease and affect 10-25% of the population, but many cases are mild and accepted without complaint.

Aetiology

The main factors thought to contribute are shown in Table.

Possible aetiological factors for recurrent aphthae

- Genetic predisposition
- Exaggerated response to trauma
- Infections
- Immunological abnormalities
- Gastrointestinal disorders
- Haematological deficiencies
- Hormonal disturbances
- Stress

Genetic factors. There is some evidence for a genetic predisposition. The family history is sometimes positive and the disease appears to affect identical twins more frequently than non-identical. However, this probably applies to a minority. A variety of HLA associations have been reported but no one hap-lotype seems to be consistently associated. In the possibly related Behcet's disease (see below) the evidence for a genetic predisposition is much stronger.

Trauma. Some patients think that the ulcers result from trauma because the early symptoms simulate pricking of the mucosa by (for instance) a toothbrush bristle. Trauma may dictate the site of ulcers in patients who already have the disorder, but most aphthae are in relatively protected sites and the masticatory mucosa is generally spared.

Infections. There is no evidence that aphthae are directly due to any microbes, and there is scanty evidence that cross-reacting antigens from streptococci or L-forms play any significant role. The hypothesis that there may be defective immunoregulation caused by herpes or other viruses is unproven.

Immunological abnormalities. Since the aetiology of recurrent aphthae is unknown, there has been a facile tendency to label them as 'autoimmune'. A great variety of immunological abnormalities have been reported, but there have been almost as many contrary findings and no convincing theory of immunopathogenesis takes into account the clinical features. It is also possible that the immunological abnormalities are as much a consequence of the ulcers as the cause. Evidence of an association with atopic (IgE-mediated) disease is unconfirmed. Circulating antibodies to crude extracts of fetal oral mucosa have been reported, but their titre is unrelated to the severity of the disease and in many patients there are no significant changes in immunoglobulin levels. Antibody-dependent cyto-toxic mechanisms have been postulated but not convincingly demonstrated. The histological features of aphthae have also been invoked to support hypotheses that the disease is either an immune complex-mediated (type III) or a cell-mediated (type IV) reaction, according to taste. However, others have failed to confirm the presence of

circulating immune complexes, and in any case the significance of such complexes, which are sometimes detectable in the absence of disease, is notoriously difficult to interpret. Depressed circulating helper/suppressor T lymphocyte ratios have been reported but others have found no difference between active and remittant phases of the disorder. Recurrent aphthae also lack virtually all features of, and any association with, typical autoimmune diseases. They also fail to respond reliably to immunosuppressive drugs and may become more severe in the immune deficiency state induced by HIV infection.

Gastrointestinal disease. Aphthae were previously known as 'dyspeptic ulcers' but are only rarely associated with gas-trointestinal disease. Any association is usually because of a deficiency, particularly of vitamin B_{12} or folate secondary to malabsorption. An association with coeliac disease (sometimes asymptomatic) has been found in approximately 5% of patients with aphthae, but a secondary haematinic deficiency, particularly folate deficiency, is probably the cause.

Haematological deficiencies. Deficiencies of vitamin B_{12}, folate or iron have been reported in up to 20% of patients with aphthae. Such deficiencies are probably more frequent in patients whose aphthae start or worsen in middle age or later. In many such patients, the deficiency is latent, the haemoglobin is within normal limits, and the main sign is micro- or macrocyto-sis of the red cells. In patients who thus prove to be vitamin B_{12} or folate deficient, remedying the deficiency may bring rapid resolution of the ulcers.

Hormonal factors. In a few women, aphthae are associated with the stressful luteal phase of the menstrual cycle, but there is no strong evidence that hormone treatment is reliably effective.

'Stress'. Some patients relate exacerbations of ulceration to times of stress, and some studies have reported a correlation. However, stress is notoriously difficult to quantify, and a recent study has found no correlation.

In brief, therefore, the aetiology of recurrent aphthae is unclear. There is no evidence that they are a form of autoim-mune disease in any accepted sense, and it is uncertain whether many of the reported immunological abnormalities are cause or effect. However, in a minority of patients there is a clear association with haematological deficiencies. The latter in turn may be secondary to disease of the small intestine or other cause of malabsorption.

That speculation about the cause of recurrent aphthae has continued for at least half a century, the variety of current theories and the contradictory findings, indicate how little is known.

Clinical features

Typical features of recurrent aphthae

- Onset frequently in childhood but peak in adolescence or early adult life
- Attacks at variable but sometimes relatively regular intervals
- Most patients are otherwise healthy
- A few have haematological defects
- Most patients are non-smokers
- Usually self-limiting eventually

Females are not significantly more frequently affected than males. The frequency of ulceration typically reaches a peak in early adult life or a little later, then gradually wanes. Recurrent aphthae are rare in the elderly and particularly in the edentu-lous. However, older persons may be affected if a haematological deficiency develops. The great majority of patients are clerical, semiprofessional or professional workers and are total non-smokers. Occasionally, aphthae start when smoking is abandoned.

The usual history is of painful ulcers recurring at intervals of approximately 3-4 weeks. Occasionally they are continuously present. Unpredictable remissions of several months may be noted. Individual minor aphthae persist for 7-10 days, then heal without scarring.

Aphthae typically affect only the non-keratinised mucosa, such as the buccal mucosa, suici or lateral borders of the tongue, but major aphthae can affect the masticatory mucosa. Ulcers are of three clinically distinguishable types.

The pain of major aphthae can interfere with eating. Moreover, major aphthae are sometimes a feature of AIDS and add to such patients' burdens.

Pathology

There is alleged to be initial lymphocytic infiltration followed by destruction of the epithelium and infiltration of the tissues by neutrophils. Mononuclear cells may also surround blood vessels (perivascular cuffing). These changes are said to be consistent with either type III or IV reactions, but true vasculitis is not seen. Overall the appearances are non-specific.

Biopsy is of no value in the diagnosis except to exclude carcinoma in the case of major aphthae. Aphthae are not preceded by vesiculation and smears will distinguish herpetiform aphthae from herpetic ulceration.

Types of recurrent aphthae

• *Minor aphthae*

The mostcommon type

Non-keratinised mucosa affected

Ulcers are shallow, rounded, 5-7 mm across, with an erythematous margin and yellowish floor

One or several ulcers may be present

• *Major aphthae*

Uncommon

Ulcers frequently several centimetres across

Sometimes mimic a malignant ulcer

Ulcers persist for several months

Masticatory mucosa such as the dorsum of the tongue or occasionally the gingivae may be involved

Scarring may follow healing

• *Herpcti/bmi aphthae*

Uncommon

Non-keratinised mucosa affected

Ulcers are 1-2 mm across

Dozens or hundreds may be present

May coalesce to form irregular ulcers

Widespread bdght erythema round the ulcers

Diagnosis and management

The most important diagnostic feature is the history of recurrences of self-healing ulcers at fairly regular intervals. The only other condition with this history is Behcet's disease. Often, increasing frequency of ulcers brings the patient to seek treatment. Otherwise most patients appear well, but haematological investigation is particularly important in older patients. Routine blood indices are informative, and usually the most important finding is an abnormal mean corpuscular volume (MCV). If macro- or microcytosis is present, further investigation is necessary to find and remedy the cause. Treatment of vitamin B_{12} deficiency or folate deficiency is sometimes sufficient to control or abolish aphthae.

Apart from the minority with underlying systemic disease, treatment is empirical and palliative only. Despite numerous clinical trials, no medication gives completely reliable relief. Patients should therefore be made to understand that the trouble may not be curable but can usually be alleviated and generally resolves eventually of its own accord.

Corticosteroids. Some patients get relief from Corlan (hydrocortisone hemisuccinate 2.5 mg) pellets allowed to dissolve in the mouth 3 times a day. Corticosteroids are unlikely to hasten healing of existing ulcers, but probably reduce the painful inflammation. The most rational form of treatment is for patients to take these pellets continuously (whether or not ulcers are present) to enable the corticosteroid to act in the very early, asymptomatic stages. This regimen is only applicable to those who have frequent ulcers (at 2- or 3-week intervals or more frequently). This should be tried for 2 months, then stopped for a month to assess any improvement and whether there is any deterioration without treatment.

Triamcinolone dental paste is a corticosteroid in a vehicle which sticks to the moist mucosa. When correctly applied the vehicle absorbs moisture and forms an adhesive gel which can remain in place for

one or several hours but it is difficult to apply a fragment of this paste to the ulcer and to get it to adhere firmly. It is only useful for patients with infrequent ulcers, for ulcers near the front of the mouth and for patients dextrous enough to be able to follow the instructions. This gel should form a protective layer over the ulcer to help make it comfortable. The corticosteroid is slowly released and has an anti-inflammatory action. Another alternative is the use of a corticosteroid asthma spray to deposit a potent corticosteroid over the ulcer.

Topical corticosteroids, used as described, have no systemic effect.

Tetracycline mouth rinses. Controlled trials both in Britain and the USA have shown that tetracycline rinses significantly reduce both the frequency and severity of aphthae. For herpeti-form aphthae particularly, the contents of a tetracycline capsule (250 mg) can be stirred in a little water and held in the mouth for 2-3 minutes, three times daily. Some patients like to use this mouth rinse regularly for 3 days each week if they have frequent ulcers. An antifungal drug may also need to be given to patients who are susceptible to superinfection by *Candida albicans.*

Chlorhexidine. A 0.2% solution has also been used as a mouth rinse for aphthae. Used three times daily after meals and held in the mouth for at least 1 minute, it has been claimed to reduce the duration and discomfort of aphthous stomatitis. Zinc sulphate or zinc chloride solutions may also have a slight beneficial effect.

Topical salicylate preparations. Salicylates have an anti-inflammatory action and also have local effects. Preparations of choline salicylate in a gel can be applied to aphthae. These preparations, which are available over the counter, sometimes appear to be helpful.

Treatment of major aphthae. Major aphthae, whether or not there is underlying disease such as HIV infection, may sometimes be so painful, persistent and resistant to conventional treatment as to be disabling. Reportedly effective treatments include thalidomide, azathioprine, cyclosporin, colchicine and dapsone. All of these are toxic in varying degrees and require specialist supervision. Their use may be justified for major aphthae even in otherwise healthy persons if they are disabled by the pain and difficulty of eating.

BEHCET'S DISEASE

Behcet's disease comprises oral aphthae, genital ulceration, ocular disease and other lesions. Unlike autoimmune diseases such as the rheumatic diseases, young adult males between 20 and 40 are predominantly affected. Behcet's disease is rare in Britain and most parts of the USA but relatively common in Turkey (Behcet was a Turk), and so common in Japan that its geographical prevalence has been mapped. This racial distribution suggests a strong genetic component. There appears to be an association of HLA-B12 with the mucocutaneous type, HLA-B5 with the ocular, and HLA-B27 with the arthritic type. It is a multisystem disease but manifestations appear in various combinations.

The oral aphthae of Behcet's disease are not distinguishable from common aphthae. They are the most consistently found feature and frequently the first manifestation. Behcet's disease should therefore be considered in the differential diagnosis of aphthous stomatitis. The frequency of other manifestations is highly variable. As a result there are no absolute criteria or reliable tests for the diagnosis.

Treatment is difficult and may depend on a multidiscipline approach.

HIV-ASSOCIATED ORAL ULCERATION

Patients with HIV infection are susceptible to severe recurrent aphthae which are not otherwise distinguishable from common aphthae. They may also suffer from necrotising mucosal ulceration. Biopsies should be taken to exclude opportunistic infections. Otherwise the aetiology is unknown. Treatment with thalidomide is frequently effective.

Atopic eczematous dermatitis affects between 2 and 20% of the population. It is probably even commoner as some patients learn to live with it without consulting their doctors. Histologically, eczema is characterized by a lymphohistiocytic infiltration around the upper dermal vessels, acanthosis and spongio-sis. Clinically, the important features are *itching, redness, scaling* and *papulovesicles.* **Atopic dermatitis** is the commonest of its many variants.

In adults, atopic dermatitis is a chronic recurrent disorder with exacerbations often related to personal psychosocial adversities. There may or may not be a history of childhood atopic dermatitis, asthma and hay fever, nevertheless many patients have a positive family history of the *atopic triad* –

dermatitis, asthma and allergic rhinitis. Serum levels of IgE are elevated. In acute cases there is erythema, oedema, exudation and intense *itching*, with resultant excoriations and erosions; there may also be clusters of papulovesicles. In chronic forms, there may be dryness, scaling and lichenification (thickening of the epidermis with deepening of the skin lines)**,** plaques, papulovesicles, excoriations, dry and wet crusts and cracks**.**

One of the serious complications associated with atopic dermatitis is the susceptibility to severe and generalized **herpes simplex type 1** infection **(eczema herpeticum),** and to **Kaposi's varicelliform eruption** after vaccination. In patients with atopic dermatitis, a few harmless-looking herpetic vesicles on the lips may soon develop into a generalized papulo vesicular eczema herpeticum.

Eczematous cheilitis is a symptomatic cheilitis, a symptom of general eczematous process of neuroallergic nature, based on the inflammation of the superficial layers of skin.

Allergens are: microorganisms, nutritional agents, medications, metals (Ni, Cr), filling materials, etc.

Eczematous cheilitis can take acute, subacute, and chronic course. Acute form is characterized by the polymorphism of elements of lesion (vesicles, crusts, scales). Lips are oedematous. Itching and burning sensation, pain and hyperemia of the lips can be revealed. The process often spreads to the skin.

Chronic eczematous cheilitis is characterized by the reduction of inflammation. Lips and affected skin around the lips are thickened, with nodules and scales. Vesicles are no more present on the lips, they are changed by scales. Chronic eczematous cheilitis often has a protracted course.

Eczematous cheilitis usually develops on intact lips. Sometimes fissures of the lips and angular cheilitis precedes the disease. In this case microbial sensibilization of lips and skin takes place.

Treatment: desensibilizational medications, local use of oinments with corticosteroids and antimicrobial agents. Consultation with immunologist is necessary.

In **acne rosacea** there is widespread erythema on the face with red papules. The rash may also involve the eyelids. These patients have hyperreactive facial vessels, with flushing in response to various stimuli such as hot tea, spicy foods and alcohol. Over a period of years this transient and recurrent flushing produces persistent erythema and papules. In a well-developed case there is usually a purplish-red hue to the face with macules, papules and telangiectasia. Although called acne rosacea, unlike acne there are neither comedones nor seborrhoea**.**

Urticaria is an intensely *itchy* condition with swelling of the dermis that raises the epidermis into weals. Acute rashes are often IgE-dependent in patients with an atopic background. In chronic cases the aetiology is mostly unknown. There are special varieties of **cold, solar** and **cholinergic urticaria** induced by cold, sunshine (action spectra 290-500 nm) and excessive sweating, respectively.

BULLOUS ERYTHEMA MULTIFORME

As the name **erythema multiforme** implies, the cutaneous reaction to circulating immune complexes (stimulated by infections, drugs, collagen diseases, etc.) is diverse, ranging from a maculo-papular rash to erythematous plaques, blisters and target lesions. The latter are diagnostic with a central, purplish area or a blister surrounded by a pale, oedematous zone, which in turn is surrounded by a rim of erythema**.** These lesions may be scattered all over the body**.** The mucous membranes of the eyes and mouth may also be affected; the condition is then referred to as the **Stevens-Johnson** syndrome. Recurrent herpes simplex infection is a common cause of recurrent erythema multiforme. Other provocating factors are bacterial infections and a variety of drugs. An association with *Mycoplasma pneumoniae* in young adults has been reported.

