CHAPTER 10.

DISEASES OF METABOLISM

Scurvy
Pellagra
Sprue
Uraemia.
SCURVY

Scurvy is a nutritional disease caused by prolonged inadequate intake of vitamin C. Although this condition was at one time very prevalent it is now rarely seen. Orban and Wentz (1960), note that it is likely to occur in bottle-fed children receiving no fresh vegetables or fruit, a condition which is referred to as "Barlow's disease". An adequate adult intake of vitamin C is considered to be 50-100 mgms per day (Stones, 1962), and since its chief function is the formation of intercellular substance, a deficiency of this vitamin will affect deposition of osteoid tissue, dentine and collagen. General clinical manifestations of scurvy include retardation of wound healing, haemorrhage into the skin, muscles and joints, anaemia and resorption of bone producing osteoporosis (Orban and Wentz, 1960; Thoma and Goldman, 1961; Bhaskar, 1961; Burket, 1961).

All investigators give a consistent description of oral lesions in scurvy (notably Orban et al., 1947; Roughton and Waldron, 1953; Comroc et al., 1954; Medina, 1956; Miller and Roth, 1957; Tiecke et al., 1959; Thoma and Goldman, 1960; Radden and Reade, 1963; Shafer et al., 1963). The gingivae are characteristically swollen, spongy and bleed easily. Petechiae may be observed on the palate, buccal mucosa and floor of the mouth. In severe cases necrosis and ulceration occur and Shafer et al. (1963), describes such lesions as exhibiting the typical bacteriological picture of acute necrotizing ulcerative gingivitis.

According to Weech (1959), the diagnosis of scurvy is based upon a history of inadequate dietary intake of vitamin C and the
obvious clinical signs of haemorrhage into skin and mucosal surfaces. Administration of vitamin C usually brings about dramatic improvement in the general and oral condition.

Roughton and Ward (1953), give an interesting report of scurvy in a male, aged 61 years. A sharply circumscribed, ulcer, approximately 2 cms in diameter was present on the palatal aspect of the upper right molar teeth. A biopsy report was non-specific, although collagen fibres were seen to be few in number and poorly formed. A dietary survey confirmed the suspicion of scurvy and the lesion rapidly healed following vitamin C administration.
Sprue is a syndrome characterized by impaired intestinal absorption of fat, fat-soluble vitamins and some carbohydrates (Ross, 1954). According to Burket (1961), it occurs chiefly in persons who have consumed a diet consisting mainly of carbohydrates and fats for long periods. The cause of the condition is unknown, but Hunter et al (1960), believe it is a result of a mixed vitamin deficiency among which folic acid appears to play the dominant role. Some writers (Thoma and Goldman, 1960; Stones, 1962), favour the earlier view that sprue is a disease of tropical countries. However, other writers (Schenken and Burns (in Anderson, 1957); Shafer et al, 1963), describe "non-tropical" sprue which occurs in temperate climates and may be similar, if not identical with tropical sprue. The disease is marked by progressive loss of weight, hyperchromatic macrocytic anaemia, hyperchlorhydria and steatorrhea.

Adlersberg and Schein (1947), divide the condition into primary and secondary forms. Primary sprue exists when no pathological change is demonstrable in the alimentary canal which would account for the syndrome. Secondary sprue appears to be associated with intestinal lesions such as lymphosarcoma and amyloidosis.

Oral lesions most frequently occur in primary sprue and are characterized by a painful, red tongue with atrophied papillae. Hunter et al (1960), Thoma and Goldman (1960), and Burket (1961), report that the surface of the tongue may be denuded in irregular shaped patches, and that ulceration frequently occurs. Adlersberg
(1943), and Hunter et al (1960), observe that such lesions may be so severe that ingestion of food through the mouth is difficult.

Oral symptoms usually disappear completely following the administration of Folic acid, vitamin B complex and vitamin C.
PELLAGRA

Pellagra, the principal syndrome associated with nicotinic acid deficiency, may exhibit mucosal, mental, neurological and cutaneous manifestations. Bernier (1959), and Stones (1962), report that other factors, such as tryptophan deficiency, may be associated with the condition. It is characterized by a red, scaly dermatitis, diarrhoea and vague symptoms such as numbness, lassitude, vertigo and anorexia.

Afonsky (1950), Bhashkar (1961), and Burkett (1961), point out that oral lesions frequently precede other symptoms by months, or even years. The mucous membrane becomes fiery red with marked pain and salivation developing. Oral involvement is usually severe and the tongue exhibits the most characteristic changes. In the acute stage of pellagra the epithelium of the entire dorsum may desquamate to produce painful, irregularly-shaped ulcers with clearly-demarcated borders. Bernier (1959), considers that such lesions may occur at any site in the mouth. From the interdental papillae ulcerative lesions may extend rapidly to involve all the gingival tissues. The spirochaete and bacilli typical of ulcerative necrotizing gingivitis may frequently be isolated from the lesions (Cheraskin and Langley, 1957; Thoma and Goldman, 1960; Burkett, 1961; Stones, 1962). Bernier (1959), notes that extensive erosions may enlarge and deepen to contain masses of necrotic tissue.

A 23-year old male seen by Weisberger (in Thoma and Goldman, 1960), had an inflamed mouth and a large ulcer in the lower left buccal sulcus
which extended into the cheek. A smear showed numerous Treponema
vincentii and fusiform bacilli. The only treatment given was
nicotinic acid (100 mgm. daily), and by the fourth day the lesion
had completely healed.
Female, Aged 65 years.

**NUTRITIONAL DEFICIENCY STOMATITIS**

This painful oral condition was first noticed 3 days previously. The patient had not been wearing the upper denture and stated that she could not remember burning her mouth.

Examination disclosed a severely ulcerated upper denture bearing area and a painful nodule on the palate corresponding to the distal border of the denture. The mucous membrane of the tongue and mandibular denture bearing areas were slightly inflamed. The upper denture was unsatisfactory and the patient stated she had difficulty masticating.

Past medical and dental histories were non-contributory and a Full and Differential Blood Count, Urinalysis and Bacteriological smear were negative. However, a Dietary analysis disclosed a marked deficiency of all nutrients.

Treatment consisted of dietary advice, therapeutic doses of vitamin A, vitamin B complex and vitamin C, and tannic acid mouthrinses. At the end of eight weeks the oral condition had improved sufficiently for impressions for new dentures to be taken.
URAEMIA

Uraemia is a term used to denote the effects of the retention of urinary constituents in the system. It arises in nephritis and in other conditions associated with renal insufficiency. Symptoms of uraemia include marked fatigue, general body dehydration, loss of weight, cardiac irregularity and an inability to maintain normal nutritional requirements because of vomiting and diarrhoea.

There are few references in the literature to oral manifestations of uraemia. Mead (1944), Schaffer (1951), Comroe et al (1954), Thoma and Goldman (1960), Burket (1961), Stones (1962), and Ship (1963), consider the principal oral changes are a urine-like odour of the breath, a yellow, dry appearance of the mucosa, a brown coating of the tongue, xerostomia and a lowered resistance to infection. Painful oral ulceration is a common finding and Ship (1963), stipulates that these ulcers are not preceded by vesicles and bullae. According to Burket (1961), they initially develop at a site of irritation and are surrounded by an area of inflammation. There is general agreement that the ulcers are covered by a greyish or yellowish membranous covering. Black (in Burket), believes that the ulcers are due to the caustic action of ammonium carbonate which is formed from the salivary urea.

Cook (1960), describes terminal uraemia in a 68-year old man. There was a marked urine-like odour of the breath and ulcerative lesions present on the lower lip and gingivae were covered by slough. The histopathological report from a biopsy specimen of a typical oral
lesion was "acute purulonecrotic inflammation and ulceration".

Ulceration in uraemia rapidly improves when a fall occurs in the B.U.N. (blood urea nitrogen) and N.P.N. (non-protein nitrogen) levels. Local treatment of the lesions includes removal of sources of irritation and maintenance of good oral hygiene. Burket advocates the use of a hydrogen peroxide mouthrinse which tends to neutralize the high alkalinity of the saliva.
CHAPTER 11.

DERMATOLOGICAL DISEASES.

