

CHAPTER 4.

VIRAL AND RICKETTSIAL INFECTIONS

Herpes Simplex

Herpes Zoster

Granuloma Inguinale

Foot and Mouth Disease

Psittacosis

The Exanthemas

The Enteroviruses

Rickettsialpox.

HERPES SIMPLEX
(Herpetic stomatitis; gingivo-stomatitis;
Recurrent herpetic stomatitis)

Herpes simplex is a virus disease which involves chiefly the mucous membrane but occasionally infects the skin and central nervous system. Oral herpetic infections are common since the virus is one of the most widely disseminated infective agents of man.

The Virus.

Herpesvirus hominis has an approximate diameter of 0.1-0.15 microns and shows a predilection for epithelial tissue where it is associated with vesiculation (Benzuly, 1956; Reade, 1961). According to Anderson (cited by Benzuly), the virus invades epithelial cells by direct contact and spreads through the bloodstream or along peripheral nerves. It is generally believed that the virus enters the body during a debilitating illness at which time it is not clinically evident. After an initial exacerbation it remains latent in the tissues particularly at mucous-epithelial junctions, and at a later time is activated by various stimuli.

The virus was first isolated from herpetic oral lesions by Dodd et al (1938), and Burnet and Williams (1939), demonstrated the development of specific herpes-neutralizing antibodies in the bloodstream of infected patients. Scott et al (1941), showed that the maximum antibody titre is present during convalescence and remains in the bloodstream at a constant, but lower level throughout life. It has been postulated that 65-90% of all adults have herpes antibodies in their blood (Scott et al, 1941; Blank and Rake in

Burtschi, 1951; Cherashkin and Langley, 1956; Burket, 1961). The high concentration of virus in vesicles during a recurrent herpetic infection, when the antibody titre is high, has aroused attention. Kerr (1952), suggests that the epithelial cell walls afford protection to the viral particles from circulating antibodies.

Clinical Considerations.

The lesions resulting from an initial infection by herpes simplex virus are known as "primary herpes"; any manifestations of herpetic infection in individuals who, as a result of previous exposure already have antibodies against this virus, are known as "recurrent herpes".

(a) Primary Herpetic Infection.

This infection is usually of a severe and generalized nature and runs a self-limiting course of 10-14 days. Scott et al (1941), found that 70% of primary infections occurred in persons under 6 years of age and 40% in children under 3 years of age. Burnet and Williams (1939), found the highest incidence among the 6-24 months age group. Infants whose mothers have antibodies to herpes are not susceptible to infection until 6 months of age, at which time their passive immunity disappears (Burket, 1961; Gardner, 1961; Shafer et al, 1963). Various investigators (including Burnet and Williams, 1939), have shown that the incidence is high in persons of low socio-economic backgrounds, but the susceptibility to infection apparently decreases with age.

Primary herpetic infection is not infrequently preceded by a debilitating condition such as an upper respiratory tract infection

(Kerr, 1952; Benzuly, 1956; Reade, 1961). However, healthy children often become infected by contact with other children suffering from a primary or secondary herpetic infection. Hence it is not unusual to find all the children in any one family affected or for the incidence to assume small epidemic proportions.

Manifestations may involve any site in the mouth and/or may occur on the skin of the face (herpes facialis), lips (herpes labialis), or chin (herpes mentalis). It is generally agreed that oral lesions are most commonly observed on the buccal and sublingual mucosa, tongue and gingivae (Stark et al, 1954; Jawetz, 1955; Benzuly, 1956; Thoma and Goldman, 1960; Reade, 1961). Cohen (1961), notes that oral lesions rarely appear first on the tonsils and Kerr (1952), observes that in severe cases lesions may extend to the larynx, oesophagus and nasal mucosa.