This is a mucocutaneous disease but, among dental patients, oral lesions are the most prominent or the only ones present.

Target lesions are red macules a centimetre or more in diameter with a bluish cyanotic centre. In severe cases skin lesions are bullous. The attack usually lasts for 3 or 4 weeks, with new crops of lesions developing over a period of about 10 days. Recurrences, usually at intervals of several months, for a year or two are characteristic and are sometimes increasingly severe.

Aetiology and pathology

The aetiology is not clear and, though the disease may be a reaction to a variety of causes, no convincing mechanism has been proposed. Infections, such as herpetic or mycoplasmal, can be triggering factors. Drugs, particularly sulphonamides and barbiturates, have also been implicated, but a positive drug history is also rare. Even when drugs have been taken, coincidence cannot always be excluded and in most patients no precipitating cause can be found.

The histological appearances are variable. Widespread necrosis of keratinocytes with eosinophilic colloid change in the superficial epithelium may be conspicuous. This is not specific but may progress to intraepithelial vesicle or bulla formation. However, subepithelial vesiculation is more frequent. Degenerative changes in the epithelium are associated with infiltration by inflammatory cells which also involve the corium and may have a perivascular distribution. Leakage of immunoglobulins from blood vessels has been reported, but vasculitis is not seen histologically.

Management

Patients should be warned of the possibility of recurrences but that the disease usually runs a limited course.

There is no specific treatment. Systemic corticosteroids may give symptomatic relief. Antibiotics are usually also given in severe cases, with the idea of preventing secondary infection. Levamisole has also been reported to be effective.

'ALLERGIC' STOMATITIS

Many otherwise harmless substances coming into contact with the skin cause hypersensitisation in susceptible subjects. When this has happened, further contact causes an inflammatory reaction. Examples are eczema or contact dermatitis caused by a wide variety of household and industrial materials. Some mucous membranes, such as those of the eyes, can also become sensitised in this way, but the different parts of the body differ widely in their response. Sulphonamide ointments, for example, are highly sensitising to the skin but cause little trouble in the eyes. The oral mucous membrane appears to show yet other differences and to be unable to mount reactions comparable with contact dermatitis, and there is no such condition as oral eczema. Most so-called allergic reactions of the mouth are due to direct irritation by the substance. Even patients who are sensitised to a material such as nickel can tolerate it in the mouth; it may then cause a characteristic rash but not oral lesions. Amalgam restorations cause no trouble in patients sensitised to mercury, though the material should not be allowed to come into contact with the skin. Similar considerations apply to methylmethacrylate. Those few people who are sensitised to the monomer can wear acrylic dentures with impunity. Inflammation under acrylic dentures, often in the past described as 'acrylic allergy', is usually candidal infection. Authenticated cases of contact hypersensitisation of the oral mucous membrane are so few as to make it questionable whether the oral mucosa can mount this type of reaction. If it does so it must be phenomenally rare.

LECTURE 2

IMMUNE-MEDIATED DISEASES (PEMPHIGUS, PEMPHIGOID, LICHEN PLANUS).

LICHEN PLANUS

Lichen planus is a common chronic inflammatory disease of skin and mucous membranes. It mainly affects patients of middle age or over. Oral lesions have characteristic appearances and distribution.

Aetiology

In spite of histological changes, which can be diagnostic, the aetiology of lichen planus remains problematical. The predominantly T lymphocyte infiltrate suggests cell-mediated immuno-logical damage to the epithelium, and a plethora of immunological abnormalities has been reported. Though it has not been possible to demonstrate humoral or lymphocytotoxic mechanisms, the inflammatory infiltrate consists mainly of T lymphocytes. Both CD4 and CDS cells are present but numbers of CDS cells may rise with disease progression and they are more numerous in relation to the epithelium. Precise trigger mechanisms remain unclear but lichen planus undoubtedly appears to be a T lymphocyte-mediated disorder.

Disease indistinguishable from lichen planus, induced by drugs (notably gold and antimalarial agents), also suggests involvement of immunological mechanisms. Oral lichen planus is also a virtually invariable feature and an early sign of graft-versus-host disease, but this does not clarify any immunological mechanisms.

Clinical features

The characteristic appearance and distriution of the lesions should be taken into account in making the diagnosis.

Oral lichen planus – typical features

- Females account for at least 65% of patients
- Patients usually over 40 years old
- Untreated disease can persist for 10 or more years
- Lesions in combination or isolation, comprised
  - Striae
  - Atrophic areas
  - Erosions
  - Plaques
- Common sites are:
  - Buccal mucosae
  - Dorsum of tongue
  - Gingivae (less frequently)
- Lesions usually bilateral and often symmetrical
- Cutaneous lesions only occasionally associated
- Usually good response to corticosteroids

Striae are most common and typically sharply denned, forming lacy, starry or annular patterns. They may occasionally be interspersed with minute, white papules. Striae may not be palpable or may be firmer than the surrounding mucosa.

Atrophic areas are red areas ofmucosal thinning often combined with striae.

Erosions are shallow irregular areas of epithelial destruction. These also can be very persistent and may be covered by a smooth, slightly raised yellowish layer of fibrin. The margins may be slightly depressed due to fibrosis and gradual healing at the periphery. Striae may radiate from the margins of these erosions.

Plaques are occasionally seen in the early stages, particularly on the dorsum of the tongue. Otherwise they may result from persistent disease and mainly affect the buccal mucosa.

Distribution

The buccal mucous membranes, particularly posteriorly, are by far the most frequently affected, but lesions may spread forward almost to the commissures. The next most common site is the tongue, either the edges or the lateral margins of the dor-sum, or less frequently the centre of the dorsum. The lips and gingivae may also occasionally be affected but the floor of the mouth and palate escape. Lesions are very often symmetrical, often strikingly so.

Symptoms

Striae alone may be asymptomatic and unnoticed by the patient, or cause roughness or slight stiffness of the mucosa. Atrophic lesions are sore, and erosions usually cause more severe symptoms still and may make eating difficult.

Gingival lichen planus

The gingivae are occasionally the only site of lichen planus, which needs to be distinguished from other forms of gingivitis. Lesions are usually atrophic so, that the gingivae appear shiny, inflamed and smooth ('desquamative gingivitis'). Striae are uncommon but sometimes present in other parts of the mouth. Gingival lichen planus may involve limited segments.

Soreness caused by atrophic lesions makes toothbrushing difficult. Plaque accumulation and associated inflammatory changes probably aggravate lichen planus. The contribution of local irritation to lichen planus is suggested by disappearance of the lesions when the teeth are extracted. Lichen planus of the denture-bearing area is virtually unknown.

Skin lesions

Lichen planus is a common skin disease but skin lesions are uncommon in those who complain of oral symptoms. Skin lesions typically form purplish papules, 2-3 mm across, with a glistening surface marked by minute fine striae, and are usually itchy. Typical sites are the flexor surface of the forearms and especially the wrists. Skin lesions help, but are not essential, to confirm the diagnosis of oral lichen planus.

Pathology

Corresponding with their clinical features, lesions fall into three distinct histological types:

• Hyperkeratosis or parakeratosis

• Saw-tooth profile of the rete ridges

• Liquefaction degradation of the basal cell layer

• Compact, band-like tymphoplasmacytic (predominantly T cell) infiltrate cells hugging the epitheliomesenchymal junction.

• CDS lymphocytes predominate in relation to the epithelium

Typical histological features of atrophic lesions are:

• Severe thinning and flattening of the epithelium

•Compact band-like, subepithelial inflammatory infiltrate hugging the epitheliomesenchymal junction.

Erosions merely show destruction of the epithelium, leaving only the fibrin-covered, granulating connective tissue floor of the lesion. Diagnosis depends on seeing atrophic lesions or striae nearby.

Diagnosis

The diagnosis of lichen planus can usually be made on the history, the appearance of the lesions and their distribution. However, dysplastic leukoplakias occasionally have a streaky white appearance. A biopsy should be taken, particularly when striae are ill denned, plaques are present or the lesions are in any other ways unusual.

Management

Patients are sometimes concerned that lichen planus is infectious and should be reassured that this is not so.

Topical application of potent anti-inflammatory corticos-teroids is usually effective but monitoring is required and these preparations are suitable only for hospital use. Possible alternatives are to use similar corticosteroids (such as beclo-methasone) from the aerosol inhalers used for asthma. Approximately six puffs from an inhaler daily, can be used to deliver enough of the corticosteroid to an ulcer. Potent corticosteroids used topically may occasionally promote thrush as a side-effect. Triamcinolone dental paste applied to the lesions is an alternative but less effective form of treatment. Gingival lichen planus is the most difficult to treat. The first essential is to maintain rigorous oral hygiene. Corticosteroids should also be used, as already described, and in this situation triamcinolone dental paste may be useful as it can readily be applied to the affected gingivae. In exceptionally severe cases, if topical treatment fails, treatment with systemic corticosteroids is effective. In unresponsive cases, cyclosporin may be effective.

Check-list for management of lichen planus

- Always check for drugs which might cause a lichenoid reaction. This is indistinguishable clinically but may respond to a change of medication
- When inflammation worsens or symptoms become more severe, consider the possibility of superinfection with *Candida.*
- Biopsy lesions which appear unusual, form homogeneous plaques or present in unusual sites
- Check for skin lesions which may aid diagnosis
- Reassure patients that the condition is not usually of great consequence despite the fact that it can produce constant irritating soreness. Tell patients that the severity waxes and wanes unpredictably and the condition may persist for many years
- Be aware that squamous carcinoma can develop in lesions, although very rarely. Follow up lesions associated with reddening, and any unusual in site, appearance or severity

Malignant change in lichen planus

The risk of and possible frequency of malignant change in lichen planus has long been controversial. Probably 1-1.5% of patients suffer this complication after 10 years. Specific risk factors have not been identified with certainty.

LUPUS ERYTHEMATOSUS

Lupus erythematosus is a connective tissue disease which has two main forms: systemic and discoid. Either can give rise to oral lesions which may appear similar to those of oral lichen planus.

Systemic lupus erythematosus has varied effects. Arthralgias and rashes are most common, but virtually any organ system can be affected. A great variety of autoantibodies, particularly antinuclear, is produced.

Discoid lupus is essentially a skin disease with mucocuta-neous lesions indistinguishable clinically from those of systemic lupus. These may be associated with arthralgias but, rarely, significant autoantibody production.

Clinically, oral lesions appear in about 20% of cases of systemic lupus, and can rarely be the presenting sign. Typical lesions are white, often striate, areas with irregular atrophic areas or shallow erosions, but the patterns, particularly those of the striae, are typically far less sharply defined than in lichen planus. They are often patchy and unilateral and may be in the vault of the palate, which lichen planus typically spares.

Lesions can form variable patterns of white and red areas. There may also be small slit-like ulcers just short of the gingi-val margins. In about 30% of cases, Sjogren's syndrome develops and rarely cervical lymphadenopathy is the first sign.

Pathology

Lesions show an irregular pattern of epithelial atrophy and acanthosis. Liquefaction degeneration of the basal cell layer is typical and there is PAS-positive thickening of the basement membrane zone and around blood vessels due to deposition of antigen – antibody omplexes. In the corium there is oedema and often a hyaline appearance. The inflammatory infiltrate is highly variable in density, typically extends deeply into the connective tissue and may have a perivascular distribution.

Lupus erythematosus shows more irregular patterns of acanthosis and lacks the band-like distribution of lymphocytes in the papillary corium of lichen planus.

In frozen sections, a band of immunoglobulins and complement (C3) with a granular texture deposited along the basement membrane may be shown by immunofluorescence. This deposit also underlies normal epithelium in systemic lupus. In paraffin sections, immunoglobulin deposits may be detectable using immunoperoxidase staining. Obvious vasculitis may occasionally be seen in systemic, but not in discoid, lupus erythemato-sus.

Diagnosis of systemic lupus erythematosus should be confirmed by the pattern of antinuclear autoantibodies. The most specific is that to double-stranded (native) DNA.

Haematological findings in active systemic lupus erythematosus include a raised ESR, anaemia and, often, leukopenia or thrombocytopenia.

Oral lesions of discoid lupus erythematosus may respond in some degree to topical cortico steroids. However, oral lesions in acute systemic lupus erythematosus may not respond to doses of corticosteroids adequate to control systemic effects of the disease. Under such circumstances, palliative treatment is needed until disease activity abates.

PEMPHIGUS VULGARIS

Pemphigus is an uncommon autoimmune disease causing vesicles or bullae on skin and mucous membranes. It is usually fatal if untreated. Females, usually aged 40-60 years, are predominantly affected. Lesions often first appear in the mouth but spread widely on the skin. Vesicles are fragile and unlikely to be seen intact in the mouth. Residual erosions often have ragged edges and are superficial, painful and tender. Gently stroking the mucosa can cause a vesicle or bulla to appear (Nikolsky's sign).

Progress of the disease is very variable. It may sometimes be fulminating with rapid development of widespread oral ulcera-tion, spread to other sites such as the eyes within a few days and I very soon afterwards to the skin.

Skin lesions consist of vesicles or bullae varying from a few millimetres to a centimetre or so across. The bullae at first contain clear fluid, which may then become purulent or haemorrhagic. Rupture of vesicles leaves painful ragged ero-sions. Protein, fluid and electrolytes are lost from the raw areas and they readily become secondarily infected. Without treatment, death usually follows, but immunosuppressive treatment is usually life-saving.

Pathology

An immunopathogenesis can be more convincingly demonstrated in pemphigus vulgaris than in any other oral disease; the histological findings are summarised in Table. The epithelial cells which lose their attachments become rounded in shape and the cytoplasm contracts around the nucleus. Small groups of these rounded-up acantholytic *(Tzanck)* cells can often be seen histologically in the contents of a vesicle or in a smear from a recently ruptured vesicle.

Pathology of pemphigus vulgaris

- Loss of intercellular adherence of suprabasal spinous cells
- Formation of clefts immediately superficial to the basal cells
- Extension of clefts to form intraepithelial vesicles
- Rupture of vesicles to form ulcers
- High title of circulating antibodies to epithelial intercellular cement substance
- Binding of antibodies to intercellular substance detectable by fluorescence microscopy

Pemphigus antibodies are tissue-specific and react only to intercellular substance of squamous epithelium. The epithelial cell surface antigen is an intercellular adhesion molecule (ICAM), termed desmoglein 3. The mechanism of breakdown of intercellular attachments appears to result from synthesis ofproteases by the epithelial cells.

Management

The diagnosis must be confirmed as early as possible. Biopsy is essential and the changes are sufficiently characteristic to make a diagnosis. Immunofluorescence microscopy should be used to exclude similar but less common diseases. Once the diagnosis has been confirmed, immunosuppressive treatment is required. There is little consensus about dosage but a typical regimen is 80-100 mg/day of prednisolone plus azathio-prine (1—1.5 mg/kg daily). Azathioprine is given to allow doses of the corticosteroid to be lowered and reduce their side-effects. Treatment can only be stopped if relapse fails to follow withdrawal, and can itself cause a significant mortality. With combined immunosuppressive treatment, the average mortality is approximately 6%.