Pemphigus
Benign Mucous Membrane Pemphigoid.
Erythema Multiforme
Mucocutaneous-Ocular Syndromes
1. Stevens Johnson Syndrome
2. Behçet's Syndrome
3. Reiter's Syndrome
4. Ectodermis Erosiva Pluriorificialis
Lupus Erythematosus
Lichen Planus
Epidermolysis Bullosa.
PEMPHIGUS

The word "pemphigus" is derived from the Greek word meaning "blister". This is a relatively uncommon and serious disease of unknown aetiology characterized by successive bullous formation on the skin and mucous membranes. As with other dermatological conditions exhibiting oral manifestations, the literature consists chiefly of reports of clinical findings; this is probably a reflection of the disease's uncertain aetiology and the difficulty of experimental work.

There are several classifications for the different clinical forms of pemphigus. However, those generally recognised are:-(a) pemphigus vulgaris, (acute or chronic), (b) pemphigus vegetans, (c) pemphigus foliaceus, and (d) pemphigus erythematodes. Oral manifestations may occur in all of these forms but are most often associated with pemphigus vulgaris (Lever, 1942; Stern, 1949; Orban and Wentz, 1960; Bhaskar, 1961).

Oral lesions are usually less characteristic than the cutaneous ones and may precede them by months or even years. The high incidence of oral involvement in pemphigus (figures vary from 55% (Lever, 1942 and Quinn, 1948) to 70% (Director, cited by Cooke, 1960)), led Stern (1949), to consider whether lesions always occur initially on mucosal surfaces. He reported that the pathogenesis of pemphigus is obscure, but the clinician should suspect the condition from incipient oral lesions even when they are unaccompanied by skin manifestations.
(a) Pemphigus vulgaris.

This is the most commonly occurring form of the disease (Andrews, 1955 and Bhaskar, 1963, call it "true pemphigus"), and it shows a marked predilection for persons of Mediterranean and Jewish origin. No investigator has yet explained this correlation. All writers (notably Lever, 1942; Andrews, 1955; Levin, 1956; Thoma and Goldman, 1960), report that oral manifestations are severe. The bullae tend to rupture as soon as they form, so that the usual picture is of superficial, painful ulcers which initially exhibit remnants of the collapsed capsule ("epithelial tags") at the peripheries. These ulcers have an irregular border and according to Ship (1963), demonstrate occasional bleeding and a greyish-yellow adherent, fibrinous covering. They show little tendency to heal and frequently extend onto the lips.

With each successive crop of bullae the erosions enlarge so that at the severest stage the entire mucous membrane of the oral cavity, larynx and pharynx may be transformed into a single erosion (Lever, 1954; Levin, 1956; Shklar and McCarthy, 1959; Orban and Wentz, 1960). Stones (1962), reports that slight friction on the mucosa causes epithelial separation (a modification of "Nikolsky's sign"), so that the wearing of dentures and normal oral hygiene are impossible. The suffering of the patient is extreme and mastication and swallowing are difficult (Orban and Wentz, 1960; Shafer et al, 1963). Prinz and Greenbaum (1939), and Sutton and Sutton (1949), point out that once the disease is established gradual loss of weight, anaemia and
Female, Aged 27 years.

**Pemphigus Vulgaris.**

The patient complained of painful oral ulcers which had been present for more than two months and were increasing in severity.

Examination revealed extensive ulceration of the tongue, gingivae and posterior edentulous areas. The lesions were multiple, confluent and covered by a necrotic surface membrane. Remnants of collapsed epithelial bullae were clearly visible.

There were no skin lesions visible and past medical and dental histories were non-contributory.

A Full and Differential Blood Count, Urinalysis, Bacteriological smear and Dietary Analysis were negative and the patient was referred to a dermatologist and on the basis of clinical findings and a histopathological examination, a diagnosis of Pemphigus vulgaris was established and prednisone therapy commenced. Prognosis for the condition was considered grave.
diminished resistance are evident.

Stern (1949), describes acute pemphigus in a female, aged 27 years. Persistent ulcerations present on the buccal mucosa, tonsils, fauces and uvula were covered by a white membrane. A diagnosis of acute necrotizing ulcerative gingivitis was made, but following the appearance of cutaneous lesions three months later, a definite diagnosis of pemphigus was established.

(b) **Pemphigus vegetans.**

Levin (1956), considers that oral lesions occur in almost every instance of pemphigus vegetans. These resemble the erosions of pemphigus vulgaris but investigators agree that they are less severe and may exhibit proliferative vegetations (Bhaskar, 1961; Shafer et al, 1963). Levin (1956), states that these are evident as soft, dark granulations and Stones (1962), adds that they may be studded with pustules. The theory of Lever (1954), that pemphigus vegetans begins and terminates as the vulgaris form has not been confirmed by histopathological evidence.

(c) and (d) **Pemphigus foliaceus and pemphigus erythematodes.**

Oral lesions in pemphigus foliaceus and pemphigus erythematodes are rare (Lever, 1954; Levin, 1956; Stones, 1962; Shafer et al, 1963), and have not been described. Shklar and McCarthy (1961 a), tend to doubt their existence as separate entities.

The histopathological features of oral and skin lesions include; (a) acantholysis and separation of the epithelium at the level of the stratum spinosum, (b) absence of inflammatory elements in the tissue surrounding the bullae, (c) microabscesses in pemphigus vegetans.
Thoma and Goldman (1960), note that once ulceration has occurred these characteristics are masked. According to Cahn (1947), examination of an ulcer reveals widely dilated vessels and an intense inflammatory infiltrate. Levin (1956), and Burket (1961), believe excision of an intact bulla is important for successful histopathological examination. However, Cooke (1960), makes the practical observation that this is almost impossible to achieve.

Since pemphigus may be fatal, an early diagnosis is of the utmost importance. Differentiation from drug eruptions, herpes simplex, erythema multiforme, lupus erythematosus and epidermolysis bullosa must be made. Burket (1961), emphasises that mucosal involvement tends to be more severe and persistent in pemphigus than in the other diseases with which it may be confused. Most writers (notably Prinz and Greenbaum, 1939; Cahn, 1947; Burket, 1961), consider that persistent vesicles and erosions which develop painlessly on an apparently normal oral mucous membrane should alert the clinician to the possible presence of pemphigus. Cooke (1963), finds epithelial smears of value in diagnosing the condition when only oral manifestations are present.

ACTH and cortisone have revolutionized the treatment and prognosis for pemphigus. According to Kierland et al (1952), adequate doses of each hormone will suppress the formation of new bullae, improve the general well-being of the patient and produce temporary remissions of varying duration. Together with Blackburn (1955), Spilka (1961), and Cooke (1963), they emphasise that, since cortisone tends to
suppress signs and symptoms of infection, the minimal therapeutic
dose should be given. Burkett (1958), makes the interesting
observations that in vitro, small amounts of ACTH and cortisone
detoxify pemphigus toxins. No confirmation of this statement could be
found in the literature.

Oral lesions require the use of bland mouthwashes, anaesthetic
troches and sprays and strict attention to oral hygiene. Antibiotics
may be necessary to control secondary infection (Andrews, 1955).
BENIGN MUCOUS MEMBRANE PEMPHIGUS
(Mucous Membrane Pemphigoid)

Oral ulceration may occur in benign, mucous membrane pemphigus, a rare bullous eruption of mucous membranes of unknown aetiology. Shklar and McCarthy (1959), consider that the oral mucous membrane is always affected in this condition. Work by Lever (1954), and McCarthy and Shklar (1958), has established benign mucous membrane pemphigus as a separate entity from pemphigus, and diagnosis depends chiefly on its benign, chronic, clinical course and histopathological picture. A comprehensive account of this disease is given by Shklar and McCarthy (1959), who found oral lesions present in all of 15 cases examined by them. Skin lesions were evident in only 3 patients. Conjunctival lesions are a frequent, serious complication and blindness commonly results from scarring.