After an incubation period of 3-9 days (Scott et al, 1941), the infection has an abrupt onset causing fever (100-105°F), irritability, anorexia and a sore throat. Oral lesions are usually preceded by a tingling or burning sensation in the sites involved (Burket and Hickman, 1942; Stark et al, 1954). Clusters of thin-walled vesicles appear 24-48 hours later and contain a straw-coloured fluid, from which virus particles can be isolated. In severe instances of primary herpetic infection Benzuly (1956), notes that these vesicles may appear in bunches or "crops" every 12-14 hours. Rupture of the vesicles is accelerated by mechanical trauma associated with mastication. According to Stark et al (1954), vesicles are rarely



Female, aged 55 years.

ACUTE PRIMARY HERPETIC STOMATITIS

The patient stated that three days previously she had developed a headache and sore throat which were rapidly followed by the appearance of oral lesions.

The mucous membrane of the entire oral cavity exhibited numerous ulcers which varied considerably in shape and size. They were most numerous on the tongue and mucous surfaces of the lips. The patient had not been able to eat for two days and had a temperature of 102° F. There was no evidence of foetor oris or lymphadenopathy.

Treatment of the condition consisted of achromycin therapy (prescribed by the patient's physician), dietary advice and frequent bland mouthrinses.

The condition healed uneventfully in approximately two weeks.

seen except in very early lesions or when they are situated in protected areas, such as the ventral surface of the tongue.

Following rupture of the vesicles, groups of multiple, small erosions are observed. These have a clean base and each is covered by a cream-coloured membrane, the collapsed roof of the vesicle (Kerr, 1952; Ship, 1963). Secondary infection of the lesions causes them to increase in size and they frequently coalesce to produce a large, deep, painful ulcer with an irregular shape and a sharply-circumscribed, erythematous areola. The floor of such a lesion is yellowish or greyish-white in colour and is covered by slough. The ulcers heal spontaneously in 5-10 days and Burket and Hickman (1942), and Shira (1957), describe healing ulcers as covered by a thick, yellowish, fibrinous mass.

Primary herpetic lesions are often accompanied by sialorrhea, submaxillary and cervical lymphadenopathy and foeter oris; also eating may be difficult. In adults the temperature may rise as high as 105°F. The lymphadenopathy usually persists for as long as 2-3 weeks after other symptoms have vanished (Benzuly, 1956).

Reade (1961), observes that, although complications are rare, the herpes simplex virus may cause an infection of the mucous membrane of the eyes and genitalia and auto-infection of the thumb and fingers, if prone to the sucking habit. Nathanson and Morin (1953), consider that it may precede other diseases such as infectious mononucleosis.

(b) Secondary Herpetic Infection.

Herpes simplex is one of the few virus infections that does not impart lasting immunity (Andrews, 1955). According to Ship et al (1960),

recurrent exacerbations occur in 38% of the population. Burket (1961), and Ship et al (1961), comment on the remarkable variety of non-specific stimuli that apparently activate recurrences which Reade (1961), considers are due to a change in the resistance of the host rather than an autogenous or heterogenous infection. These stimuli include fever, lowered general resistance, exposure to sunlight, allergy, trauma, nerve injury, menstruation and pregnancy, fatigue, natural or induced emotional stress. Kerr (1952b), believes that many factors are involved in reactivation of the virus.

The lesions in the recurrent form of herpetic infection are essentially the same as those seen in the primary infection, the main exception being that the recurrences occur in a localized area, most frequently on the lips as "cold sores", and are not accompanied by general signs and symptoms (Hilleman, 1950; Kerr, 1952b; Krugman and Ward, 1958). Burnett and Scherp (1957), and Orban and Wentz (1960), state that, probably because of limited immunity, lesions are not as severe as those seen in the primary infection.

The formation of vesicles is frequently preceded by symptoms of burning and an itching sensation. During the following 24 hours a cluster of vesicles erupts on the erythematous mucous membrane or a solitary vesicle may appear which is frequently confused with aphthous lesions. Each ulcer has an irregular margin, a sero-haemorrhagic base and unlike the primary lesions is not surrounded by an erythematous areola (Ship et al, 1961). Reade (1961), considers that the submaxillary and cervical lymph nodes are frequently enlarged and

tender to palpation. Within 7-10 days after the onset of symptoms, the lesions heal completely without scarring. The frequency of recurrence varies widely from one lesion every few years to weekly or even daily episodes of ulceration (Ship et al, 1961).