Pemphigus vulgaris – key clinical features

- Females predominantly affected, usually aged 40-60 years
- Lesions often first in the mouth but spread widely on the skin
- Lesions consist of fragile vesicles and bullae
- Ruptured vesicles form irregular erosions on the mucosa
- Nikolsky's sign may be positive
- Widespread skin involvement is fatal if untreated
- Good response to prolonged immunosuppressive treatment

MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid is an uncommon chronic disease causing bullae, painful erosions and mucosal scarring. Skin involvement is uncommon and often trivial. Lesions are rarely widespread and progress is very slow. 'Desquamative gingivitis' can be a manifestation. Nikolsky's sign should be positive and a striking clinical finding is sometimes that the epithelium slides away underneath the edge of the scalpel when a biopsy is attempted. In the mouth, bleeding into bullae can cause them to appear as blood blisters. Rupture of erosions leaves raw areas with well-defined margins. Individual erosions persist for some weeks then slowly heal, usually without scarring. Further erosions may develop nearby and this process may persist for a year or more. Lesions may remain localised to the mouth for very long periods and may never involve other sites.

Mucous membrane pemphigoid – key clinical features

- Females mainly affected and usually elderly
- Oral mucosa often the first site
- Involvement of other mucosae, particularly the eyes, may cause scarring and blindness
- Skin involvement absent or minimal
- Indolent, non-fatal disease
- Oral bullae are subepithelial and frequently seen intact

Pathology

Histologically there is loss of attachment and separation of the full thickness of the epithelium from the connective tissue at the basement membrane. Epithelium, though separated, remains for a time intact and forms the roof of a bulla. The floor of the bulla is formed by connective tissue alone, infiltrated with inflammatory cells. The disease is immunologically mediated, and binding of immunoglobulin or more frequently of complement components along the basement membrane zone can be demonstrated. Circulating autoantibodies are detectable by sensitive techniques.

Management

The diagnosis is confirmed by biopsy and immunofluorescence microscopy but it is preferable to obtain an intact vesicle or bulla.

Oral mucous membrane pemphigoid can often be effectively controlled with topical cortico steroids. Doses are small and without systemic effects.

Because of the possible risk to sight, ocular examination is necessary if early changes in the eyes are suspected. If the eyes become involved, systemic corticosteroids have to be given and are effective.

Desquamative gingivitis

The term *'desquamative gingivitis'* is a clinical description, not a diagnosis. It is used for conditions in which the gingivae appear red or raw. Usually the whole of the attached gingiva of varying numbers of teeth is affected.

Lichen planus is the most common cause. The gingivae then appear smooth, red and translucent due to the thinness of the atrophic epithelium. In older patients mucous membrane pemphigoid may cause gingival erosions. Pemphigus vulgaris is another possible cause. In all cases the appearances are strikingly different from simple marginal gingivitis, and the diagnosis should be confirmed by biopsy.

The differential diagnosis of blistering diseases

Disease	**History**	**Age of onset**	**Lesions**	**Distribution**
Pemphigus	Weakness, wasting, no pruritus	40-60 years	Skin-coloured normal skin, thin/ruptured bullae	Mouth, face, scalp, chest, axillae
Pemphigoid	Prodromal urticaria / eczema, occasional pruritus	60-80 years, may occur in children	Tense bullae, on ery-thematous skin	Generalized, rarely in oropharynx
Dermatitis herpetiformis	Intense itching and burning sensation	20-40 years	Erythematous papules, vesicles, urticarial weals	Scalp, face, extensor areas
Erythema multiforme	Exposure to drugs, fever, malaise	Usually below 30 years	Macules, papules, vesicles, bullae, target lesions	Hands, trunk
Porphyria cutanea tarda	May follow alcohol, oestrogens, etc.	30-40 years	Vesicles, bullae, hypertrichosis	Symmetrical, sun-exposed areas: hands, face, ears

LECTURE 3

ORAL MANIFESTATIONS OF HEMATOLOGICAL, ENDOCRINE, CARDIOVASCULAR DISORDERS AND GASTROINTESTINAL DISEASES.

Hematologic Diseases

Leukemia

The leukemias are "malignant neoplasias of white blood cell precursors, characterized by (1) diffuse replacement of the bone marrow with proliferating leukemic cells; (2) abnormal numbers and forms of immature white cells in the circulating blood; and (3) widespread infiltrates in the liver, spleen, lymph nodes and other sites throughout the body.

According to the type of white blood cell involved, leukemias can be ***lymphocytic*** or ***myelocytic***; a subgroup of the myelocytic leukemias is ***monocytic leukemia***. According to their evolution, leukemias can be ***acute***, which is rapidly fatal; ***subacute***; or ***chronic***. The replacement of the bone marrow elements by leukemic cells reduces normal white blood cell and platelet production, leading to anaemia and bleeding disorders. Some patients may have normal blood counts while leukemic cells are present in the bone marrow; this type of disease is called ***aleukemic leukemia***.

Oral and periodontal manifestations of leukemia consist of the following: leukemic infiltration of the periodontium, bleeding, oral ulcerations and infections. Leukemic cells can infiltrate the gingiva and, less frequently, the alveolar bone. Gingival infiltration often results in ***leukemic gingival enlargement***.

Leukemic gingival enlargement is not found in edentulous patients or in patients with chronic leukemia. Leukemic gingival enlargement consists of a basic infiltration of the gingival corium by leukemic cells that creates gingival pockets where bacterial plaque accumulates, initiating a secondary inflammatory lesion that contributes also to the enlargement of the gingiva.

Clinically, the gingiva appears initially bluish red and cyanotic, with a rounding and tenderness of the gingival margin; then it increases in size, most often in the interdental papilla and partially covering the crowns of the teeth (fig.44).

Microscopically, the gingiva exhibits a dense, diffuse infiltration of predominantly immature leukocytes in the attached as well as the marginal gingiva. Occasional mitotic figures indicative of ectopic hematopoiesis may be seen. The normal connective tissue components of the gingiva are displaced by the leukemic cells. The nature of the cells depends on the type of leukemia. The cellular accumulation is denser in all the reticular connective tissue layer. In almost all cases, the papillary layer contains comparatively few leukocytes. The blood vessels are distended and contain predominantly leukemic cells, and the red blood cells are reduced in number. The epithelium presents a variety of changes. It may be thinned or hyperplastic. Degeneration associated with intercellular and intracellular oedema and leukocytic infiltration with diminished surface keratinization are common findings.

The microscopic picture of the marginal gingiva differs from that of the remainder of the gingiva in that it usually exhibits a notable inflammatory component in addition to the leukemic cells. Scattered foci of plasma cells and lymphocytes with oedema and degeneration are common findings. The inner aspect of the marginal gingiva is usually ulcerated, and marginal necrosis with pseudomembrane formation may also be seen.

The periodontal ligament and alveolar bone may also be involved in acute and subacute leukemia. The periodontal ligament may be infiltrated with mature and immature leukocytes. The marrow of the alveolar bone exhibits a variety of changes, such as localized areas of necrosis, thrombosis of the blood vessels, infiltration with mature and immature leukocytes, occasional red blood cells, and replacement of the fatty marrow by fibrous tissue.

In leukemic mice, the presence of infiltrate in marrow spaces and the periodontal ligament results in osteoporosis of the alveolar bone with destruction of the supporting bone and disappearance of the periodontal fibers.

The abnormal accumulation of leukemic cells in the dermal and subcutaneous connective tissue is called ***leukemia cutis*** and forms elevated flat macules and papules.

Bleeding. Gingival hemorrhage is a common finding in leukemic patients, even in the absence of clinically detectable gingivitis. Bleeding gingiva can be an early sign of leukemia. It is due to the thrombocytopenia that results from replacement of the bone marrow cells by leukemic cells and also from the inhibition of normal stem cell function by leukemic cells or their products.

Oral Ulcerations and Infections. The granulocytopenia resulting from the replacement of bone marrow cells by leukemic cells reduces the tissue resistance to opportunistic microorganisms and leads to ulcerations and infections. Discrete, punched-out ulcers penetrating deeply into the submucosa and covered by a firmly attached white slough can be found in the oral mucosa. These lesions occur in sites of trauma such as the buccal mucosa in relation to the line of occlusion or the palate. Patients with past history of herpes infection may develop herpetic oral ulcers, frequently in multiple sites and large atypical forms, after chemotherapy is instituted.

Gingival bacterial infection in leukemic patients can be a primary bacterial infection or result from an increased severity of existing gingival or periodontal disease. Lesions of acute necrotizing ulcerative gingivitis may also be seen in terminal cases of leukemia.

In leukemia, the response to irritation is altered, so that the cellular component of the inflammatory exudate differs both quantitatively and qualitatively from that that occurs in nonleukemic individuals. There is a pronounced infiltration of immature leukemic cells in addition to the usual inflammatory cells.

The inflamed gingiva differs clinically from inflamed gingiva in nonleukemic individuals. It is a peculiar bluish red, is markedly sponge-like and friable, and bleeds persistently on the slightest provocation or even spontaneously. This markedly altered and degenerated tissue is extremely susceptible to bacterial infection, which can be so severe as to cause acute gingival necrosis and pseudomembrane formation. These are secondary oral changes superimposed on the oral tissues altered by the blood disturbance and produce associated disturbances that may be a source of considerable difficulty to the patient, such as systemic toxic effects, loss of appetite, nausea, blood loss from persistent gingival bleeding, and constant gnawing pain. By eliminating local irritants, it is possible to alleviate severe oral changes in leukemia.

Chronic Leukemia

In chronic leukemia, clinical oral changes suggesting a hematologic disturbance are very rare.

The microscopic changes in chronic leukemia may consist of replacement of the normal fatty marrow of the jaws by islands of mature lymphocytes or lymphocytic infiltration of the marginal gingiva without dramatic clinical manifestations.

Gingival Biopsy and Leukemia

The existence of leukemia is sometimes revealed by a gingival biopsy performed to clarify the nature of a troublesome gingival condition. In such cases, the gingival findings must be corroborated by medical examination and hematologic study. The absence of leukemic involvement in a gingival biopsy specimen does not rule out the possibility of leukemia. In chronic leukemia, the gingiva may simply present inflammatory changes, with no suggestion of a hematologic disturbance. In patients with recognized leukemia, the gingival biopsy indicates the extent to which leukemic infiltration is responsible for the altered clinical appearance of the gingiva. *Although such findings are of interest, their benefit to the patient is insufficient to warrant routine gingival biopsy studies in patients with leukemia.*

Anaemias

Anaemias are deficiencies in the quantity or quality of the blood as manifested by a reduction in the number of erythrocytes and in the amount of hemoglobin. Anaemia may be the result of blood loss, defective blood formation, or increased blood destruction.

Anaemias are classified according to cellular morphology and hemoglobin content as (1) macrocytic hyperchromic anaemia (pernicious anaemia), (2) microcytic hypochromic anaemia (iron deficiency anaemia), (3) sickle cell anaemia, or (4) normocytic-normochromic anaemia (hemolytic or aplas-tic anaemia).

Pernicious anaemia results in tongue changes in 75% of cases. The tongue appears red, smooth, and shiny owing to atrophy of the papillae. There is also marked pallor of the gingiva.

Iron deficiency anaemia induces similar tongue and gingival changes. A syndrome consisting of glossitis and ulceration of the oral mucosa and oropharynx, inducing dysphagia (***Plummer-Vinson syndrome***), has been described in patients with iron deficiency anaemia.

Sickle cell anaemia is a hereditary form of chronic hemolytic anaemia that occurs almost exclusively in blacks. It is characterized by pallor, jaundice, weakness, rheumatoid manifestations, and leg ulcers. Oral changes include generalized osteoporosis of the jaws, with a peculiar stepladder alignment of the trabeculae of the interdental septa and pallor and yellowish discoloration of the oral mucosa. Periodontal infections may precipitate sickle cell crisis. ***Aplastic anaemias*** result from a failure of the bone marrow to produce erythrocytes. Their etiology is usually the effect of toxic drugs on the marrow. Oral changes include pale discoloration of the oral mucosa and increased susceptibility to infection owing to the concomitant neutropenia.

Thrombocytopenic Purpura

Thrombocytopenic purpura may be idiopathic (i.e., of unknown etiology, as in Werlhof's disease), or it may occur secondary to some known etiologic factor responsible for a reduction in the amount of functioning marrow and a resultant reduction in the number of circulating platelets. Such etiologic factors include aplasia of the marrow; crowding out of the megakaryocytes in the marrow, as, for example, in leukemia; replacement of the marrow by tumor; and destruction of the marrow by irradiation or radium or by drugs such as benzene, aminopyrine, and arsenical agents.

Thrombocytopenic purpura is characterized by a low platelet count, a prolonged clot retraction and bleeding time, and a normal or slightly prolonged clotting time. There is spontaneous bleeding into the skin or from mucous membranes. Petechiae and hemorrhagic vesicles occur in the oral cavity, particularly in the palate and the buccal mucosa. *The gingivae are swollen, soft, and friable. Bleeding occurs spontaneously or on the slightest provocation and is difficult to control.* Gingival changes represent an abnormal response to ***local irritation***; the severity of the gingival condition is dramatically alleviated by removal of the local irritants.

Diabets

Diabetes is an extremely important disease from a periodontal standpoint. It is a complicated metabolic disease characterized by hypofunction or lack of function of the cells of the islets of Langerhans in the pancreas, leading to high blood glucose levels and excretion of sugar in the urine. Two basic types of primary diabetes mellitus have been described: insulin-dependent and non-insulin-dependent.

Insulin-dependent diabetes mellitus (IDDM) (type I) is also known as juvenile diabetes or juvenile-onset diabetes (fig.45, 46), although it may sometimes appear at older ages. This type of diabetes results from an absolute lack of insulin, is very unstable and difficult to control, has a marked tendency toward ketosis and coma, is not preceded by obesity, and requires injected insulin to be controlled. Patients with the disease present with the symptoms traditionally associated with diabetes: polyphagia, polydipsia, polyuria, predisposition to infections, and anorexia.

Non-insulin-dependent diabetes mellitus (NIDDM) (type II) is the adult type (i.e., onset usually after age 45). It generally occurs in obese individuals and can often be controlled by diet or by oral hypoglycemic agents. The development of ketosis and coma is not common. Adult-onset diabetes has the same symptoms as juvenile diabetes but in a less severe form.

Oral Manifestations of Diabetes

The following findings have been described in the oral mucosa: cheilosis and a tendency toward drying and cracking; burning sensations; decrease in salivary flow; and alterations in the flora of the oral cavity, with greater predominance of Candida albicans, hemolytic streptococci, and staphylococci. These changes, however, are not specific, and terms such as diabetic stomatitis should not be used. Perhaps the most striking changes in uncontrolled diabetes are the reduction in defense mechanisms and the increased susceptibility to infections leading to destructive periodontal disease. Control of diabetes may be attained by diet or by the administration of insulin and/or other drugs. In well-controlled diabetes, none of the previously mentioned changes is found. There is a normal tissue response, no increase in the incidence of caries, a normally developed dentition, and a normal defense against infections. However, the possibility that the control of the disease may be inadequate makes it advisable to exercise special care in the periodontal treatment of individuals with controlled diabetes.