According to Cooke (1960), in benign mucous membrane pemphigus intra-oral bullae frequently appear on the palate and gingivae. In contrast to the bullae of pemphigus vulgaris, the lips are rarely affected. The lesions are small, may be few in number, and usually cause little discomfort. The bullae are slow to rupture and produce clean, raw erosions. Lever (1942), Levin (1956), Shafer et al (1963), and Ship (1963), note that the erosions show little tendency to enlarge by peripheral extension as is typical of pemphigus vulgaris. Because these erosions are slow to heal, they frequently break down into ulcerations. Ship (1963), considers that such ulcers remain small in size, and in contradistinction to those of pemphigus vulgaris, usually do not coalesce.
All writers reviewed agree that the typical histopathological changes in benign mucous membrane pemphigus are: (a) the sub-epithelial formation of bullae with the entire epithelial layer separating from the underlying connective tissue; (b) lack of acantholysis; (c) lack of intraepithelial vesicle formation (Lever, 1954; Levin, 1956; Shklar and McCarthy, 1959; Cooke, 1960; Shklar and McCarthy, 1961; Shafer et al, 1963).

Cooke (1960), reports benign mucous membrane pemphigus in 3 females aged 28, 65 and 73 years with a history of ulceration and vesicles on the palate and gingivae for 8 months, 3 years and 12 years respectively. The tongue and buccal mucosa were unaffected and Nikolsky's sign was negative. However, Lever (1954), reports that this diagnostic test is usually positive in this disorder.
ERYTHEMA MULTIFORME

Erythema multiforme is described by Mackenzie (1963), as "an acute, inflammatory disease of skin and mucous membranes which often recurs. A variety of clinical forms occur, of which ulcerative lesions of the oral mucous membrane are often the most prominent". The condition runs a course of two to four weeks and is accompanied by malaise and fever. Lighterman (1958), describes the skin lesions as erythematopapular, maculopapular, or vesiculobullous. The general consensus of opinion is that it affects young adults chiefly in the spring and autumn months (Newman, 1956; Cheraskin and Langley, 1956; Kwapis, 1957; Cooke, 1960; Bhaskar, 1961; Shafer et al, 1963; and others).

Efforts towards finding a specific aetiopathological agent for erythema multiforme have been unsuccessful. Some writers feel it may be an allergic reaction to foods and drugs, or a sensitization to a form of bacterial infection (Chipps, 1951; Whinston, 1952; Shira, 1957; Stones, 1962; Shafer et al, 1963). Fish (1948), and de Fooz (1959), consider a virus responsible, and Anderson et al (cited by Cooke, 1960), demonstrated that an attack may be preceded by a herpetic infection. Fleming (1958), is probably more correct when he states there may be more than one causative factor.

Prinz and Greenbaum (1939), and Orban and Wentz (1960), consider the incidence of oral lesions in erythema multiforme is 50%, while Burket (1958), and Ship (1963), give the less conservative estimate of 85–92%. The lesions may precede skin involvement; and
Whinston (1952), and Lighterman (1958), have reported cases in which oral lesions were the only manifestation.

The painful oral condition is usually the patient's chief complaint. All writers reviewed agree that, following the breakdown of vesicles and bullae on the oral mucosa, superficial ulcers with irregular margins form. Ship (1963), considers that these ulcers may present a "mosaic" appearance, particularly when they coalesce. Involvement of the oral mucous membrane may be so severe that eating and drinking are impossible. Salivation is increased and because of secondary infection of oral lesions a marked foetor oris is usually present, (Kwapis, 1957; Miller and Hartenstein, 1961). The ulcers form chiefly on the lips, buccal mucosa and tongue; Shira (1957), and Burket (1961), note that gingival tissues are usually spared. Jacobus (1949), describes extensive ulceration and painful desquamation of the lips and buccal mucosa in a 51-year-old man.

Shafer et al (1963), point out that the varied nature of the lesions may present diagnostic difficulties, particularly when cutaneous lesions are absent. The condition must be differentiated from pemphigus, drug eruptions and herpetic lesions. Cooke (1960), and Burket (1961), report that oral involvement in erythema multiforme is more severe and the lesions more widely distributed than in herpetic stomatitis.

Clinical findings are reported by Whinston (1952), Cooke (1960), Napoli et al (1960), McKenzie (1963), and others. A 72-year old Negro seen by Lighterman (1958), had ulcers and areas of erythema
on the lower lip, floor of the mouth, buccal mucosa, tip of tongue and hard and soft palates. Interspersed among these were the necrotic remnants of ruptured vesicles. Since the history did not elicit the recent use of new foods or drugs a diagnosis of erythema multiforme was made.

In the absence of an established aetiology, therapy is basically symptomatic (Kwapis, 1957). Antibiotics are used to counter secondary infection and acute symptoms may be suppressed with cortisone preparations (Sherman, 1959, recommends prednisone or prednisolone). Moe (1948), believes massive doses of vitamin B are of value. Bernier (1959), cautions that since the disease is self-limiting intensive drug therapy should be avoided. Mild alkaline mouthwashes, avoidance of hot, spicy foods and use of medicaments and anaesthetic lozenges are usually helpful for the painful oral condition.
THE MUCO-CUTANEOUS OCULAR SYNDROMES.

1. STEVENS-JOHNSON SYNDROME.

This is an eruptive disorder of the skin and mucous membrane with an abrupt onset and severe systemic symptoms including general prostration, malaise and fever. Andrews (1955), states that bilateral conjunctivitis, corneal ulcers, epistaxis, rhinitis and genital involvement may occur. The average age of 31 patients seen in Sydney by Claxton (1963), was 19 years and the duration of symptoms ranged from 10-43 days. Rakower (1954), observes that there is frequently a preceding history of upper respiratory tract infection.

The aetiology of this condition is unknown. However, de Focc (1959), and Claus (1960), report that an unidentified virus is suspected. Cohlan (1960), and Claxton (1963), describe instances following the administration of sulphamethoxy pyridazine. Chipps (1951), and Claxton (1963), agree that this syndrome may occur more frequently with wider use of an increasing variety of drugs, most of which are potentially capable of producing hypersensitivity.

Oral manifestations occur early in the course of this disease (Andrews, 1955), and are characterized by rupture of vesicles which are situated chiefly on the lips and buccal mucosa. These erosions are covered by thick, greyish-white pseudomembranes which slough and cause bleeding and crust formation (Robinson and McCrum, 1950; Chipps, 1951; Claus, 1960, Shafer et al, 1963). The ulcers frequently
coalesce to involve extensive areas of denudation which make eating difficult. Thomas (1950), Theodore (1952), Andrews (1955) and Claxton (1963), report pulmonary involvement as a complication of severe cases. Theodore (1952), and Gardner (1961), state that unlike erythema multiforme this syndrome is not recurrent; however, Thoma and Goldman (1960), are of the opinion that recurrent attacks may involve only the mucous membranes.

The recent literature contains numerous reports of Stevens-Johnson syndrome (notably Lozana, 1955; Kwapis, 1957; Juntke, 1959; Claus, 1960; Cohlan, 1960; Claxton, 1963). Because the syndrome runs a self-limiting course efficacy of treatment is not assessable, (Rakower, 1954). General supportive measures are most important, while antibiotics are useful for controlling secondary infection. Claxton (1963), reports that response to steroids has been inconsistent. Claus (1960), notes encouraging results with gamma-globulin. Attention to strict oral hygiene and use of anaesthetic lozenges relieves oral discomfort.

2. BENÇET'S SYNDROME.

This rarely occurring, serious condition, sometimes referred to as the "Triple Symptom Complex", consists of simultaneous or intermittent ulceration of the mouth, external genitalia and iritis of one or both eyes (Phillips and Scott, 1955; Schulze, 1960; Linenberg, 1963). Fraser-Moodie (1953), emphasises that lesions in all three areas may not be present simultaneously; the presence in
two is referred to as an "abortive" form of the disease (Theodore, 1952; Andrews, 1955). According to Thomas (1947), Fraser-Moodie (1953), and Stones (1962), this syndrome primarily affects men in the third decade of life.

The oral lesions consist of discrete, painful, "punched-out" ulcers which vary in shape and have an erythematous halo. The base is often covered by a greyish exudate. According to Linenberg (1963), and Shafer et al (1963), these ulcers occur on the lips, gingivae, buccal mucosa and tongue, and the ulceration is seldom as severe as that seen in Stevens-Johnson syndrome.

This syndrome may be further differentiated from Stevens-Johnson disease by the absence of constitutional symptoms (Thorne, 1963), and erythematous macules and vesicles on the oral mucous membrane (Fraser-Moodie, 1953). The ulcers, which frequently heal with scarring, are identical with severe aphthous lesions.