There is disagreement in the literature regarding the redevelopment of lesions on the same intra-oral site. It has been suggested that a local tissue immunity is conferred on a site following initial infection. However, Benzuly (1956), states that recurrences do occur in the same location owing to the intracellular character of the herpes simplex virus. This statement remains to be confirmed.

Messler and Schour (1959), declare that the usual site of recurrent herpetic infection is a "transitional zone". These include:-

- (a) The transitional zone from the epithelial attachment to the attached gingiva.
- (b) The transitional zone from the attached gingiva to the buccal and lingual oral mucosa.
- (c) The lateral margin of the tongue
- (d) The transitional zone of the lip
- (e) Junction of the hard and soft palate.

Histopathological and Cytological Findings.

The essential histopathological lesion caused by the herpes simplex virus is an intraepithelial vesicle produced by intra and extracellular oedema and degeneration (Cahn and Bartels, 1942; Reade, 1963). The epithelial cells near the basal cell layer undergo "ballooning degeneration" which produces fragmentation of the cells and vesicle formation (Cahn, 1950; Stark et al, 1954; Cooke, 1960).



FIG. 164

Epithelial smear in herpetic stomatitis. Two cells showing eosinophilic intranuclear inclusion bodies, and margination of the chromatin. Haematoxylin and eosin. $\times 560$. (*Brit. dent. J.* 1958.)

(Cooke, 1958)