A variety of periodontal changes have been described in diabetic patients, such as a tendency toward abscess formation, diabetic periodontoclasia, enlarged gingiva, sessile or pedunculated gingival polyps,

polypoid gingival proliferations, and loosened teeth. Very severe gingival inflammation, deep periodontal pockets, rapid bone loss, and frequent periodontal abscesses often occur in diabetic patients with poor oral hygiene. The distribution and severity of local irritants affect the severity of periodontal disease in diabetics. Diabetes does not cause gingivitis or periodontal pockets, but there are indications that it alters the response of the periodontal tissues to local irritants, hastening bone loss and retarding postsurgical healing of the periodontal tissues. Frequent periodontal abscesses appear to be an important feature of periodontal disease in diabetics.

Periodontal Condition in Patients with Down Syndrome and Some other Patological Syndromes

Down syndrome (mongolism, trisomy is a congenital disease caused by a chromosomal abnormality and characterized by mental deficiency and growth retardation. The prevalence of periodontal disease in Down syndrome is high (occurring in almost 100% of patients younger than 30 years old). Although plaque, calculus, and local irritants (e.g., diastemata, crowding of teeth, high frenum attachments, and malocclusion) are present and oral hygiene is poor, the severity of periodontal destruction exceeds that explainable by local factors alone.

Periodontal disease in Down syndrome is characterized by formation of deep periodontal pockets associated with substantial plaque accumulation and moderate gingivitis. These findings are usually generalized, although they tend to be more severe in the lower anterior region; marked recession is also sometimes seen in this region, apparently associated with high frenum attachment. The disease progresses rapidly. Acute necrotizing lesions are a frequent finding.

Two factors have been proposed to explain the high prevalence and increased severity of periodontal destruction associated with Down syndrome: a reduced resistance to infections because of poor circulation, especially in areas of terminal vascularization such as the gingival tissue, and a defect in T-cell maturation and in polymorphonuclear leukocyte chemotaxis. Increased numbers of Prevotella melaninogenica have been reported in the mouths of children with Down syndrome.

Chediak-Higashi Syndrome is a rare disease that affects the production of organelles mostly in the melanocytes, platelets, and phagocytes. It is characterized by the partial albinism, mild bleeding disorders, recurrent bacterial infections and rapidly destructive periodontitis.

Hypophosphatasia is a rare familial skeletal disease characterized by rickets, poor cranial bone formation, craneostenosis, and premature loss of primary teeth, particularly the incisors. Patients have a low level of serum alkaline phosphatase, and phosphoethanolamine is present in serum and urine.

Teeth are lost with no clinical evidence of gingival inflammation and show reduced cementum formation.6 In patients with minimal bone abnormalities, premature loss of deciduous teeth may be the only symptom of hypophosphatasia. In adolescents, this disease resembles localized juvenile periodontitis.

Leukocyte Adhesion Deficiency belongs to rare cases and begin during or immediately after eruption of the primary teeth. Extremely acute inflammation and proliferation of the gingival tissues, with rapid destruction of bone, are found. Profound defects in peripheral blood neutrophils and monocytes and an absence of neutrophils in the gingival tissues have been noted in patients with leukocyte adhesion deficiency; these patients also have frequent respiratory tract infections and sometimes otitis media. All primary teeth are affected, but the permanent dentition may not be affected. these vessels, so that bacteria can be pumped into the
bloodstream.
Fewer that 15% of cases of infective endocarditis can be related to dental operations but in these cases extractions have been the precipitating factor in over 95%. Viridans streptococci, such as those which colonise the teeth, are of low virulence but may be able to colonise heart valves because of attachment mechanisms which also enable them to cause dental disease. Factors determining susceptibility to infective endocarditis are difficult to identify. For example, children with Down'ssyndrome — who are prone to severe periodontal disease, have
multiple immune defects and, frequently, congenital cardiac defects — are not particularly susceptible to infective endocarditis. Currently, advanced age, especially if there is periodontal sepsis, is the main risk factor. Infective endocarditis is rare in children and the peak incidence and mortality is after the age of 60 years.

Dental management in major types of cardiac diseases

Valvular or related defects (congenital or due to past rheumatic fever) or who have a prosthetic replacement, susceptible to infective endocarditis

Prophylactic antibiotic cover, particularly before extractions, is mandatory

Ischaemic heart disease with or without severe hypertension and cardiac failure

Routine dentistry presents little hazard but the risk of dangerous arrhythmias must be minimised

Local anaesthetics in normal dosage have only theoretical dangers, but pain and anxiety must be minimised

The main risk is from general anaesthesia

Patients chiefly at risk are severe hypertensives and those who have angina or have had a myocardial infarct. Anxiety or pain can cause outpouring of adrenaline which can both greatly increase the load on the heart and also precipitate dangerous dysrhythmias. There is some evidence that dental infections, particularly chronic periodontal disease, are possibly a risk factor for atherosclerotic coronary artery disease.

Patients should be asked whether routine dental treatment under local anaesthesia is acceptable, and in any session of treatment as little or as much may be done as they feel able to tolerate. Oral temazepam may be helpful (5 mg on the preceding night and again half an hour before treatment, and the patient accompanied by a responsible adult). If sedation is required, relative analgesia is safer because nitrous oxide has no cardiorespiratory depressant effects and is more controllable, but it should be administered by an expert.

Local anaesthesia for patients with cardiac disease

For local anaesthesia, an effective surface anaesthestic should be applied and the injection given very slowly to minimise pain. The most effective agent is 2% lidocaine with epinephrine and, after half a century of use, no local anaesthetic has been shown to be safer. The adrenaline (epinephrine) content can theoretically cause a hypertensive reaction in patients receiving beta-blocker antihypertensives, because of an unopposed alpha-adrenergic effect, but only if doses are considerably larger than used in dentistry.

Though patients with cardiovascular disease need to be treated with care, the risks of routine dental treatment under local anaesthesia (despite many statements to the contrary) and of significant adverse reactions are very low.

Patients at risk from infective endocarditis

Normally, bacteria entering the bloodstream are rapidly cleared by circulating leucocytes, but if there is a cardiac defect which can be colonised, infective endocarditis can develop. There are many sources of bacteraemias, such as cardiac surgery, intravenous catheterisation and intravenous drug addiction. Bacteraemias can also be detected in over 80% ofpersons after extractions and even after toothbrushing, but the numbers of bacteria released are often very small. Even in a patient with a heart lesion, infective endocarditis does not necessarily follow. Relatively few bacteria inhabit the oral mucosa, and most are being constantly washed away by the saliva. By contrast, vast numbers of bacteria inhabit the gingival margins when oral hygiene is poor and even greater numbers occupy periodontal pockets. These bacteria are in close contact with dilated, thinwalled blood vessels. Movement of teeth in their sockets repeatedly compresses and stretches or ruptures these vessels, so that bacteria can be pumped into the bloodstream.

Once infective endocarditis develops, vegetations of bacteria and fibrin form on the valves, which are progressively destroyed. Cardiac failure is the main cause of death but emboli and bacteria released into the bloodstream can also cause renal or cerebral damage. Prevention is all-important.

Infective endocarditis does not appear to be a risk after myocardial infarction or coronary artery bypasses, or for wearers of cardiac pacemakers, and antibiotic cover is not recommended for dental procedures. It should be noted that the onset of infective endocarditis is typically very insidious. Even when antibiotic cover has been given, patients must be made to understand that they should report to the dentist if they develop any mild, unexplained, febrile illness within 3 months of the dental treatment. Delay in diagnosis is the main factor affecting survival in infective endocarditis.
Prophylaxis is recommended for dental extractions, scaling or periodontal surgery. Prophylaxis is not considered necessary for other procedures such as orthodontic manipulations unless there is likely to be significant damage to the gingival margins.
Under local or no anaesthesia
• Patients not allergic to the penicillins and who have not received penicillin more than once in the previous month
Amoxycillin
Adults 3 g single oral dose taken under supervision, 1 hour
before dental procedure
Children 5-10 years Half adult dose
Children under 5 years Quarter adult dose
• Patients allergic to penicillins or who have received penicillin more than once in the previous month
Clindamycin
Adults 600 mg single oral dose taken under supervision,
1 hour before dental procedure
Children 5-10 years Half adult dose
Precautions
1. When clindamycin is used, periodontal or other multistage procedures should not be repeated at intervals of less than 2 weeks.
2. Whatever antibiotic cover has been given, patients must be instructed to report to the dentist any mild, unexplained, febrile illness developing within 3 months of the dental treatment.

GASTRIC REGURGITATION
Chronic vomiting of gastric acid contents due to such causes as hypertrophic pyloric stenosis can lead to erosion of the palatal aspect of the anterior teeth particularly. This type of dental erosion is an important diagnostic sign of self-induced vomiting in bulimia.

CROHN'S DISEASE
Crohn's disease is of unknown aetiology. It most frequently affects the ileocaecal region, causing thickening and ulceration. Effects include abdominal pain, variable constipation or diarrhoea and, sometimes, obstruction and malabsorption. Joint pain can also be troublesome. Orofacial involvement may occasionally precede abdominal symptoms.

Typical orofacial features of Crohn's disease
Diffuse soft or tense swelling of the lips, or mucosal thickening
Cobblestone thickening of the buccal mucosa, with fissuring and
hyperplastic folds
Gingivae may be erythematous and swollen
Sometimes, painful mucosal ulcers, linear or resembling aphthae
Mucosal tags in sulcuses sometimes present
Glossitis due to iron, folate or vitamin B12 deficiency can result
from malabsorption

Vitamins Deficiencies
Deficiency of vitamin A results in ocular manifestations and keratinizing metaplasia of the epithelium.
The following periodontal changes have been reported in vitamin A-deficient rats: hyperplasia and hyperkeratinization of the gingival epithelium with proliferation of the junctional epithelium, and

retardation of gingival wound healing. In the presence of local irritation, vitamin A-deficient rats develop periodontal pockets that are deeper than those in non-vitamin A-deficient animals and exhibit associated epithelial hyperkeratosis.There is little information regarding the effects of vitamin A deficiency on the oral structures in humans. Several epidemiologic studies have failed to demonstrate any relation between this vitamin and periodontal disease (Frandsen A.M., 1963).

Vitamin D, or calciferol, is essential for the absorption of calcium from the gastrointestinal tract and for the maintenance of the calcium-phosphorus balance. Deficiency in vitamin D and/or imbalance in calcium-phosphorus intake results in rickets in the very young animals and osteomalacia in adults.

The effect of such deficiency or imbalance on the periodontal tissues of young dogs results in osteoporosis of alveolar bone; osteoid that forms at a normal rate but remains uncalcified; failure of osteoid to resorb, which leads to its excessive accumulation; reduction in the width of the periodontal space; a normal rate of cementum formation, but defective calcification and some cementum resorption; and distortion of the growth pattern of alveolar bone.

In animals with osteomalacia, there is a rapid, generalized, severe osteoclastic resorption of alveolar bone, proliferation of fibroblasts that replace both bone and marrow, and a new bone formation around the remnants of unresorbed bony trabeculae.

Radiographically, there is a generalized partial to complete disappearance of the lamina dura and reduced density of the supporting bone, loss of trabeculae, increased radiolucency of the trabecular interstices, and increased prominence of the remaining trabeculae. Microscopic and radiographic changes in the periodontium are almost identical with those seen in experimentally induced hyperparathyroidism (Becks H., Collins D.A., Feutog R.M., 1946).

No relationship has been demonstrated between deficiencies in vitamin E and oral disease, but systemic vitamin E appears to accelerate gingival wound healing in the rat.

B Complex Deficiency. The vitamin B complex includes thiamine, riboflavin, niacin, pyridoxine (B6), biotin, folic acid, and cobalamin (B12). Oral disease is rarely due to a deficiency in just one component of the B complex group; the deficiency is generally multiple.

Oral changes common to B complex deficiencies are gingivitis, glossitis, glossodynia, angular cheilitis, and inflammation of the entire oral mucosa. The gingivitis in vitamin B deficiencies is nonspecific, as it is caused mostly by a bacterial plaque.

The following oral changes are typical to thiamine deficiency: hypersensitivity of the oral mucosa; minute vesicles (simulating herpes) on the buccal mucosa, under the tongue, or on the palate; and erosion of the oral mucosa.

The symptoms of riboflavin deficiency (ariboflavinosis) include glossitis, angular cheilitis, seborrheic dermatitis, and a superficial vascularizing keratitis. The glossitis is characterized by a magenta discoloration and atrophy of the papillae. In mild to moderate cases, the dorsum exhibits a patchy atrophy of the lingual papillae. In severe deficiency, the entire dorsum is flat, with a dry and often fissured surface.

Angular cheilitis begins as an inflammation of the commissure of the lips, followed by erosion, ulceration, and fissuring. Riboflavin deficiency is not the only cause of angular cheilitis. Loss of vertical dimension, together with drooling of saliva into the angles of the lips, may produce a condition similar to angular cheilitis. Candidiasis may develop in the commissures of debilitated persons.

Changes observed in riboflavin-deficient animals include severe lesions of the gingivae, periodontal tissues, and the oral mucosa (including noma).

Niacin deficiency results in pellagra, which is characterized by dermatitis, gastrointestinal disturbances, neurologic and mental disturbances (dermatitis, diarrhea, and dementia), glossitis, gingivitis, and generalized stomatitis.

Glossitis and stomatitis may be the earliest clinical signs of niacin deficiency. The gingiva may be involved in aniacinosis with or without tongue changes. The most frequent finding is acute necrotizing ulcerative gingivitis, usually in areas of local irritation.

Oral manifestations of vitamin B complex and niacin deficiency in experimental animals include black tongue and gingival inflammation with destruction of the gingiva, periodontal ligament, and alveolar bone. Necrosis of the gingiva and other oral tissues and leukopenia are terminal features of niacin deficiency in experimental animals.

Folic acid deficiency results in macrocytic anaemia with megaloblastic erythropoiesis, with oral changes and gastrointestinal lesions, diarrhea, and intestinal malabsorption (Afonsky D., 1995)

Folic acid-deficient animals demonstrate necrosis of the gingiva, periodontal ligament, and alveolar bone without inflammation. The absence of inflammation is the result of deficiency-induced granulocytopenia. In humans with sprue and other folic acid deficiency states, there is a generalized stomatitis, which may be accompanied by ulcerated glossitis and cheilitis. Ulcerative stomatitis is an early indication of the toxic effect of folic acid antagonists used in the treatment of leukemia (Shaw J.H., 1962).

In a series of human studies, a significant reduction of gingival inflammation has been reported after systemic or local use of folic acid, when compared with placebo. This reduction occurred with no change in plaque accumulation. The same authors have postulated that the gingival changes associated with pregnancy and oral contraceptives may be partly related to suboptimal levels of folic acid in the gingiva. In a clinical study of pregnant women, a reduction in gingival inflammation occurred with the use of topical folate mouth rinses; no change was found with systemic folic acid. A relationship has also been assumed between phenytoin-induced gingival overgrowth and folic acid, based on the interference of folic acid absorption and utilization by phenytoin (Vogel R., 1980).