Thorne (1963), describes Behçet's syndrome in a woman, aged 30 years, who had experienced recurrent oral ulcers all her life. Two years prior to diagnosis ulcers had also appeared as genital lesions. A 36-year old man seen by O'Donnell (1947), exhibited ulceration in the oral cavity, external genitalia and inflammation of the right eye.

This syndrome has proved refractory to all forms of treatment. ACTH, produced remissions in two of four patients treated by Phillips and Scott (1955). Linenberg (1963), reports success with
intramuscular injection of dexamethasone and topical application of triamcinolone acetonide to the oral ulcers. Unfortunately, the disease is recurrent and blindness is a frequent result (Andrews, 1955).

3. REITER’S SYNDROME.

Reiter’s disease chiefly affects young males and is characterized by arthritis, urethritis and conjunctivitis. According to Warthin (cited by Robinson and McCrum, 1950), Stones (1962), Pindberg et al (1963), and Shafer et al (1963), ulcerative lesions of the oral mucosa may occur. These are situated principally on the buccal mucosa, lips and gingivae and resemble aphthous ulcers.

In each of four patients with Reiter’s syndrome seen by Gorlin and Chaudhry (1960 a), there were ulcers on the tongue. Ogryzlo and Graham (1950), report the condition in a 35-year old man who developed arthritic disturbances of the knee joints following an injury; he subsequently exhibited oral and genital ulceration. These authors report a dramatic response to ACTH or cortisone. However, Andrews (1955), cautions that, while these drugs may cause prompt remissions, they do not prevent recurrences.

4. ECTODERMIS EROSIVA PLURIFORMICIALIS

Shafer et al (1963), describe this as an acute disease consisting of lesions of the oral mucosa, conjunctiva, genitalia and skin of the extremities. Fever and a sore throat are usually marked (Theodore, 1952).
The oral lesions are severe and consist of painful ulcers following a vesiculobullous eruption. Ulcerations of the pharynx may be extensive (Robinson and McCrumb, 1950; Theodore, 1952; Gardner, 1961), and associated with oedema, so that swallowing and breathing are difficult.

**Relationship of Mucocutaneous - Ocular Diseases to Erythema Multiforme.**

Examination of the literature relating to these conditions reveals that all are of unknown aetiology and may exhibit cutaneous and mucous membrane involvement. Because the original definitions of the syndromes have been extended, differentiation is frequently difficult. A definite diagnosis of Behçet's syndrome is perplexing when only two of the symptoms of the triad are evident. Robinson and McCrumb (1950), claim that Stevens-Johnson syndrome is difficult to diagnose when cutaneous lesions are absent.

The terminology of these conditions is confusing because of the broad range of signs and symptoms, and the tendency of early investigators to name diseases by the appearance of the variable lesions. For example, some authors consider Stevens-Johnson syndrome synonymous with erythema multiforme (Rakower, 1954; Burket, 1958; de Fozó, 1959; Claus, 1960), or erythema multiforme bullosa (Nathan et al, 1948; Jacobus, 1949), or ectodermis erosiva pluriorificialis (Andrews, 1955; Sherman, 1959). Despite obvious points of similarity Bernier (1959), believes the association between Stevens-Johnson syndrome and erythema multiforme is yet to be proved.
In an attempt to clarify the terminology Thomas (1950), Ashby and Lazar (1951), and Kwapis (1957), suggested that the more severe types be called "erythema multiforme major", and the less severe types "erythema multiforme minor".

**Comparison of Oral Manifestations in the Mucocutaneous-Ocular Diseases.**
(After Robinson and McCrumb, 1950).

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<th>Extensive Ulcers on Ulcerative</th>
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Robinson and McCrumb (1950), analysed and compared these syndromes and concluded that they are all (with the possible exception of Reiter's syndrome), variants of erythema multiforme and should be included under the common title of "erythema multiforme exudativum". Since their publication, recent writers (notably Theodore, 1952; Bhaskar, 1961; Gardner, 1961; Shafer et al, 1963), have referred to these syndromes as a form of erythema multiforme.
LUPUS ERYTHEMATOSUS.

Lupus erythematosus is an inflammatory dermatitis of unknown etiology which exhibits several forms, any of which may exhibit oral ulceration. The condition is aggravated by exposure to sunlight and shows a marked predilection for females. Two chief forms are generally recognised:

(a) A more commonly occurring chronic, discoid or benign form which involves the skin and mucous membranes only.

(b) A rarer and frequently fatal, acute, disseminated form in which cutaneous lesions are associated with a diversity of systemic manifestations.

Despite the fact that the benign form of lupus erythematosus apparently may sometimes develop into the systemic form, Andrews (1955), firmly believes that these two forms of the disease are not closely connected.

Sugarman (1953), presents a comprehensive account of the disorder and reports that all types are characterized by persistent, cutaneous plaques which recur frequently and heal with scarring. The face and hands are most often affected and in the systemic form a "butterfly" shaped lesion may occur across the bridge of the nose and cheeks.

As reported, the frequency of oral manifestations in lupus erythematosus varies although the majority of opinion is that they occur in 25% of cases (Tiecke et al, 1959; Bhaskar, 1961; Burket, 1961; Gardner, 1961). According to Ormsby and Montgomery (1954),
Burket (1961), Gardner (1961), and Shafer et al (1963), the lesions, which usually co-exist with cutaneous lesions, are most frequently seen in association with the benign form. Gardner (1961), emphasises the fact that oral lesions are not so well defined as the cutaneous lesions.

A consistent description of oral lesions in lupus erythematosus is given by most authors (notably Prinz and Greenbaum, 1939; Sugarman, 1953; Ormsby and Montgomery, 1954; Orban and Wentz, 1960; Bhaskar, 1961; Stones, 1962; Shafer et al, 1963). Initially the oral mucous membrane appears erythematous, atrophic and easily traumatised. When fully developed the lesion is seen as a slightly elevated, white plaque with dark, reddish-purple margins. This frequently erodes to form an extensive, shallow ulcer with which a burning sensation may be associated (Bernier, 1959).

The oral lesions of the systemic form are more destructive than those of the benign form and the erosions are covered by grey, necrotic pseudomembranes bordered by red margins. The lesions may occur at any oral site but Prinz and Greenbaum (1939), and Curtis and Fiegelman (1959), consider the buccal mucosa opposite the third molar teeth to be the most frequently affected.

Shklar and McCarthy (1961 a), clarify the confusion existing in early literature in a detailed account of the histopathological and histochemical changes in the benign form of lupus erythematosus. This is typified by hyperkeratosis or parakeratosis, hydropic degeneration of the basal cell layer and basophilic degeneration of
collagen and elastic fibres. Bhaskar (1961), emphasises that these features are not pathognomonic.

Lupus erythematosus in its early stages must be distinguished from erythema multiforme, pemphigus, and in its later form from leukoplakia and erosive lichen planus (Orban and Wentz, 1960). Diagnosis of the systemic form was facilitated in 1943 when Margraves (cited by Andrews, 1955), described the "Lupus Erythematosus phenomenon" which can be easily identified in the peripheral blood or bone marrow when the serum of the patient is added to normal blood. It consists of a clump of neutrophils surrounding a mass of deeply-staining chromatin contained in a phagocyte.

Ulceration of the palate and tongue was present in an 18-year old girl seen by Spies et al (1955). Treatment with ACTH relieved the symptoms but the patient suffered twenty remissions over a four year period. These authors point out the interesting fact that the "Lupus Erythematosus phenomenon" was negative following the administration of ACTH and cortisone, and positive after their withdrawal and before systemic symptoms recurred.