Severe vitamin C deficiency in humans results in scurvy, a disease characterized by a hemorrhagic diathesis and retardation of wound healing. Vitamin C is required in the human diet but not in that of other animals except other primates, guinea pigs, and some rare flying mammals. Vitamin C is abundant in fruits and vegetables. Scurvy is uncommon in countries that have adequate food supplies, but it may appear in infants in their first year of life if formulas are not fortified with vitamins and in the very elderly, especially those living alone and on restricted diets. Alcoholism also may predispose an individual to scurvy.

Clinical manifestations of scurvy include hemorrhagic lesions into the muscles of the extremities, the joints, and sometimes the nail beds; petechial hemorrhages, often around hair follicles; increased susceptibility to infections; and impaired wound healing. Bleeding, swollen gingivae, and loosened teeth are also common features of scurvy.

Vitamin C deficiency (scurvy) results in defective formation and maintenance of collagen, retardation or cessation of osteoid formation, and impaired osteoblastic function. Vitamin C deficiency is also characterized by increased capillary permeability, susceptibility to traumatic hemorrhages, hyporeactivity of the contractile elements of the peripheral blood vessels, and sluggishness of blood flow (Cotran R.S., Kumar V. et al., 1989).

LECTURE 4

TONGUE DISORDERS. CHEILITIS. ETIOLOGY, PATHOGENESIS.

GLOSSITIS

MICROGLOSSIA (HYPOGLOSSIA)

Clinical Features

Microglossia is an uncommon developmental condition of unknown cause that is characterized by an abnormally small tongue. In rare instances, virtually the entire tongue may be missing (aglossia). Isolated microglossia is known to occur, and mild degrees of microglossia may be difficult to detect and may go unnoticed. However, most reported cases have been associated with one of a group of over- lapping conditions known as oromandibular-limb hypogenesis syndromes. These syndromes feature associated limb anomalies, such as hypodactylia (i.e., absence of digits) and hypomelia (i.e., hypoplasia of part or all of a limb). Other patients have had coexisting anomalies, such as cleft palate, intraoral bands, and sinus inversus. Microglossia frequently is associated with hypoplasia of the mandible, and the lower incisors may be missing.

Treatment and Prognosis

Treatment of the patient with microglossia depends on the nature and severity of the condition. Surgery and orthodontics may improve oral function. Surprisingly, speech development often is quite good but depends on tongue size.

MACROCLOSSIA

Macroglossia is an uncommon condition characterized by enlargement of the tongue. The enlargement may be caused by a wide variety of conditions, including both congenital malformations and acquired diseases. The most frequent causes are vascular malformations and muscular hypertrophy. Box l lists the most common and important causes of macroglossia.

Box 1 ***Causes of Macroglossia***

Congenital and hereditary

- Vascular malformations
    1. Lymphangioma
    2. Hemangioma
- Hemihyperplasia
- Cretinism
- Beckwith-Wtedemann syndrome
- Down syndrome
- Mucopolysaccharidoses
- Neurofibromatosis
- Multiple endocrine neoplasia, type 2B

Acquired

- Edentulous patients
- Amyloidosis
- Myxedema
- Acromegaly
- Angioedema
- Carcinoma and other tumors

Clinical Features

Macroglossia most commonly occurs in children and can range from mild to severe in degree. In infants, macroglossia may be manifested first by noisy breathing, drooling, and difficulty in eating. The tongue enlargement may result in a lisping speech. The pressure of the tongue against the mandible and teeth can

produce a crenated lateral border to the tongue, open bite, and mandibular prognathism. If the tongue constantly protrudes from the mouth, it may ulcerate and become secondarily infected or may even undergo necrosis. Severe macroglossia can produce airway obstruction.

Macroglossia is a characteristic feature of *Beckwith-Wiedemann syndrome*, a rare hereditary condition that includes many other possible defects, such as:

- Omphalocele (i.e., protrusion of part of the intestine through a defect in the abdominal wall at the umbilicus)
- Visccromegaly
- Gigantism
- Neonatal hypoglycemia

Individuals with Beckwith-Wiedemann syndrome have an increased risk for several childhood visceral tumors, including Wilms tumor, adrenal carcinoma, and
hepatoblastoma. Facial features may include nevus flammeus of the forehead and eyelids, linear indentations of the earlobcs, and maxillary hypoplasia (resulting in relative mandibular prognathism). The mode of inheritance of Beckwith-Wicdemann syndrome is uncertain, but autosomal dominant transmission has been suggested, with variable expressivity and incomplete pcnctrance.

In palients with hypothyrotdism or Beckwith-Wiedemann syndrome, the tongue usually shows a diffuse, smooth, generalized enlargement. In those with other forms of macroglossia, the tongue usually has a multinodular appearance. Examples of this nodular type include amyloidosis and ncoplastic conditions, such as ncurofibromatosis and multiple endocrine neoplasia, type 2B.

In patients with lymphangiomas, the tongue surface is characteristically pebbly and exhibits multiple vesiclelikc blebs that represent superficial dilated lymphatic channels. The enlarged tongue in those with Down syndrome typically demonstrates a papillary, fissured surface.

In patients with hemifacial hyperplasia, the enlargement will be unilateral. Some patients with neurofibromatosis also can have unilateral lingual enlargement.

In edentulous patients the tongue often appears elevated and tends to spread out laterally because of loss of the surrounding teeth; as a result, wearing a denture may become difficult.

Histopathologic features

The microscopic appearance of macroglossia depends on the specific cause. In some cases, such as the tongue enlargement seen in Down syndrome or edentulous patients, no histologic abnormality can be detected. When macroglossia is due to tumor, a neoplastic proliferation of a particular tissue can be found (e.g., lymphatic vessels, blood vessels, neural tissue). Muscular enlargement occurs in those with hemihyperplasia and Beckwith-Wiedemann syndrome. In the patient with amyloidosis, an abnormal protein material is deposited in the tongue.

Treatment and Prognosis

The treatment and prognosis of macroglossia depend on the cause and severity of the condition. In mild cases, surgical treatment may not be necessary, although speech therapy may be helpful if speech is affected. In symptomatic patients, reduction glossectomy may be needed.

ANKYLOCLOSSIA (TONGUE-TIE)

Ankyloglossia is a developmental anomaly of the tongue characterized by a short, thick lingual frenum resulting in limitation of tongue movement. It has been reported to occur in 1.7% to 4.4% of neonates and is four times more common in boys than in girls. In adults, mild forms arc not unusual, but severe ankyloglossia is a relatively uncommon condition that has been estimated to occur in about 2 to 3 of every 10,000 people.

Clinical features

Ankyloglossia can range in severity from mild cases with little clinical significance to rare examples of complete ankylogiossia in which the tongue is actually fused to the floor of the mouth. Sometimes the frenum extends forward and attaches to the tip of the tongue, and there may be slight clefting of the tip.

Some investigators have speculated that ankyloglossia may contribute to the development of an anterior open bite because the inability to raise the tongue to thereof of the mouth prevents development of the normal adult swallowing pattern. However, others have questioned this theory. It also is possible that a high mucogingival attachment of the lingual frenum may lead to periodontal problems.

It has been suggested that tongue-tic may result in speech defects. Usually, however, the shortened frenum results in only minor difficulties because most people can compensate for the limitation in tongue movement. Yet there are rare examples of patients who have experienced an immediate noticeable improvement in speech after surgical correction of ankyloglossia. Recent reports from Japan have theorized that some ankyloglossia cases can be associated with an upward and forward displacement of the epiglottis and larynx, resulting in various degrees of dyspnea.

Treatment and Prognosis

Because most cases of ankyloglossia result in few or no clinical problems, treatment is often unnecessary. If there are functional or periodontal difficulties, a frcnectomy may allow greater freedom of tongue movement. In young children it often is recommended that surgery lie postponed until age 4 or 5. Because the tongue is always short at birth, it is difficult in the infant's early life to assess the degree of tongue limitation caused by ankyloglossia. As the infant grows, the tongue becomes longer and thinner at the tip, often decreasing the severity of the tongue-tie. The condition probably is self-correcting in many cases because it is less common in adults.

LINGUAL THYROID

During the third to fourth week of fetal life, the thyroid gland begins as an epithelial proliferation in the floor of the pharyngeal gut. By the seventh embryonic week, this thyroid bud normally descends into the neck to its final resting position anterior to the trachea and larynx. The site where this descending bud invaginates later becomes the foramen cecum, located at the junction of the anterior two thirds and posterior third of the tongue in the midline. If the primitive gland does not descend normally, ectopic thyroid tissue may be found between the foramen cecum and the epiglottis. Of all ectopic thyroids, 90% are found in this region.

Clinical features

Based on autopsy studies, small asymptomatic remnants of thyroid tissue can be discovered on the posterior dorsal tongue in about 10% of both men and women. However, clinically evident or symptomatic lingual thyroids arc much less common and are four to seven times more frequent in females, presumably because of hormonal influences. Symptoms most often develop during puberty, adolescence, pregnancy, or menopause. In 70% of cases, this ectopic gland is the patient's only thyroid tissue.

Lingual thyroids may range from small, asymptomatic nodular lesions to large masses that can block the airway. The most common clinical symptoms arc dysphagia, dysphonia, and dyspnea. The mass often is vascular, but the physical appearance is variable and there arc no reliable features to distinguish it from other masses that might develop in this area. Hypothyroidism has been reported in up to 33% of patients. Many authors say that lingual thyroid enlargement is a secondary phenomenon, compensating for thyroid hypofunction. Interestingly, as many as 75% of patients with infantile hypothyroidism have some ectopic thyroid tissue.

Diagnosis is best established by thyroid scan using iodine isotopes or tcchnetium 99m. Computed tomography (CT) and magnetic resonance imaging (MRI) can be helpful in delineating the size and extent of the lesion. Biopsy is often avoided because of the risk of hemorrhage and because the mass may represent the patient's only functioning thyroid tissue. In some cases, incisional biopsy maybe needed to confirm the diagnosis or to rule out malignant changes.

Treatment and Prognosis

No treatment except periodic follow-up is required for patients with asymptomatic lingual thyroids. In symptomatic patients, suppressive therapy with supplemental thyroid hormone often can reduce the size of the lesion. Some authors advise that this treatment also should be tried in asymptomatic patients to prevent possible subsequent enlargement. If hormone therapy does not eliminate symptoms, surgical

removal or ablation with radioactive iodine-131 can be performed. If the mass is surgically excised, autotransplantation to another body site can be attempted to maintain functional thyroid tissue and to prevent hypothyroidism.

Rare examples of carcinomas arising in lingual thyroids have been reported; malignancy develops in about 1 % of identified cases. Although lingual thyroids are decidedly more common in females, this predilection for females is less pronounced for lingual thyroid carcinomas. Because a disproportionate number of these malignancies have been documented in males, some authors have advocated prophylactic excision of lingual thyroids in men older than 30 years of age.

FISSURED TONGUE (SCROTAL TONGUE)

Fissured tongue is relatively common. Numerous grooves, or fissures, are present on the dorsal tongue surface. The cause is uncertain, but heredity appears to play a significant role. There is evidence that the condition may be either a polygenic trait or an autosomal dominant trait with incomplete penetrance. Aging or local environmental factors also may contribute to its development.

Clinical Features

Patients with fissured tongue exhibit multiple grooves, or furrows, on the surface of the tongue, ranging from 2 to 6 mm in depth. Considerable variation can be seen. In the most severe cases, numerous fissures cover the entire dorsal surface and divide the tongue papillae into multiple separate "islands." Some patients have fissures that a re located mostly on the dorsolateral areas of the tongue. Other patients exhibit a large central fissure, with smaller fissures branching outward at right angles. The condition is usually asymptomatic, although some patients may complain of mild burning or soreness.

Most studies have shown that the prevalence of fissured tongue ranges from *2%* to 5% of the overall population. The condition may be seen in children or adults, but the prevalence and severity appear to increase with age. In some investigations, a male predilection has been noted.

A strong association has been found between fissured tongue and geographic tongue, with many patients having both conditions. A hereditary basis also has been suggested for geographic tongue, and the same gene or genes may possibly be linked to both conditions. In fact, it even has been suggested that geographic tongue may cause fissured tongue. Fissured tongue also may be a component of Melkersson-Rosenthal syndrome.

Histopathologic Features

Microscopic examination of fissured tongue reveals hyperplasia of the rete ridges and loss of the keratin "hairs" on the surface of the filiform papillae. The papillae vary in size and often are separated by deep grooves. Polymorphonuclear leukocytes can be seen migrating into the epithelium, often forming microabscesses in the upper epithelial layers. A mixed inflammatory cell infiltrate is present in the lamina propria.

Treatment and Prognosis

Fissured tongue is a benign condition, and no specific treatment is indicated. The patient should be encouraged to brush the tongue, because food or debris entrapped in the grooves may act as a source of irritation.

HAIRY TONGUE (BLACK HAIRY TONGUE)

Hairy tongue is characterized by marked accumulation of keratin on the filiform papillae of the dorsal tongue, resulting in a hairlike appearance. The condition apparently represents an increase in keratin production or a decrease in normal keratin desquamation. Hairy tongue is found in about 0.5% of adults. Although the cause is uncertain, many affected people are heavy smokers. Other possible associated factors include the following:

- Antibiotic therapy
- Poor oral hygiene
- General debilitation
- Radiation therapy

- Use of oxidizing mouthwashes or antacids
- Overgrowth of fungal or bacterial organisms

Clinical Features

Hairy tongue most commonly affects the midline just anterior to the circumvallatc papillae, sparing the lateral and anterior borders. The elongated papillae are usually brown, yellow, or black as a result of growth of pigment-producing bacteria or staining from tobacco and food. Sometimes most of the dorsal tongue may be involved, resulting in a thick, matted appearance. Multiple individual elongated filiform papillae may be elevated by usinggauzeor a dental instrument. The condition is typically asymptomatic, although occasional patients complain of a gagging sensation or a bad taste in the mouth. Because the diagnosis usually can be made from the clinical appearance, biopsy is unnecessary in most instances.

Because of the similarity in names, care should be taken to avoid confusing hairy tongue with hairy leukoplakia, which typically occurs on the lateral border of the tongue. Hairy leukoplakia is caused by the Epstein-Barr virus and is usually associated with human immunodeficiency virus (HIV) infection or other immunosuppressive conditions.

Histopathologic Features

On histopathologic examination, hairy tongue is characterized by marked elongation and hyperparakeratosis of the filiform papillae. Usually, numerous bacteria can be seen growing on the epithelial surface.

Treatment and Prognosis

Hairy tongue is a benign condition with no serious sequelae. The major concern is often the aesthetic appearance of the tongue along with possible associated bad breath. Any predisposing factors, such as tobacco, antibiotics, or mouthwashes, should be eliminated, and excellent oral hygiene should be encouraged. Desqua-mation of the hyperkeratotic papillae can be promoted by periodic scraping or brushing with a toothbrush or tongue scraper. Keratolytic agents, such as podophyllin, also have been tried with success, but for safety reasons their use probably should not be encouraged.

ERYTHEMA MIGRANS (GEOGRAPHIC TONGUE; BENIGN MIGRATORY GLOSSITIS; WANDERING RASH OF THE TONGUE; ERYTHEMA AREATA MICRANS; STOMATITIS AREATA MIGRANS)

Erythema migrans is a common benign condition that primarily affects the tongue. It is often detected on routine examination of the oral mucosa. The lesion occurs in 1% to 3% of the population. Females are affected more frequently than males by a 2:1 ratio. Patients may occasionally consult a health care professional if they happen to notice the unusual appearance of their tongue or if the lingual mucosa becomes sensitive to hot or spicy foods as a result of the process.

Even though erythema migrans has been documented for many years, the etiopathogenesis is still unknown. Some investigators have suggested that erythema migrans occurs with increased frequency in atopic individuals, thus raising the possibility that it represents a type of hyperscnsitivity to an environmental factor. In addition, the lesions of erythema migrans in one female patient reportedly waxed and waned predictably with oral contraceptive therapy, suggesting that hormonal factors may be relevant.

Clinical Features

The characteristic lesions of erythema migrans arc seen on the anterior two thirds of the dorsal tongue mucosa. They appear as multiple, well-demarcated zones of erythema, concentrated at the tip and lateral borders of the tongue. This erythema is due to atrophy of the filiform papillae, and these atrophic areas are typically surrounded at least partially by a slightly elevated, yellowish-white, serpentine or scalloped border. The patient who is aware of the process is often able to describe the lesions as appearing quickly in one area, healing within a few days or weeks, then developing in a very different area. Frequently, the lesion begins as a small white patch, which then develops a central erythematous atrophic zone and enlarges centrifugally. Often patients with fissured tongue are affected with erythema migrans as well. Some patients may have only a solitary lesion, but this is uncommon. The lesions are usually

asymptomatic, although a burning sensation or sensitivity to hot or spicy foods may be noted when the lesions are active. Only rarely is the burning sensation more constant and severe.

Very infrequently, erythema migrans may occur on oral mucosal sites other than the tongue. In these instances, the tongue is almost always affected; however, other lesions develop on the buccal mucosa, on the labial mucosa, and (less frequently) on the soft palate. These lesions typically produce no symptoms, and they can be identified by a yellowish-white serpentine or scalloped border that surrounds an erythematous zone. These features should prevent confusion with such conditions as candidiasis or erythroplakia.

Histopathologic Features

If a biopsy specimen of the peripheral region of erythema migrans is examined, a characteristic histopathologic pattern is observed. Hyperparakeratosis, spongiosis, acanthosis, and elongation of the epithelial rete ridges are seen. In addition, collections of neutrophils (Munro abscesses) arc observed within the epithelium; lymphocytes and neutrophils involve the lamina propria. The intense neutrophilic infiltrate may be responsible for the destruction of the superficial portion of the epithelium, thus producing an atrophic, reddened mucosa as the lesion progresses. Because these histopathologic features are reminiscent of psoriasis, this is called a psoriasiform mucositis. In one case-control study of psoriatic patients, erythema migrans occurred at a rate of about 10%; only 2.5% of an age-matched and sex-matched population were affected. A Brazilian study determined that both psoriatics and patients with benign migratory glossitis were more likely to have the same human leukocyte antigen (HLA) group, namely HLA-Cw6. Whether these findings mean that erythema migrans represents oral psoriasis or that psoriatics are just more susceptible to erythema migrans is open to debate.

Treatment and Prognosis

Generally, no treatment is indicated for patients with erythema migrans. Reassuring the patient that the condition is completely benign is often all that is necessary. Infrequently, patients may complain of tenderness or a burning sensation that is so severe that it disrupts their lifestyle. In such cases, topical corticosteroids, such as fluocinonide or betamethasonegel, may provide relief when applied as a thin film several times a day to the lesional areas. One uncontrolled study has recently suggested that zinc supplementation may be effective for symptomatic erythema migrans.

MEDIAN RHOMBOID GLOSSITIS

Median rhomboid glossitis is an abnormality in the midline of the dorsum of the tongue at the junction of the anterior two thirds with the posterior third. The site suggests that it is developmental but it is not seen in children and it is no longer accepted that it results from persistence of the tuberculum impar.

Clinically, median rhomboid glossitis is seen in adults and is typically symptomless. It appears as a nodular red or pink area of depapillation. Alternatively it may be white.

Its chief importance is that the histological features have sometimes been mistaken for a carcinoma and it has been treated accordingly. Quite apart from the need for proper histological assessment, carcinoma virtually never develops in this site.

Histologically, the appearances are also variable and include irregular (pseudoepitheliomatous) hyperplasia with an inflammatory infiltrate, a granular cell tumour or candidosis (the white variant).

Management. Reassurance is usually the main requirement. Candidosis can be recognised by finding hyphae in a Gram-slained smear and can be treated with an antifungal drug. However, a pink or lob-abnormality will remain. Observation is required to ct any enlargement of the area but a need for biopsy is unlikely.

BURNING MOUTH SYNDROME (STOMATOPYROSIS; STOMATODYNIA; GLOSSOPYROSIS; GLOSSODYNIA; BURNING TONGUE SYNDROME)

Burning mouth syndrome is a common dysesthesia (distortion of a sense) typically described by the patient as a burning sensation of the oral mucosa in the absence of clinically apparent mucosal alterations. Although the tongue is most commonly affected (glossopyrosis), other mucosal surfaces may be symptomatic (sto-matopyrosis). In addition to the burning sensation, some patients also experience

mucosal pain (stomatodynia, glossodynia). Idiopathic burning and painful sensations (the "dynias") also can affect the urogenital (vulvodynia) and intestinal mucosa. The scalded mouth syndrome is an apparently unrelated immune response to certain medications, especially angiotensin-converting enzyme (ACE) inhibitors.

Various local and systemic factors have been postulated to cause this condition (Box 1), but none have been proven. The fact that most patients are post-menopausal women has led to the common belief that estrogen or progesterone deficit is responsible, but a strong correlation between such deficits and burning tongue syndrome has not been established. Some evidence exists for an autoimmune origin. Abnormal levels of antinuclear antibody (ANA) and rheumatoid factor (RF), for example, are found in the serum of more than 50% of patients, although these may also be found in older persons without burning mouth syndrome. The disorder has been reported to be strongly associated with depression and anxiety states, leading some authorities to consider it a psychosomatic disease. Well-controlled comparison studies, however, are lacking.

Burning tongue syndrome affects *2%* to 3% of adults to some degree (14% of post-menopausal women). Asians and Native Americans have a considerably higher risk than whites or blacks, and there is increasing prevalence with advancing age, especially after 55 years of age. This disorder is one of the most common problems encountered in the clinical practice of oral and maxillofacial pathology.

Box 1. ***Local and Systemic Factors Reportedly Associated with Burning Tongue Syndrome (Glossopyrosis)***

Local factors

- Xerostomia
- Chronic mouth breathing
- Chronic tongue thrust habit
- Chronic mechanical trauma
- Referred pain from teeth or tonsils
- Trigeminal neuralgia
- Atypical facial pain or neuralgia
- Angioedema (angioneurotic edema)
- Oral candidiasis
- Temporomandibular dysfunction
- Oral submucous fibrosis
- Fusospirochetal infection
- Contact stomatitis (allergy)
- Trauma to lingual nerve

Systemic factors

- Vitamin B deficiency
    1. Vitamin B, or B_2 deficiency
    2. Pernicious anemia ($B_{|2}$)
    3. Pellagra (niacin deficiency)
    4. Folic acid deficiency
- Diabetes mellitus
- Chronic gastritis or regurgitation
- Chronic gastric hypoacidity
- Hypothyroidism
- Mercurialism
- Estrogen deficiency
- Anxiety, stress, depression
- Parkinson's disease
- Acquired immunodeficiency syndrome (AIDS)

Clinical Features

Women are 4 to 7 times more likely to have burning tongue syndrome than men. The syndrome is rare before the age of 30 years (40 years for men) and the onset in women usually occurs within 3 to 12 years after menopause.

This disorder also has a typically spontaneous onset, although it may be quite gradual. The dorsum of the tongue develops a burning sensation, usually strongest in the anterior third. Occasionally, patients will describe an irritated or raw feeling. Mucosal changes are seldom visible, although some patients will show diminished numbers and size of filiform papillae, and individuals who rub their tongue against the teeth often have erythematous and edematous papillae on the tip of the tongue. If the dorsum is significantly erythematous and smooth, an underlying systemic or local infectious process, such as anemia or erythematous candidiasis, should be suspected.

Close questioning often determines that additional oral sites are affected similarly, especially the anterior hard palate and the lips. There is seldom a significant decrease in stimulated salivary output in tests, despite the frequent patient complaint of xerostomia. Salivary levels of various proteins, immunoglobulins, and phosphates may be elevated, and there may be a decreased salivary pH or buffering capacity.

One frequently described pattern is that of mild discomfort on awakening, with increasing intensity throughout the day. Other affected patients describe a waxing and waning pattern that occurs over several days or weeks. Usually the condition does not interfere with sleep. A persistently altered (salty, bitter) or diminished taste may accompany the burning sensation. Contact with hot food or liquids often intensifies the symptoms. A minority describe a constant degree of discomfort.

As with other chronic discomforts, affected patients frequently demonstrate psychologic dysfunction, usually depression, anxiety, or irritability. The dysfunction often disappears, however, with resolution of the burning or painful tongue condition, and there is no correlation between duration and intensity of the burning sensation and the amount of psychologic dysfunction.

Treatment and Prognosis

If an underlying systemic or local cause can be identified and corrected, the lingual symptoms should disappear. Almost two thirds of patients with idiopathic disease show at least some improvement of their symptoms when they take one of the moodaltering drugs (e.g., chlordiazepoxide). Additional therapies that have been used include clonazepam, alpha-lipoic acid (thioctic acid, a neuroprotective drug), amitriptyline, transcuta-neous electrical nerve stimulation, analgesics, antibiotics, antifungals, vitamin B complex, and psychologic counseling. However, none of these treatments has been proven to be effective in a double-blind, placebo-controlled trial.

The long-term prognosis for idiopathic burning tongue or mouth syndrome is variable. Some patients experience a spontaneous or gradual remission months or years after the onset of symptoms. However, other patients may continue to experience symptoms throughout the rest of their lives. Even though the condition is chronic and may not always respond to therapy, patients should be reassured that it is benign and not a symptom of oral cancer.

DYSCEUSIA AND HYPOCEUSIA (PHANTOM TASTE; DISTORTED TASTE)

Dysgeusia is defined as a persistent abnormal taste. It is much less common than simple deficiencies in smell (hyposmia, anosmia) and taste (hypogeusia, ageusia) perception, which are found in approximately 2 million adult Americans. Dysgeusia is less tolerated than hypogeusia or hyposmia, explaining why it accounts for more than a third of patients in chemosensory centers.

Most cases of dysgeusia are produced by or associated with an underlying systemic disorder or by radiation therapy to the head and neck region (Box 2). Trauma, tumors, or inflammation of the peripheral nerves of the gustatory system usually produce transient hypogeusia rather than dysgeusia. In contrast, relatively common upper respiratory infections produce a temporary and mild dysgcusia in almost one third of cases, although they seldom produce hypogeusia. CNS neoplasms predominantly produce dysgeusia, not hypogeusia or ageusia, and taste hallucinations are fairly common during migraine headaches, Bell's palsy, or herpes zoster of the geniculate ganglion. Ischemia and infarction of the brainstem can lead to ageusia of only half of the tongue (hemiageusia) on the same side as the brainstem lesion.

The perception of a particular taste depends on its concentration in a liquid environment; hence, persons with severe dry mouth may suffer from both hypogeusia and dysgeusia. In addition, more than 200 drugs are known to produce taste disturbances (Table 1). Even without medication-induced alterations, 40% of persons with clinical depression complain of dysgeusia. The clinician should be especially diligent in assessing local, intraoral causes of dysgeusia, such as periodontal or dental abscess, oral candidiasis, and routine gingivitis or periodontitis. The latter may produce a salty taste because of the high sodium chloride content of oozing crevicular fluids.

Box 2 ***Local and Systemic Factors Associated With Altered Taste Sensations (Dysgeusia) or Diminished Taste Sensations (Hypogeusia)***

Local factors

- Oral candidiasis
- Oral trichomonasis
- Desquamative gingivitis
- Oral galvanism
- Periodontitis or gingivitis
- Chlorhexidine rinse
- Oral lichen planus
- Xerostomia

Systemic factors

- Vitamin A deficiency
- Vitamin B_{12} deficiency
- Zinc deficiency
- Iron deficiency
- Nutritional overdose (zinc, vitamin A, pyridoxine)
- Food sensitivity or allergy
- Sjogren syndrome
- Chorda tympani nerve damage
- Anorexia, cachexia, bulimia
- Severe vomiting during pregnancy
- Liver dysfunction
- Crohn's disease
- Cystic fibres is
- Familial dysautonomia
- Addison's disease
- Turner syndrome
- Alcoholism
- Medications (200+ types)
- Psychosis or depression
- Pesticide ingestion
- Lead, copper, or mercury poisoning
- Temporal arteritis
- Bralnstem ischemia or infarction
- Migraine headaches
- Temporal lobe central nervous system (CMS) tumor
- Nerve trauma, gustatory nerves
- Herpes zoster, geniculate ganglion
- Upper respiratory infection
- Chronic gastritis or regurgitation
- Bell's palsy
- Radiation therapy to head and neck

Clinical Features

In contrast to hypogeusia, dysgeusia is discerned promptly and distressingly by affected individuals. The clinician must be certain that the patient's alteration is, in fact, a taste disorder rather than an olfactory one, because 75% of "flavor" information (e.g., taste, aroma, texture, temperature, irritating properties) is derived from smell. Abnormal taste function should be verified through formal taste testing by using standard tastants that are representative of each of the four primary taste qualities (e.g., sweet, sour, salty, bitter) in a nonodorous solution. Additional electrical and chemical analysis of taste bud function is frequently required. Because this is outside the scope of most general practices, patients are typically referred to a taste and smell center.

Affected patients may describe their altered taste as one of the primary ones, but many describe the new taste as metallic, foul, or rancid. The latter two arc more likely to be associated with aberrant odor perception (parosmia) than with dysgcusia. The altered taste may require a stimulus, such as certain foods or liquids, in which case the taste is said to be distorted. If no stimulus is required, the dysgeusia is classified as a "phantom" taste.

Treatment and Prognosis

If an underlying disease or process is identified and treated successfully, the taste function should return to normal. For idiopathic cases there is no effective phar-macologic or surgical therapy. Dysgeusia in particular tends significantly to affect lifestyles and interpersonal relationships, perhaps leading to depression, anxiety, or nutritional deficiencies from altered eating habits. Fortunately, two-thirds of dysgeusia patients experience spontaneous resolution (average duration, 10 months). Idiopathic hypogeusia is less of a problem for the patient, but tends to slowly become worse over time. Occasionally, even this will undergo spontaneous resolution.