There appears to be no specific form of treatment for lupus erythematosus; ACTH and cortisone induce only temporary clinical remissions and in most of the patients with the acute condition seen by Kierland et al (1952), the disease progressed to a fatal termination in spite of repeated courses of cortisone. Tiecke et al (1959), Orban and Wentz (1960), Urbach (1961), note encouraging results with quinacline hydrochloride ("Atabrine"), in the treatment of the benign
form. However, despite the fact that most authors (notably Lever, 1954; Michelson, 1954; Urbach, 1961; Shafer et al., 1963), consider acute lupus erythematosus as invariably fatal, an Editorial in the Journal of the American Medical Association (1963), reports that the present prognosis is good. The recommendation by Bernier (1959), that oral lesions may be surgically excised appears worthless.
**LICHEN PLANUS**

Lichen planus is a relatively common, benign, chronic, inflammatory disease of the skin and mucous membrane. According to Shklar and McCarthy (1961), the mucosal surface most frequently involved is that of the oral cavity. The aetiology is unknown, but numerous clinical observations confirm the fact that it frequently occurs in adults under nervous strain (Sutton and Sutton, 1949; Cawley and Kerr, 1952; Thoma and Goldman, 1960; Burkett, 1961; Shklar and McCarthy, 1961; Shafer et al., 1963). Oral ulceration associated with lichen planus is generally considered to be rare. However, in a detailed report of three cases Darling and Crabb (1955), claim that it is more common than is generally believed.

The oral manifestations of lichen planus are well described by Cawley and Kerr (1952), Cooke (1954), and Shklar and McCarthy (1961). The fundamental oral lesion, a slightly-elevated, grey or glistening-white papule, is found principally on the buccal mucosa and/or tongue. The appearance of the lesions depends on the various arrangements of the papules. In a survey of 50 patients with oral lichen planus, Cooke (1954), found that the following types of patterns and lesions may be arbitrarily identified: linear, discrete papular, confluent papular, reticular, annular and pigmented, vesicular or bullous and atrophic or erosive. He described ulceration as being a possible sequela of any of the following:

(a) the erosive or atrophic form which is not preceded by vesicle formation. Cooke (1954), found 28% of his patients had this form of lichen planus.
(b) Rupture of vesicles or bullae. Burket (1961), and Ship (1963), noted that these vesicles may initially simulate those of herpes simplex infection.

Ulcers from the breakdown of vesicles are multiple, shallow, irregular in outline and heal rapidly (Cooke, 1954; Ship, 1963). Those associated with the erosive form of lichen planus may be extensive, usually have a raised, yellowish base and are accompanied by severe, if not constant pain (Darling and Crabb, 1955; Burket, 1958; Shklar and McCarthy, 1961; Ship, 1963). The tissue adjacent to both types of ulcers exhibit the white striations and papules of the typical lesion of oral lichen planus. These are an important aid to diagnosis.

Ship (1963), reports that ulcerations in the erosive form of lichen planus are seen most frequently on the mandibular mucobuccal fold and the buccal mucosa. Shklar and McCarthy (1961), consider that the lesions most commonly occur along the occlusal plane of the buccal mucosa because they are associated with local trauma. There is some confusion regarding the bullous lesions for Burket (1961), states they are rarely seen on the tongue while Shklar and McCarthy (1961), believe they occur most often on the lateral borders of the tongue.

Histopathological examination of the ulcers of lichen planus reveals the typical features of mucosal ulceration; a surface layer of fibrin densely infiltrated with polymorphonuclear leucocytes, and a deeper zone of infiltration by lymphocytes, plasma cells or histiocytes. The classical histopathological features of lichen
planus are evident in the tissues adjacent to the ulcerative lesion and include: (a) a leucocytic infiltration in the connective tissue, (b) hydropic degeneration of the basal cell layer, (c) parakeratosis, and (d) acanthosis.

Diagnosis of the ulcerative form of lichen planus may present special difficulties, particularly when cutaneous lesions are absent. Ulcers should be differentiated from those of lupus erythematosus, secondary syphilis and pemphigus. Despite the fact that Robinson (1961), Shafer et al (1963), and others consider the histopathological features of lichen planus are pathognomonic, Shklar and McCarthy (1961 a), are adamant that diagnosis must depend on a correlation of clinical with histopathological evidence.

A 58-year old woman seen by Darling and Crabb (1955), had slightly painful and extensive ulcers on the lateral borders of her tongue, both lips, buccal mucosa and palate. These lesions had been present for seven years and were surrounded by the typical white striations of lichen planus.

Treatment of lichen planus is unsatisfactory and largely empirical. Measures to increase the patient's general health include attention to hygiene and to diet, and, wherever possible establishment of freedom from anxiety (Darling and Crabb, 1954). Burket (1958), and Shklar and McCarthy (1961), believe that reassurance of the patient as to the benign nature of the condition is most important.

Oral lesions are generally considered to be more intractable than cutaneous ones(Thoma and Goldman, 1960; Burket, 1961; Shklar and McCarthy, 1961; Stones, 1962). It is important that ulcerated areas
should be relieved of irritating influences. Cooke (1954), and Stones (1962), recommend the local application of 1% gentian violet. Despite these measures the clinician must expect periods of spontaneous remission and exacerbation.
EPIDERMOLYSIS BULLOSA.

Epidermolysis bullosa is a rare, intractable, hereditary disease usually recognisable at birth and characterized by the development of vesicles and bullae on the skin and mucous membranes, either spontaneously or following minor trauma. Two chief forms of the disease are described: (Andrews, 1955; Lewis et al, 1955; Bowyer and Owens, 1961; Kaslick and Brustein, 1961; Stones, 1962; Shafer et al, 1963).

(a) A simple, benign form in which the lesions heal without scarring and rarely occur in the mouth.

(b) An extremely severe dystrophic, or scarring form, with a poor prognosis. In a comprehensive review of the literature Kaslick and Brustein (1961), state that oral manifestations are shown in 16% of instances of this form of the disease.

On the oral mucous membrane the bullae are frequently preceded by white spots, and according to Orban and Wentz (1960), may be seen as small "blood blisters" which rapidly break down into ulcers. Shafer et al (1963), point out that lesions in the pharynx or larynx may cause hoarseness and dysphagia. Microstomia associated with scarring from healed buccal lesions is a frequent finding.

The histopathological picture is an interesting one and investigators vary in their reports. Andrews (1955), states that the epithelium shows no noteworthy changes. Orban and Wentz (1960), note that the epithelium is thin and filled with coagulated blood.
Sutton and Sutton (1949), report the absence of strands of fibrillar tissue which probably binds the epithelium to underlying connective tissue.

Various aetiologica theories have been propounded to explain this genetic condition. The most widely accepted one, put forward by Engman and Mook (cited by Bowyer and Owens, 1961), is that a deficiency of elastic fibres in the superficial connective tissue renders the epithelium susceptible to bullous formation. Kaslick and Brustein (1961), report that other investigators believe the condition is a result of epithelial fragility.

Bowyer and Owens (1961), describe dystrophic epidermolysis bullosa in a 14-year old girl. Trauma from the extraction of grossly carious teeth produced the formation of a large bulla on the lower lip. This subsequently formed an extensive ulcer.

In a 12-year old boy, seen by Kaslick and Brustein (1961), there were numerous cutaneous lesions present and a large bulla on the sublingual tissues. Four ulcers present on the tongue were each covered by a grey slough.

There is no specific treatment for epidermolysis bullosa. Antibiotics are useful for controlling secondary infection of the lesions and Kaslick and Brustein (1961), report that corticosteroids are only of temporary value. Sutton and Sutton (1949), make the important observation that, considering the condition's basic histopathology, it is difficult to see how it can be successfully treated.
CHAPTER 12.

DISEASES OF ALLERGY

a) Stomatitis venenata
b) Stomatitis medicamentosa
c) Food Allergy.
"Allergy" is a broad term used generally to encompass the hypersensitivity state acquired by exposure to a specific material, and the altered capacity of the living organism to react upon re-exposure to this allergen (Shafer et al, 1963). Nearly all instances of allergy depend upon the combination of an antigen, (usually but not always a protein or polysaccharide), with an antibody produced by the host as a result of previous exposure to the antigen. Rostenberg (1957), points out that "antibody" in this sense does not necessarily mean a conventional circulating antibody, but a cell with specifically altered properties towards the antigen.

The exact nature of the mechanism of allergic reactions has not been fully defined. Kabat (1959), considers that the combination of antigen and antibody causes liberation of histamine, or some histamine-like substance, which is responsible for many of the manifestations of allergic reactions. However, there is not complete agreement that all manifestations are explained by a histamine liberation. In the case of drugs causing allergic reactions, no easy explanation of all the responses can be made (Kreshover, 1958).

Relatively little attention has been paid in the literature to oral allergic lesions. Apart from broad considerations in general textbooks (Tiecke et al, 1959; Thoma and Goldman, 1960; Burket, 1961; Stones, 1962; Shafer et al, 1963), only sporadic reports of clinical findings are available.
It is generally agreed that oral manifestations of allergy are infrequent. Curtis and Taylor (1947), and Swanson (cited by Burkot, 1961), attribute this to lubrication of the oral mucosa with mucous, lack of hair follicles and the absence of a well-developed layer of keratin. When they occur the symptoms are non-specific and include erythematous areas, oedema vesicles, bullae and ulceration.

Diagnosis of an allergic disorder depends primarily on a detailed history. Harkavy (1948), and Kreshover (1958), emphasise the importance of excluding conditions such as blood, endocrine and nutritional disorders, which may produce similar lesions. Schaffer (1951), points out that allergic phenomena in the mouth may also resemble galvanic lesions.

The following types of allergic response may produce oral ulceration:—

(a) Stomatitis venenata

(b) Stomatitis medicamentosa

(c) Food Allergy.

(a) **STOMATITIS VENENATA** (Contact Allergy)

In this type of reaction oral lesions occur at a localized site after contact of the causative agent with the sensitized tissues. Kreshover (1958), reports that the mechanism by which the mucosa becomes sensitized is probably the attachment of the offending agent to proteins of the epithelial cells, the resulting molecule acting as the antigen which then excites the production of antibody. According to Shafer et al (1963), the response to a true contactant
does not appear immediately as does a reaction to a simple irritating substance. This delay occurs while sensitization is proceeding and Burket (1961), notes that it may be prolonged.

The incidence of stomatitis venenata is low when compared with that of contact dermatitis. Kreshover (1958), suggests that this is because, with the continued diluting action of saliva, the causative agent usually has only a brief period of contact with the mucous membrane.

The more common causes of stomatitis venenata are listed by Burket (1961), as:-

(a) Medicaments used in dental practice - antibiotics, iodine compounds.

(b) Dental filling and denture base materials such as acrylic, vulcanite and amalgam.

(c) Dental and cosmetic preparations used by the patient - dentifrices, lipstick, denture adhesive and cleaning powders.

Oral lesions are usually observed as inflammatory reactions with various amounts of sloughing or ulceration developing. Initially there is itching and a burning sensation of the mucosa (Sidi and Casalis cited by Cohen, 1955), Cheraskin and Langley, 1956; Shira, 1957; Thoma and Goldman, 1960; Bhaskar, 1961; Shafer et al, 1963). Secondary infection of the lesions occurs frequently and from these more extensive lesions spirochaetes and bacilli, typical of acute necrotizing ulcerative gingivitis, may be isolated, (Cheraskin and Langley, 1957; Thoma and Goldman, 1960).
Sugarman (1950), described oedematous lips, ulceration of the buccal mucosa, tongue and swelling of the floor of the mouth in a patient following the chewing of mint-flavoured chewing gum. These manifestations rapidly cleared on removal of the mint gum and reappeared within one hour when the same brand of gum was again chewed.

Cinnamon oil in toothpaste was the cause of oral vesicles and ulceration in a patient seen by Lanbach et al (1953). The ulcers spread to involve the perioral region and were covered by yellow crusts and surrounded by erythema and oedema.

Local use of penicillin in the form of ointments and tablets frequently produces oral manifestations (Farrington et al, 1947; Cook, 1948; Cohen, 1955; Cormia et al (in Shira, 1957); Kreshover, 1958). According to Cross (1949), these may first appear as erythematous macules and Shira (1957), considers that multiple, shallow ulcers may develop. Wright and Rule (in Cook, 1948), studied the severity of the oral reaction to the salt base of penicillin. They concluded that the most severe symptoms developed when the calcium salt was used.

Patch tests are tests of epithelial sensitivity to a contactant and are always carried out in conjunction with a controlling agent. Curtis and Slaughter (1947), believe this means of testing is useful in isolating an offending agent and establishing a working basis for treatment. However, Cohen (1956), considers that patch tests cannot replace a well-studied history and cautions that they can be positive to substances which are not causing the disease.
(b) **STOMATITIS MEDICAMENTOSA.** (Drug Allergy; Drug Sensitivity; Drug Idiosyncrasy)

According to Shafer et al (1963), stomatitis medicamentosa includes a variety of sensitivity reactions following the absorption of any one of a selection of drugs and chemicals. Tiecke et al (1959), emphasise that this condition should not be confused with the toxicity associated with the dosage of a drug given. Shafer et al (1963), warn that one of the commonest allergic reactions to a drug is similar to serum sickness and includes skin lesions, arthralgia, fever and lymphadenopathy.

Oral manifestations of drug allergy occur less frequently than analogous cutaneous reactions (Shira, 1957; Shafer et al, 1963), and may be accompanied by mild fever and malaise. They are characterized by the rapid appearance of diffuse vesicles which produce superficial ulcers covered by a greyish membrane (Shira, 1957; Bernier, 1959; Tiecke et al, 1959; Orban and Wentz, 1960; Burket, 1961). Such ulcers may occur at any site on the oral mucosa and may cause severe tissue destruction.

Beham and Perr (1948), report a painful oral ulcerative condition in three patients following streptomycin therapy. In one case the oral mucosa and faucets developed yellow vesicles which eroded to form multiple ulcers covered by grey, necrotic pseudomembranes. Pallister (1949), and de Sousa (in Cohen, 1955), describe similar oral lesions caused by streptomycin.
Colby et al (1961), note swelling, superficial necrosis and ulceration following the administration of pyridium for treatment of a urinary tract infection. These lesions developed rapidly and subsided in a few days when the drug was discontinued.

An interesting account of an allergic reaction in a patient prone to recurrent aphthous ulcers is given by Ship et al (1962). Two days after a biopsy of a lingual ulcer, 0.5% diphenhydramine hydrochloride was used topically prior to removal of the sutures. Five days later seventy oral ulcers were evident and the patient was later shown to be allergic to this local anaesthetic.

(c) FOOD ALLERGY.

Tiecke et al (1959), and Thoma and Goldman (1960), use the term "Protein Allergy" to designate allergic responses due to sensitization to proteins, usually those contained in certain foodstuffs such as fish, pork, cheese, fresh milk, egg, chocolate, potato or oranges. Schaffer (1951), considers it as the most commonly occurring form of allergy seen in the mouth. More recently Stones (1962), claims that non-protein containing foods may cause similar manifestations. Prinz and Greenbaum (1939), observe that patients may become sensitized to any food or condiment.

The most prominent manifestations of food allergy are angioneurotic oedema, urticaria and eczema. Schaffer (1951), Dernier (1959), Orban and Wentz (1960), Thoma and Goldman (1960), and Stones (1962), consider that oral herpetic-like ulcers may form, which tend to coalesce. Schaffer (1951), states that in a very
sensitive patient the clinical/symptoms will appear in two to four minutes after ingestion. Tuft and Girsh (in Ship et al, 1962), report aphthous-like ulcers on the oral mucous membrane as a reaction to foodstuffs containing acetic and citric acids. Elimination of these foods caused remission in some instances.

Thoma and Goldman (1960), consider that proof of whether a particular food is the cause of an allergic reaction should be based on relief obtained by avoidance, and recurrence upon ingestion.

Oral manifestations of allergy usually regress with discontinuance of the offending agent. Shafer et al (1963), note that acute signs may be relieved by administration of antihistamine or cortisone preparations.

Oral ulceration should be treated with bland mouthwashes. If the tissue destruction is severe antibiotic therapy is indicated.
CHAPTER 13.

THE INTOXICATIONS

Mercury
Bismuth
Gold
Thallium
Lead
Phosphorus
Arsenic
Zinc
Chromic Acid.
THE INTOXICATIONS

The introduction of modern drugs and the enforcement of rigorous public health measures have almost completely eliminated intoxication from the absorption of harmful chemicals. When it does occur, according to Cheraskin (1961), ulceration is one of the commonest findings associated with this state. In most cases elimination of the toxic material brings about complete recovery. Burkett (1961), points out that deposition of chemicals in the oral soft tissues interferes with resistance of these tissues to infection.

MERCURIALISM

Bernier (1959), Bahimo and Shimasaki (1960), Burkett (1961), and Stones (1962), agree that the incidence of mercurial poisoning has markedly decreased since the replacement of mercuric salts by antibiotics for the treatment of syphilis. However, mercurial diuretics are still widely used in medicine and Burkett (1961), states that these compounds are readily absorbed into the body by inhalation, ingestion, injection and inoculation.