Table 1 ***Examples of Pharmaceutical***
Agents that May Be Associated With Altered Taste

PHARMACEUTICAL ACTION	EXAMPLES
Anticoagulant	Phenindione
Antihistamine	Chlorpheniramine maleate
Antihypertensive or diuretic	Captopril, diazoxide, ethacrynic acid
Antimicrobial	Amphotericin B, ampicillin, griseofulvin,
Antineoplastic or immunosuppressant	idoxuridine, lincomycin, metronidazole,
Antiparkinsonian agent	streptomycin, tetracycline, tyrothricin
Antipsychotic or anticonvulsant	Doxorubicin, methotrexate, vincristine,
Antirheumatic	azathioprine, carmustine
Antiseptic	Baclofen, chlormezanone, levodopa
Antithyroid agent	Carbamazepine, lithium, phenytoin
Hypoglycemic	Allopurinol, colchicine, gold, levamisole,
Opiate	peniciliamine, phenylbutazone
Sympathomimetic	Hexetidine and chlorhexidine
Vasodilator	Carbimazole, methimazole, thiouracil
	Clipizide, phenformin
	Codeine, morphine
	Amphetamines, phenmetrazine
	Oxyfedrine, bamifylline

CHEILITIS

EXFOLIATIVE CHEILITIS

Exfoliative cheilitis is a persistent scaling and flaking of the vermilion border, usually involving both lips. The process arises from excessive production and subsequent desquamation of superficial keratin. A significant percentage of cases appears related to chronic injury secondary to habits such as lip licking, biting, picking, or sucking. Those cases proven to arise from chronic injury are termed factitious cheilitis.

Many patients deny chronic self-irritation of the area. The patient may be experiencing associated personality disturbances, psychologic difficulties, or stress. In a review of 48 patients with exfoliative cheilitis, 87% exhibited psychiatric conditions and 47% also demonstrated abnormal thyroid function. Evidence suggests that there may be a link between thyroid dysfunction and some psychiatric disturbances.

In other cases, no evidence of chronic injury is evident. In these patients other causes, such as atopy, chronic Candida infection, actinic cheilitis, cheilitis glan-dularis, hypervitaminosis A, and photosensilivity, should be ruled out. In a review of 165 patients with AIDS, over one quarter had alterations that resembled exfoliative cheilitis. In this group, the lip alterations appeared secondary to chronic candidal infestation. The most common presentation of bacterial or fungal infections of the lips is angular cheilitis; diffuse primary infection of the entire lip is very unusual. Most diffuse cases represent a secondary candidal infection in areas of low-grade trauma of the vermilion border of the lip (cfieilocandidiasis).

In one review of 75 patients with chronic cheilitis, a thorough evaluation revealed that over one third represented irritant contact dermatitis (often secondary to chronic lip licking). In 25% of the patients, the cheilitis was discovered to be an allergic contact mucositis. Atopic eczema was thought to be the cause in 19% of cases; the remaining portion was related to a wide variety of pathoses.

In spite of a thorough investigation, there often remain a number of patients with classic exfoliative cheilitis for which no underlying cause can be found. These idiopathic cases are most troublesome and often resistant to a wide variety of interventions.

Clinical Features

A marked female predominance is seen in cases of factitious origin, with most cases affecting those younger than 30 years of age. Mild cases feature chronic dryness, scaling, or cracking of the vermilion border of the lip. With progression, the vermilion can become covered with a thickened, yellowish hyperkeratotic crust that can be hemorrhagic or that may exhibit extensive fissuring. The perioral skin may become involved and exhibit areas of crusted erythema. Although this pattern may be confused with perioral dermatitis, the most appropriate name for this process is circumoral dermatitis. Both lips or just the lower lip may be involved.

In patients with chronic cheilitis, development of fissures on the vermilion border is not rare. In a prevalence study of over 20,000 patients, these fissures involved either lip and were slightly more common in the upper lip. In contrast to typical exfoliative cheilitis, these fissures demonstrate a significant male predilection and a prevalence rate of approximately 0.6%. The majority arises in young adults, with rare occurrence noted in children and the elderly.

Although the cause is unknown, proposed contributing factors include overexposure to sun, wind, and cold weather; mouth breathing; bacterial or fungal infections; and smoking. Application of lipstick or chapstick appears protective- Fissure occurrence also may be related to a physiologic weakness of the tissues. Those affecting the lower lip typically occur in the midline, whereas fissures on the upper vermilion most frequently involve a lateral position. These are the sites of prenatal merging of the mandibular and maxillary processes.

Treatment and Prognosis

In those cases associated with an obvious cause, elimination of the trigger typically results in resolution of the changes. In those cases with no underlying physical, infectious, or allergic cause, psychotherapy (often combined with mild tranquilization or stress reduction) may achieve resolution. Although highly variable, protective moisturizing preparations are occasionally successful in resistant cases.

Casesthat result from Candida infections often do not resolve until the chronic trauma also is eliminated. Initial topical antifungal agents, antibiotics, or both can be administered to patients in whom

chronic trauma is not obvious or is denied. If the condition does not resolve, further investigation is warranted in an attempt to discover the true source of the lip alterations.

In cases for which no cause can be found, therapeutic Interventions often are not successful. Reports have documented lack of response to cryosurgery, antibiotics, antifungals, corticosteroids, vitamin supplements, petrolatum gels, sunscreens, and moisturizing preparations.

Hydrocortisone and iodoquinol (antibacterial and antimycotic) cream has been used to resolve chronic lip fissures in some patients. Other reported therapies include topical silver nitrate, salicylic acid, and various antibacterial and antifungal formulations. In many cases, resistance to topical therapy or frequent recurrence is noted. In these cases, cryotherapy or excision with or without Z-plasty has been successfully used.

ACTINIC CHEILOSIS (ACTINIC CHEILITIS)

Actinic cheilosis is a common premalignant alteration of the lower lip vermilion that results from long-term or excessive exposure to the ultraviolet component of sunlight. It is a problem confined predominantly to light-complexioned people with a tendency to sunburn easily. Outdoor occupation obviously is associated with this problem, leading to the popular use of terms such as *farmer's lip* and *sailor's lip*. A person with chronic sunlight exposure and compromised immunity, especially a transplant recipient, has an elevated risk of developing a cancer of the lower lip vermilion.

Actinic cheilosts is similar to actinic keratosls of the skin in its pathophysiologic and biologic behavior.

Clinical Features

Actinic cheilosis seldom occurs in persons younger than 45 years of age. It has a strong male predilection, with a male-to-female ratio as high as 10:1 in some studies.

The lesion develops so slowly that patients often are not aware of a change. The earliest clinical changes include atrophy of the lower lip vermilion border, characterized by a smooth surface and blotchy pale areas. Blurring of the margin between the vermilion zone and the cutaneous portion of the lip is typically seen. As the lesion progresses, rough, scaly areas develop on the drier portions of the vermilion. These areas thicken and may appear as leukoplakic lesions, especially when they extend near the wet line of the lip. The patient may report that the scaly materiai can be peeled off with some difficulty, only to reform again within a few days.

With further progression, chronic focal ulceration may develop in one or more sites, especially at places of mild trauma from cigarettes or pipe stems. Such ulcerations may last for months and often suggest progression to early squamous cell carcinoma.

Histopathologic Features

Actinic cheilosis is usually characterized by an atrophic stratified squamous epithelium, often demonstrating marked keratin production. Varying degrees of epithelial dysplasla may be encountered. A mild chronic inflammatory cell infiltrate commonly is present subjacent to the dysplastic epithelium. The underlying connective tissue invariably demonstrates a band of amorphous, acellular, basophilic change known as solar (actinic) elastosis, an ultraviolet light-induced alteration of collagen and elastic fibers.

Treatment and Prognosis

Many of the changes associated with actinic cheilosis are probably irreversible, but patients should be encouraged to use lip balms with sunscreens to prevent further damage. Areas of induration, thickening, ulceration, or leukoplakia should be submitted for biopsy to rule out carcinoma. In clinically severe cases without malignancy, a lip shave procedure (vermilionectomy) may be performed. The vermilion mucosa is removed, and either a portion of the intraoral labial mucosa is pulled forward or the wound is allowed to heal by secondary intention. Alternative treatments include CO_2 laser ablation and electrodesiccation. Long-term follow-up is recommended. Of course, if a squamous cell carcinoma is identified, the involved lip is treated accordingly.

Squamous cell carcinoma, usually well differentiated, develops over time in 6% to 10% of actinic chcilosis cases reported from medical centers. Such malignant transformation seldom occurs before 60

years of age, with the resulting carcinoma typically enlarging slowly and metastasizing only at a late stage.

CHEILITIS GLANDULARIS

Cheilitis glandularis is a rare inflammatory condition of the minor salivary glands. The cause is uncertain, although several etiologic factors have been suggested, including actinic damage, tobacco, syphilis, poor hygiene, and heredity.

Clinical Features

Cheilitis glandularis characteristically occurs on the lower lip, although there are also purported cases involving the upper lip and palate. Affected individuals experience swelling and eversion of the lower lip as a result of hypertrophy and inflammation of the glands. The openings of the minor salivary ducts are inflamed and dilated, and pressure on the glands may produce mucopurulent secretions from the ductal openings. The condition most often has been reported in middle-aged and older men, although cases also have been described in women and children. However, some of the childhood cases may represent other entities, such as exfollative cheilitis.

Historically, cheilitis glandularis has been classified into three types, based on the severity of the disease:

1. Simple
2. Superficial suppurative (Baelz's disease)
3. Deep suppurative (cheilitis glandularis apostem-atosa)

The latter two types represent progressive stages of the disease with bacterial involvement and are characterized by increasing inflammation, suppuration, ulcer-ation, and swelling of the lip.

Hisiopathologic Features

The microscopic findings of cheilitis glandularis are not specific and usually consist of chronic sialadenitis and ductal dilatation. Concomitant dysplastic changes may be observed in the overlying surface epithelium in some cases.

Treatment and Prognosis

The treatment of choice for most cases of persistent cheilitis glandularis associated with actinic damage is verrnilionectomy (lip shave), which usually produces a satisfactory cosmetic result. A significant percentage of cases (18% to 35%) have been associated with the development of squamous cell carcinoma of the overlying epithelium of the lip. Because actinic damage has been implicated in many cases of cheilitis glandularis, it is likely that this same solar radiation is responsible for the malignant degeneration.

ANGULAR STOMATITIS(ANGULAR CHEILITIS)

Angular stomatitis is typically caused by leakage of candida-infected saliva at the angles of the mouth. It can be seen in infantile thrush, in denture wearers or in association with chronic hyperplastic candidosis. It is a characteristic sign of candidul infection.

Clinically, there is mild inflammation at the angles of the mouth. In elderly patients with demure-induced stomatitis, inflammation frequently extends along folds of the facial skin extending from the angles of the mouth. These folds have frequently hut unjustifiably been ascribed to 'closed bile', but in fact are due to sagging of the facial tissues with age. Such folds are difficult to eliminate except by plastic surgery.

Treatment of intraoral candidal infection alone causes angular stomatitis to resolve. If there is coinfeclion with *Staphylococcus aureus,* local application of fusidic iicid cream may be required.

CRACKED LIP

Aetiology. Chronic (self-induced) trauma amd maceration, mouth breathing. Also found in: Crohn’s disease, Down’s syndrome.

Incidence. Common during cold, windy, winter weather.

Clinical features. Usually single persistent painful vertical fissure: bleeds on stretching lip and on opening mouth wide.

Investigation. Clinical features diagnostic.
Treatment. Bland creams; rarely excision (curative).

OROFACIAL GRANULOMATOSIS

Since its introduction in 1985 by Wiesenfeld, orofacial granulomatiosis has become a well-accepted and unifying term encompassing a variety of clinical presentations that, upon biopsy, reveal the presence of non-specific granulomatous inflammation. The conditions previously designated as ***Melkersson-Rosenthal syndrome*** and ***cheilitis granulomatosa of Miescher*** are subsets of orofacial granulomatosis, and neither represent a specific disease.

The disorder is somewhat analogous to aphthous stomatitis, in that the cause is idiopathic but appears to represent an abnormal immune reaction. Sometimes oral lesions are seen that are identical to idiopathic orofacial granulomatosis but represent a secondary reaction to one or more of a variety of factors.

Because clinical and histopathologic features of orofacial granulomatosis can be produced by a variety of underlying causes, this diagnosis is the beginning, not the end, of the patient's evaluation. After initial diagnosis, the patient should be evaluated for several systemic diseases and local processes that may be responsible for similar oral lesions. If features diagnostic of one of these more specific disorders are discovered, the final diagnosis is altered appropriately.

Table 1 ***Systemic evaluation of patients with orofacial granulomatosis***

Systemic cause	Preliminary screening procedures
Chronic granulomatous disease	Neutrophil nitroblue tetrazolium reduction test. Perform if medical history of chronic infections is noted.
Crohn's disease	Hematologic evaluation for evidence of gastrointestinal malabsorption or leukocyte scintigraphy; if initial screen is positive, recommended esophagogastrodduodenoscopy, and small bowel radiographs
Sarcoidosis	Serum angiotensin-converting enzyme and chest radiograph
Tuberculosis	Skin test and chest radiograph

Table 2 ***Interventions to rule out local causes for orofacial granulomatosis***

Local cause	Intervention
Chronic oral infection	Eliminate all oral foci of infection
Foreign material	The foreign debris noted in iatrogenic gingivitis is often subtle and difficult to associate definitively with the diffuse inflammatory process. If lesions are non-migrating and isolated to gingiva, response to local excision of a single focus should be evaluated.
Allergy	Cosmetics, foods, food additives, flavorings, oral hygiene products, and dental restorative metals have been implicated. Patch testing or elimination diet may discover the offending antigen.

Clinical features

The clinical presentation of orofacial granulomatosis is highly variable. By far, the most frequent site of involvement is the lips. The labial tissues demonstrate a nontender, persistent swelling that may involve one or both lips. On rare occasions, superficial amber vesicles, resembling lymphangiomas, are found. When these signs are combined with facial paralysis and a fissured tongue, the clinical presentation is called ***Melkersson-Rosenthal syndrome***. Involvement of the lips alone is called ***cheilitis granulomatosa (of Miescher)***. Some consider cheilitis granulomatosa an oligosymptomatic form of Melkersson-Roselthal syndrome, but it appears best to include all of these under the term orofacial granulomatosis. In addition to labial edema, swelling of other parts of the face may be seen.

Intraoral sites also seen be affected, and the predominant lesions are edema, ulcers, and papules. The tongue may develop fissures, edema, paraesthesia, erosions, or taste alteration. The gingiva can develop swelling, erythema, pain, or erosions. The buccal mucosa often exhibits a cobblestone appearance of edematous mucosa or focal areas of submucosal enlargement. Linear hyperplastic folds may occur in the mucobuccal fold, with linear ulcerations appear in the base of these folds. The palate may have papules or large areas of hyperplastic tissue. Hyposalivation is rarely reported.

Histopathologic features

In classic cases of cheilitis granulomatosa, edema is present in the superficial lamina poropria with dilation of lymphatic vessels and scattered lymphocytes seen diffusely and in clusters. Fibrosis may be present in long-term lesions. Scattered aggregates of noncaseating granulomatous inflammation, consisting of lymphocytes and epithelioid histiocytes, are present, with or without multinucleated giant cells. Typically, the granulomas appear to cluster around scattered vessels and are not as well formed or discrete as those seen in sarcoidosis.

Special stains for fungal organisms and acid-fast bacteria are negative. No dissolvable, pigmented, or polarizable foreign material should be present. When the lesions are confined to the gingiva, a through search should be made because many cases of granulomatous gingivitis are due to subtle collections of foreign material.

Diagnosis

The initial diagnosis of orofacial granulomatosis is made upon histopathologic demonstration of granulomatous inflammation that is associated with negative special stains for organisms and no foreign material. Based on the clinical and historical findings, one or more conditions may have to be considered in the differential diagnosis. It should be stressed that no one cause for the granulomas will be found when large groups of patients with orofacial granulomatosis are studied.