All writers describe the presence of oral ulceration in mercurialism. This is a result of the deposition of mercuric sulphide, which Burkett (1961), considers is more harmful than either bismuth sulphide or lead sulphide to the soft tissues. The ulcers are usually accompanied by ptyalism, a metallic taste, fetid breath and severe constitutional symptoms. Although these oral changes may be striking, Shafer et al (1963), maintain that they are not pathognomonic.
Ulceration commences at a gingival inflammatory site as a greyish-white pseudo-membrane which sloughs to form a necrotic lesion. This rapidly spreads to involve the tongue and buccal mucosa. Multiple ulcers may coalesce to form an extensive lesion with a base of exposed bone. Akers (1936), Cheraskin and Langley (1956), Tiecke et al (1959), consider that periostitis and osteomyelitis may develop from secondary an infection of such/untreated lesion.

An instance of intoxication from a prolonged course of mercurial diuretics is reported by Rahimo and Shimasaki (1960). A large, necrotic ulcer developed on the buccal mucosa and invaded underlying muscle. Histopathological examination revealed an acute inflammatory reaction.

There have been some references in earlier literature concerning the effect on the soft tissues of the mercury content of amalgam. Frykholm (1957), by showing that it contains an insufficient amount of mercury, discounted earlier reports that amalgam may cause oral lesions. Cheraskin and Langley (1956), Frykholm (1957), and Burket (1961), favour the view that such lesions probably occur as allergic reactions in patients sensitive to mercury. However, Bernier (1959), is adamant that there has been insufficient evidence to support this theory. It is noteworthy that lesions resembling those of mercurialism may occasionally be caused by galvanism.

**Acrodynia** (Pink's Disease; Swift's Disease)

This syndrome, which primarily affects young children, is thought to be the result of an unusual idiosyncrasy or sensitivity to mercury
contained in teething powders, ointments or tablets (Warkany and Hubbard, 1953; Bilderback, 1954; Cohen and Weinstein, 1961). It is characterized by painful, red extremities, mental apathy, hypertension and tachycardia. Spies (1959), and Shafer et al. (1963), claim that gingival ulceration may occur. Nussey (1954), describes an ulcer on the lower ridge in an 18-months old boy.

**BISMUTHISM**

Shafer et al. (1963), report that bismuth preparations are still commonly used for treating certain dermatological and gastro-intestinal disorders.

The most outstanding oral characteristic of bismuthism is the gingival "bismuth line" caused by the deposition of blue-black bismuth sulphide granules. Burket (1961), claims that in most instances this is accompanied by symptoms resembling those characteristic of necrotizing ulcerative gingivitis. Other writers (Bernier, 1959; Tiecke et al, 1959; Matheson, 1960; Thoma and Goldman, 1960), favour the view that oral ulceration occurs only in severe cases of bismuthism. Burket (1961), notes that large, painful, shallow ulcers are sometimes seen on the buccal mucosa in the molar region.

As in mercurialism, soft tissue lesions in bismuthism invariably commence where a local inflammation already exists. Brabant (1962), emphasises the importance of maintaining healthy gingivae before and during bismuth therapy.

**GOLD**

Intoxication from gold may result from its therapeutic use for the treatment of rheumatoid arthritis and certain dermatological
conditions such as lupus erythematosus. Stones (1962), considers that oral manifestations of gold intoxication are rare, but Burket (1961), estimates that stomatitis is seen in 10-40% of all patients receiving gold therapy. In my opinion this figure is probably an overestimation since patients receiving gold therapy are closely supervised.

According to Nathanson (1960), vesiculation and ulceration of the oral mucous membrane occurs in the more acute cases of gold intoxication. Stones (1962), notes an instance of ulceration which was accompanied by a sore tongue and metallic taste.

**THALLIUM**

Although thallium is used in certain industrial processes, most instances of poisoning are a result of accidental ingestion. Cheraskin and Langley (1956), state that ulcers sometimes appear on the lips and buccal mucosa. Prinz and Greenbaum (1939), report that in many instances of thallium poisoning a generalized oral ulcerative condition has been present.

**PLUMBISM**

Lead poisoning is still a disease of importance in industry and an occasional hazard in childhood because of the use of lead-containing paints (Cohen and Ahrens, 1959; Goldberg et al, 1963). According to Prinz and Greenbaum (1939), oral manifestations of plumbism are important for the early recognition of an intoxication state.

The principal oral diagnostic sign of plumbism is the gingival "Burtonian", or "lead line" of precipitated lead sulphide.
Shafer et al (1968), consider it to be more diffuse than that seen in bismuthism. However, Cheraskin and Langley (1956), and Burket (1961), describe the presence of an acute, ulcerative gingivitis closely resembling necrotizing ulcerative gingivitis.

**PHOSPHORUS**

This chemical is still widely used in industry but since the introduction of strict industrial safety measures, intoxication is rarely seen. Ulceration of the oral mucous membrane may accompany phosphorus necrosis of the maxilla or mandible ("phossy jaw"). It usually affects the buccal or gingival tissues and is associated with a foetid breath (Cheraskin and Langley, 1956; Tiecke et al, 1959; Burket, 1961).

**ARSENISM**

Since arsenic preparations have been largely supplanted by antibiotics for the treatment of syphilis, intoxication is a result of industrial exposure or deliberate or accidental ingestion (Bernier, 1959; McConnell, 1959). Accepted Dental Remedies (1963), emphasises the penetrating properties of arsenic and the hazards of its use in dental devitalizing procedures.

Symptoms of arsenism may be severe and in these cases deep, persistent, painful ulcers develop on the oral mucous membrane. Gingival ulceration is considered a common finding and is usually associated with ptyalism, a foetid breath, a metallic taste and a
dry, burning sensation in the mouth (Cherashkin and Langley, 1956; Tiecke et al., 1959; Nathanson, 1960; Burket, 1961).

**ZINC**

Zinc intoxication occurs chiefly from industrial exposure. According to Prinz and Greenbaum (1939), oral manifestations of this condition are rare, but Thoma and Goldman (1960), report that the corrosive action of zinc and the chloride of zinc may produce mucous membrane ulceration.

**CHROMIC ACID**

Prinz and Greenbaum (1939), and Burket (1961), consider that oral ulceration may result from exposure to chromic acid used in industrial sprays. The ulcers occur chiefly in the anterior part of the mouth. Walters et al. (cited by Norman, 1958), describe them as multiple, small and sharply-defined.
CHAPTER 14.

ULCERATION ASSOCIATED WITH TUMOURS

The Squamous-Cell Carcinoma
ULCERATION AND TUMOUR GROWTH.

A tumour is an excessive, usually progressive growth of tissue which proceeds without regard for surrounding tissue or the organism as a whole. Whether the tumour be benign or malignant, the added nutritional requirements of the growing lesion are met by an enlargement of the vascular supporting tissue. However, when tumour growth exceeds the growth of the supporting stroma peripheral tissue cells undergo degeneration due to deprivation of nutrition. This normally causes death of these cells, sloughing and the appearance of an ulcer (Payling Wright, 1956; Muir, 1938).

In highly malignant tissues this unequal tissue relationship is characteristic, and ulceration, an early and striking feature, may assume importance in diagnosis and prognosis. Mathis (1956a), and Erich (1959), point out that the higher the rate of reproduction shown by the tumour the greater is the tendency towards ulceration (e.g. squamous-cell carcinoma). Conversely, the better differentiated the tumour, the less is the tendency towards ulceration (e.g. basal-cell carcinoma or benign tumours). This does not mean that all highly malignant tumours invariably exhibit ulceration early in their growth. For instance, in the oral cavity a squamous-cell carcinoma situated on the gingival epithelium may penetrate deeply into the underlying bone before exhibiting ulceration. A similar lesion on the buccal mucosa would probably ulcerate almost immediately after growth commences.

Mathis (1956a), considers that ulceration exhibited by well-
differentiated or benign tumours is usually a result of exposure to traumatic influences. In such cases the degree of ulceration depends on the size, location and nature of the surface of the lesion, as well as the size and nature of the injury. Because any growth in the oral cavity is exposed to a variety of mechanical, physical and chemical stimuli, surface ulceration is a frequent finding.

One of the characteristics of tumour growth is a decreased tissue response to injury or bacterial invasion (Muir, 1958). Secondary infection of a tumour surface produces destruction and sloughing.

With increased emphasis being placed on the early detection and treatment of oral malignancies, the literature dealing with this subject is profuse, but for the most part, references consist of reports of clinical findings. One must rely on pathology textbooks (notably Bernier, 1959; Tiecke et al, 1959; Thoma and Goldman, 1960; Burket, 1961; Stones, 1962; Shafer et al, 1963), for a general description of oral lesions.
THE SQUAMOUS-CELL CARCINOMA.

The squamous-cell carcinoma is universally regarded as the most commonly occurring oral malignancy. Because it arises from the surface epithelium, it usually exhibits ulceration early in its growth. This is in contrast to the sarcoma which develops in the underlying connective tissue and does not ulcerate until it reaches an advanced stage (Kruger, 1963).

Holt and Easson (1952), and Bhaskar (1961), estimate that 60% of the intra-oral squamous-cell carcinomas exhibit ulceration. In a study of 189 lesions Gardner et al (1963a), found 50% associated with ulceration.

Initial Form of Intraoral Squamous-Cell Carcinoma.
(Bernier and Clark in Bernier, 1959).

<table>
<thead>
<tr>
<th>Initial form of lesion</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>398</td>
<td>100</td>
</tr>
<tr>
<td>Ulcer</td>
<td>233</td>
<td>60</td>
</tr>
<tr>
<td>Growth</td>
<td>118</td>
<td>30</td>
</tr>
<tr>
<td>Inflammation</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Keratosis</td>
<td>13</td>
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</tr>
<tr>
<td>Swelling</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Sinus tract</td>
<td>1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

In its early stage of development the lesion is either papillomatous with an elevated, warty appearance or flat, depressed
and indurated. Usually both types ulcerate rapidly and Mead (1944), describes the ulcer as surrounded by a wall of granulation tissue which may be destroyed as rapidly as it forms. The carcinomatous ulcer is generally described as a superficial or deep lesion with prominent, rolled edges and an indurated base. The rolled border is considered by Mead (1944), to be of significance in differentiating the lesion from an ulcerated gumma. Castiglione (1961), draws attention to the fact that although the entire base of the ulcer is firm and moves en masse on palpation, it is the hard edge of the ulcer that reveals most typically the "wooden" hardness. Pain is usually not a prominent feature unless secondary infection supervenes.

According to Gardner et al (1963), the behaviour of a squamous-cell carcinoma of the lip is more closely related to carcinoma of the skin than carcinoma of the mucous membrane. It most frequently occurs at the centre of the lower lip on the margin of the vermilion border and the skin. Bernier (1941), Thoma and Goldman (1960), Stones (1962), and Shafer et al (1963), describe the initial lesion as a small nodule which infiltrates the submucosa and breaks down to produce surface ulceration. As growth progresses the carcinoma may appear as an exophytic proliferation, which eventually ulcerates from trauma, or as a small, round crater-like defect (Woodbury, 1948; Tiecke et al, 1959; Stones, 1962; Gardner et al, 1963; Shafer et al, 1963).

A squamous-cell carcinoma occurring on the tongue most frequently involves the lateral borders (Bernier, 1941; Sharp, 1951; Schaffer, 1952;
Thoma and Goldman, 1960; Castigliano, 1961; Gardner et al, 1963 a,b; Shafer et al, 1963), and may escape detection because of its initial benign appearance. The lesion commonly starts as a minute area of overgrowth, noticeable upon digital palpation (Sharp, 1951), and normal tongue tissue is rapidly replaced with tumour tissue. Superficial ulcers, either of primary origin, or secondary to papillary or nodular growth, are present in 80% of instances, and are highly aggressive. In the more advanced stage the lesion presents the appearance of a crater with indurated, rolled edges. Regional tenderness is common, and in far advanced cases pain may be referred to the ear and temporal region (Schaffer, 1952). Contrary to most reports, Popescu and Iancu (1963), analysed 63 lingual carcinomas and found that induration did not extend into the musculature.

Cheraskin and Langley (1964), and Gardner et al (1963), claim that carcinoma of the buccal mucosa commonly occurs opposite the occlusal plane of the molar teeth. It may cover a wide area and presents considerable variation in appearance. Sharp (1951), believes that papillary lesions in this site are as a rule only partially ulcerated.

On the floor of the mouth a carcinoma usually commences on one side of the midline (Woodbury, 1948; Gardner et al, 1963a; Shafer et al, 1963), and frequently resembles a benign ulcer which is not uncommon in this region. At first the patient may feel with the tongue only an indurated growth, but later, after becoming ulcerated, pain, difficulty in speech, excessive salivation and bleeding may occur.
Male, Aged 68 years.

**SQUAMOUS - CELL CARCINOMA**

The patient reported with an untreated lesion of the upper left maxilla which was rapidly increasing in size and had caused considerable pain and discomfort for six months. During this period the patient had not been able to masticate his food and had lost two stone in weight. He noticed increasing difficulty in breathing through the left nostril.

Examination disclosed a fungating ulcer in the upper left premolar region extending from the crest of the alveolar ridge to the tuberosity and involving buccal tissues. The lesion was firm on palpation but no cervical lymph nodes were palpable.

A biopsy specimen was removed immediately and histopathological examination showed the presence of a poorly-differentiated squamous-cell carcinoma. Serological tests for syphilis and tuberculosis were negative.

The patient was referred to a radiotherapist who later reported complete regression of the lesion following Cobalt 60 therapy.
Sharp et al (1956), believe that the superficial ulcer with rolled and indurated edges is more common here than a papillary or nodular type of growth.

Ulcers associated with gingival carcinoma may be mistaken for simple mucosal ulcers or periodontal lesions. According to Bernier (1959), and Thoma and Goldman (1960), they may exhibit a raised, indurated margin containing nodules. Sharp (1948), advises that palpation of the indurated border is essential in differentiating these lesions. Advanced lesions frequently cause gingival haemorrhage and extensive destruction of alveolar bone.

Shafer et al (1963), describe carcinoma of the palate as a painful, poorly defined lesion situated on one side of the midline and one which may extend laterally to include the gingival tissue, or distally to involve the tonsils. On the hard palate it frequently appears as a superficial ulcer, 1–2 cms. in diameter and, if its growth is advanced, may cause palatal perforation (Bernier, 1959; Thoma and Goldman, 1960). Sharp (1948), favours the view that such carcinomatous lesions of the soft palate are usually large growths or papillary lesions.

The histopathological appearance of a squamous-cell carcinoma of the oral mucous membrane varies with the degree of differentiation exhibited by the epithelial cells. In general however, they tend to be moderately well-differentiated growths with some evidence of keratinization (Colby et al, 1961; Shafer et al, 1963). The well-differentiated lesion, which shows little tendency for primary
ulceration, consists of sheets and nests of cells obviously originating from squamous epithelium. A prominent feature is the presence of individual cell keratinization and the arrangement of cells in whorls of keratin known as "epithelial pearls" (Bushton and Cooke, 1959; Shafer et al, 1963). Poorly-differentiated carcinomas bear little resemblance to their cell of origin and tend to ulcerate early in the course of their rapid growth. They frequently present diagnostic difficulties because of the presence of bizarre cells which contain numerous mitotic figures. A characteristic feature is the invasion by epithelium of the underlying connective tissue.

Broders (1926), introduced a system of tumour grading based on the varying degrees of cellular differentiation. Grade 1 is a highly-differentiated lesion which tends to grow slowly and shows little evidence of ulceration. Grade 4 represents a poorly-differentiated tumour which develops rapidly, metastasizes early and has a poor prognosis. Despite the fact that this classification is unsatisfactory in that a tumour may show different degrees of differentiation, it has been widely accepted by investigators as a convenient means of referring to the type and nature of the lesion.

In every instance of ulceration in the oral cavity a thorough investigation of the nature of the lesion is essential when any doubt of its true nature remains, a tissue specimen should be immediately removed for histopathological examination. In spite of the accessibility of the oral cavity, Cutler (1953), observes that, in a large number of patients, an oral malignancy is not diagnosed until a late stage.
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