Treatment and prognosis

The first goal of management should be discovery of the initiating cause, although this may be most difficult. Often the trigger is elusive. Local measures to resolve the clinical manifestations can be attempted but, as would be expected, recurrences are common. The individual lesions have been treated with a variety of interventions, with variable results. Intralesional corticosteroids, radiotherapy, salazosulfapyridine, hydroxychloroquine sulfate, azathioprine, cyclosporine A, methotrexate, danazol, dapsone, clofazimine, metronidazole, and numerous other antibiotics have been tried. Currently, most investigators administer intralesional corticosteroids to control the progression of this disease. Because of the natural variability of the disease's progression and the occurrence of spontaneous remissions, therapies are difficult to assess. In the absence of a response to other treatment, surgical recontouring has been used by some but carries a considerable risk of recurrence and rarely appears to be warranted.

The prognosis is highly variable. No therapy has proved to be the "silver bullet" in resolving the individual lesions. In some cases, lesions resolve spontaneously, with or without therapy; in others, they continue to progress in spite of a myriad of therapeutic attempts to stop the progression. The "lucky" subset of patients includes those who have resolved their problems by the exclusion of the offending agent.

LECTURE 5

ORAL PREMALIGNANCY. CLINIC, DIAGNOSIS, DENTIST'S TACTICS.

Precancer terminology.

- ***Precancerous lesion (precancer, premalignancy)***. A benign, morphologically altered tissue that has a greater than normal risk of malignant transformation.
- ***Precancerous condition***. A disease or patient habit that does not necessarily alter the clinical appearance of local tissue but is associated with a greater than normal risk of precancerous lesion or cancer development in that tissue.
- ***Malignant transformation potential***. The risk of cancer being present in a precancerous lesion or condition, either at initial diagnosis or in the future (usually expressed in percentages). The potential for mucosa without precancerous lesions or conditions is called "normal".
- ***Relative risk***. A specific epidemiologic measure of the association between exposure to a particular factor and the risk of acquiring a disease, expressed as a ratio of the incidence or prevalence of a disease among those exposed and those not exposed to the factor.

Precancrous lesions of the oral, pharyngeal, and laryngeal mucosa

Disease name	Malignant transformation potential
Proliferative verrucous leukoplakia	++++++
Nicotine palatinus in reverse smokers	+++++
Erythroplakia	+++++
Oral submucous fibrosis	+++++
Erythroleukoplakia	++++
Granular leukoplakia	++++
Laryngeal keratosis	+++
Actinic cheilosis	+++
Smooth, thick leukoplakia	++
Smooth, red tongue of Plummer-Vinson syndrome	++
Smokeless tobacco keratosis	+
Lichen planus (erosive forms)	+?
Smooth, thin leukoplakia	+/-

ORAL SUBMUCOUS FIBROSIS

Oral submucous fibrosis is a chronic, progressive, scarring, high-risk precancerous condition of the oral mucosa seen primarily on the Indian subcontinent and in Southeast Asia. It has been linked to the chronic placement in the mouth of a betel quid or *paan* and is found in 0.4% of India's villagers. The quid consists typically of areca nut and slaked lime, usually with tobacco and sometimes with sweeteners and condiments, wrapped in a betel leaf. The slaked lime acts to release an alkaloid **(arecaidine)** from the areca nut, producing a feeling of euphoria and well being in the user. Villagers habitually chew betel quids from an early age, frequently for 16 to 24 hours daily.

The condition is characterized by a mucosal rigidity of varied intensity caused by a fibroelastic hyperplasia and modification of the superficial connective tissue. The submucosal changes may be a response to the areca nut; the epithelial alterations and carcinogenesis may be the result of tobacco contact. Nutritional deficiency increases the risk and severity of fibrosis, and some persons seem to have a genetic predisposition to it. A few individuals have developed the disease after only a few contacts with areca nut.

Clinical Features

Oral submucous fibrosis often is first noted in young adult betel quid users, whose chief complaint is an inability to open the mouth ***(trismus),*** often accompanied by mucosal pain while eating spicy foods. An interincisal distance of less than 20 mm is considered severe; in advanced cases, the jaws may actually be inseparable. Females are more susceptible to these changes than males.

Vesicles, petechiae, melanosis, xerostomia, and a generalized oral burning sensation **(stomatopyrosis)** are usually the first signs and symptoms. The buccal mucosa, retromolar area, and soft palate are the most commonly affected sites. The mucosa in these regions develops a blotchy, marblelike pallor and a progressive stiffness of subepithelial tissues. When the tongue is involved, it becomes rather immobile, is frequently diminished in size, and may be devoid of papillae. Submucosal fibrous bands are palpable on the buccal mucosa, soft palate, and labial mucosa of fully developed cases. Leukoplakia of the surface mucosa often is noted.

Betel quid chewers also may exhibit a brownish-red discoloration of the mucosa with an irregular surface that tends to desquamate. This particular change, known as **betel chewer's mucosa,** is not believed to be precancerous.

Histopathologic Features

Oral submucous fibrosis is characterized by the submucosal deposition of extremely dense and avascular collagenous connective tissue with variable numbers of chronic inflammatory cells, sometimes imparting a lichenoid appearance. Epithelial changes include subepithelial vesicles in early lesions and hyperkeratosis with marked epithelial atrophy in older lesions. Epithelial dysplasia is found in 10% to 15% of cases submitted for biopsy, and carcinoma is found in at least 6% of sampled cases.

The lesions of so-called betel chewer's mucosa are histopathologically similar to morsicatio buccarum, except that the ragged keratinaceous surface is covered by encrustations of betel quid ingredients.

Treatment and Prognosis

Unlike tobacco pouch keratosis, oral submucous fibrosis does not regress with habit cessation. Patients with mild cases may be treated with intralesional corticosteroids to reduce the symptoms; surgical splitting or excision of the fibrous bands may improve mouth opening and mobility in the later stages of the disease. One recent study showed that intralesional injections of interferon *gamma* improved maximum mouth opening, reduced mucosal burning, and increased suppleness of the buccal tissues.

Frequent evaluation for development of oral squamous cell carcinoma is essential because a 17-year malignant transformation rate of 8% has been determined for betel quid users in India. Overall, persons with oral submucous fibrosis are at least 19 times more likely to develop oral cancer than persons without the disease.

NICOTINE STOMATITIS (NICOTINE PALATINUS; SMOKER'S PALATE)

Once a common mucosal change of the hard palate, ***nicotine stomatitis*** has become less common as cigar and pipe smoking have lost popularity. Although this lesion is a white keratotic change obviously associated with tobacco smoking, it does not appear to have a pre-malignant nature, perhaps because it develops in response to heat rather than the chemicals in tobacco smoke. Because pipe smoking generates more heat on the palate than other forms of smoking, nicotine stomatitis has been associated most often with this habit. Similar changes can also be produced by the long-term use of extremely hot beverages.

In some South American and Southeast Asian cultures, hand-rolled cigarettes and cigars are smoked with the lit end held within the mouth. This "reverse smoking" habit produces a pronounced palatal keratosis, or ***reverse smoker's palate,*** which has a significant potential to develop dysplasia or carcinoma.

Clinical Features

Nicotine stomatitis most commonly is found in men older than 45 years of age. With long-term exposure to heat, the palatal mucosa becomes diffusely gray or white; numerous slightly elevated papules are noted,

usually with punctate red centers. Such papules represent inflamed minor salivary glands and their ductal orifices. The mucosa that covers the papules frequently appears whiter than the surrounding epithelium.

The palatal keratin may become so thickened that a fissured or "dried mud" appearance is imparted. The whiteness usually involves marginal gingiva and interdental papillae, and leukoplakia of the buccal mucosa is occasionally seen. A heavy brown or black tobacco stain may be present on the teeth.

Histopathologic Features

Nicotine stomatitis is characterized by hyperkeratosis and acanthosis of the palatal epithelium and mild, patchy, chronic inflammation of subepithelial connective tissue and mucous glands. Squamous metaplasia of the excretory ducts is usually seen and an inflammatory exudate may be noted within the duct lumina. In cases with papular elevation, hyperplastic ductal epithelium may be seen near the orifice. The degree of epithelial hyperplasia and hyperkeratosis appears to correlate positively with the duration and the level of heat exposure. Epithelial dysplasia rarely is seen.

Treatment and Prognosis

Nicotine stomatitis is completely reversible, even when it has been present for many decades. The palate returns to normal, usually within 1 to 2 weeks of smoking cessation. Although this is not a precancerous lesion and no treatment is needed, the patient nevertheless should be encouraged to stop smoking (and other high-risk areas should be examined closely). Any white lesion of the palatal mucosa that persists after 1 month of habit cessation should be considered a true leukoplakia and managed accordingly.

ACTINIC KERATOSIS (SOLAR KERATOSIS)

Actinic keratosis is a common cutaneous premalignant lesion that is caused by cumulative ultraviolet radiation to sun-exposed skin, especially in fair-skinned people. Ultraviolet light exposure can produce mutations in the p53 tumor suppressor gene, an alteration found frequently in this and other precancers and cancers of the head and neck region. A similar phenomenon, **actinic cheilosis,** is associated with sun damage to the lower lip vermilion.

The lesion will develop on the skin of more than 50% of all white adults with significant lifetime sun exposure, and in the U.S. white population the prevalence rate is 15% for older men and 6% for older women. The prevalence increases with advancing age. Although the exact frequency of malignant transformation is unknown, it has been estimated that only one in a thousand individual lesions will become invasive. In high-risk populations, however, at least 13% of affected patients will develop invasive squamous cell carcinoma from at least one of their actinic keratoses.

Clinical Features

Actinic keratosis seldom is found in persons younger than 40 years of age. The face and neck, the dorsum of the hands, the forearms, and the scalp of bald-headed men are the most common sites of occurrence. Individual lesions are irregular scaly plaques, which vary in color from normal to white, gray, or brown, and may be superimposed on an erythematous background. The keratotic scale peels off with varying degrees of difficulty. Palpation reveals a “sandpaper”, roughened texture, and some lesions can be felt more easily than thay can be seen. Typically, a lesion is smaller than 7 mm in diameter but may reach a size of 2 cm, usually with minimal elevation above the surface of the skin. Occasional lesions, however, produce so much keratin that a “horn” may be seen arising from the central area. Other skin lesions, such as verruca vulgaris or seborrheic keratosis, also may produce keratin or **cutaneous horns**.

Histopathologic Features

Histopathologically, actinic keratosis is characterized by hyperparakeratosis and acanthosis. Teardrop-shaped rete ridges typically extend down from the epithelium; by definition, some degree of epithelial dysplasia is present. When full-thickness dysplasia is noted, this is termed ***bowenoid actinic keratosis***. Suprabasilar acantholysis may be seen, as may melanosis and a lichenoid inflammatory infiltrate. The dermis exhibits a band of pale basophilic change, which represents sun-damaged collagen and elastic fibers (***solar elastosis***). In this band of sun-damaged connective tissue, there is a fourfold increase in the

amount of elastic fibers and band thickness is increased with increased exposure to actinic rays. Variable numbers of chronic inflammatory cells are typically present.

Treatment and Prognosis

Because of its precancerous nature, it is usually recommended that actinic keratosis be destroyed by cryotherapy with liquid nitrogen, topical application of 5-fluorouracil, curettage, electrodesiccation, or surgical excision. Recurrence is rare, but additional lesions frequently arise in adjacent sun-damaged skin. Long-term follow-up, therefore, is recommended.

KERATOACANTHOMA ("SELF-HEALING" CARCINOMA; PSEUDOCARCINOMA)

Keratoacanthoma is a self-limiting, epithelial proliferation with a strong clinical and histopathologic similarity to well-differentiated ***squamous cell carcinoma*.** In fact, some authorities consider it to represent an extremely well-differentiated form of squamous cell carcinoma. Cutaneous lesions presumably arise from the infundibulum of hair follicles. Intraoral lesions have been reported, but they are rare and, in fact, some authorities do not accept keratoacanthoma as an intraoral disease.

The cause of this lesion is unknown, but sun damage and human papillomavirus (HPV), possibly subtypes 26 or 37, have been proposed. The association with sun damage is suggested by the fact that most solitary lesions are found on sun-exposed skin, predominantly in the elderly. In addition, keratoacanthoma-like lesions have been produced in animals by the cutaneous application of carcinogens.

There appears to be a hereditary predisposition for multiple lesions, and the lesions occur with increased frequency in immunosuppressed patients and those with ***Muir-Torre syndrome*** (sebaceous neoplasms, keratoacanthomas, and gastrointestinal carcinomas).

Clinical Features

Keratoacanthoma rarely occurs in patients before 45 years of age and shows a male predilection. Almost 95 % of solitary lesions are found on sun-exposed skin, and 8% of all cases are found on the outer edge of the vermilion border of the lips, with equal frequency on both the upper and lower lips.

Keratoacanthoma appears as a firm, nontender, well-demarcated, sessile, dome-shaped nodule with a central plug of keratin, although lesions reported as intraoral keratoacanthoma usually have lacked the central plug. The outer portion of the nodule has a normal texture and color but may be erythematous. The central keratin plug is yellowish, brown, or black and has an irregular, crusted, often verruciform surface.

Rapid enlargement is typical, with the lesion usually attaining a diameter of 1 to 2 cm within 6 weeks. This critical feature helps to distinguish it from the more slowly enlarging squamous cell carcinoma. Most lesions regress spontaneously within 6 to 12 months of onset, frequently leaving a depressed scar in the area.

Occasional patients demonstrate large numbers of keratoacanthomas. One multiple-lesion variant, the Ferguson Smith type, manifests in early life and appears to be hereditary; the lesions are not likely to involute spontaneously. Another variant manifests as hundreds of small papules of the skin and upper digestive tract (eruptive Grzybowski type) and may be associated with internal malignancy.

Histopathologic Features

Keratoacanthoma of the skin and lip vermilion warrants excisional or large incisional biopsy with inclusion of adjacent, clinically normal epithelium for proper histopathologic interpretation; this is because the overall pattern of the tumor is diagnostically more important than the appearance of individual cells. The cells appear mature, although considerable dyskeratosis (abnormal or premature keratin production) is typically seen in the form of deeply located individually keratinizing lesional cells and keratin pearls similar to those found in well-differentiated squamous cell carcinoma.

The surface epithelium at the lateral edge of the tumor appears normal; at the lip of the central crater, however, a characteristic acute angle is formed between the overlying epithelium and the lesion. The crater is filled with keratin, and the epithelium at the base of the crater proliferates downward. This action often elicits a pronounced chronic inflammatory cell response. Downward proliferation does not

extend below the level of the sweat glands in skin lesions or into underlying muscle in vermilion lesions. Late-stage lesions show considerably more keratinization of the deeper aspects of the tumor than do early lesions.

Treatment and Prognosis

Despite the propensity of keratoacanthoma to involute of its own accord, surgical excision of large lesions is indicated for optimal aesthetic appearance because significant scarring may otherwise occur. After excision, 2 % of treated patients experience recurrence. Aggressive behavior and malignant transformation into carcinoma have been reported in a small proportion of keratoacanthomas, but the close histopathologic similarities between this lesion and squamous cell carcinoma make it difficult to rule out the possibility of misinterpretation of the microscopic section.

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