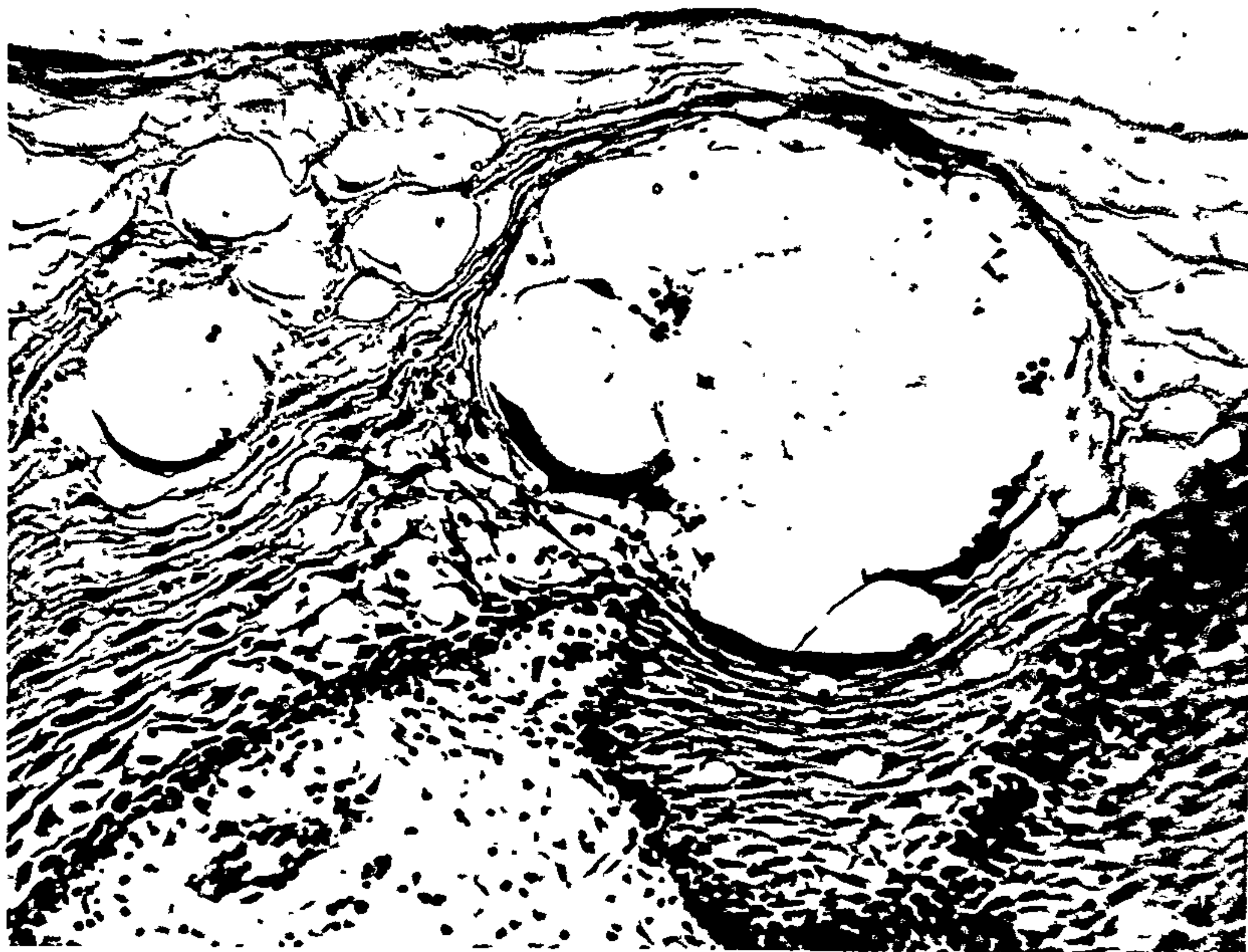


FIG. 165

Reticular degeneration and formation of an intra-epidermal herpetic vesicle in the buccal mucosa. Haematoxylin and eosin. $\times 135$.

(Rushton and Cooke, 1959)

Stark et al report that this feature is most prominent in the intact vesicle but may also be seen at the periphery of a ruptured vesicle.

When the vesicle ruptures the surface of the ulcer which forms is covered by an exudate consisting of fibrin, polymorphonuclear leucocytes and degenerating epithelial cells. Kerr (1952b), reports that evidence of peripheral epithelial regeneration is present after 48-72 hours.

The nuclei of some of the affected epithelial cells may undergo mitotic division to form multinucleated cells, or "giant epithelial cells". In cells so affected intranuclear inclusion bodies of Lipschutz are found. These are situated within nuclei and are seen to be eosinophilic, ovoid and homogeneous. They are variously considered as colonies of virus, degenerated remnants of the affected cell or a combination of both (Gahn and Bartels, 1942; Cooke, 1960; Reade, 1961).

Diagnosis.

Oral herpetic infections are usually diagnosed on the basis of the history and clinical findings. Laboratory confirmation may be obtained by isolation of the virus, finding of specific neutralizing antibodies in the patient's serum and microscopic examination (Barrow, 1954). Rushton and Cooke (1959), suggest that examination of smears of vesicle scrapings is a practical means of diagnosis. The microscopic picture is characterized by the presence of "ballooning degeneration" of the epithelial cells and multinucleated giant cells. Stark et al (1954), Cooke (1958), and Rushton and Cooke (1959), point out that these features are also present in smears from lesions of

herpes zoster. However, Cooke (1960), observes that the clinical features of these two conditions are so distinctive that difficulty in their differentiation is unlikely to occur.

A fluorescence antibody method, reliable for differentiating herpes simplex infections from recurrent aphthous lesions, has been described by Griffin (1963). He found that fifty-four of fifty-six clinical cases of recurrent or acute herpes simplex infection exhibited positive fluorescence of the multinucleated giant cells and ballooning degeneration cells when stained with specific fluorescein isothiocyanate-labelled herpes simplex immune serum or globulin. All cases that exhibited positive fluorescence presented multinucleated giant cells and ballooning degeneration cells in smear examinations. Thirty-seven cases of recurrent aphthous ulcers were negative for specific fluorescence and did not exhibit the typical epithelial changes in smears.

Herpangina differs from herpetic infections by exhibiting lesions confined to the anterior pillars of the fauces and the soft palate, and by having more severe constitutional symptoms (Krugman and Ward, 1958; Cooke, 1960). Herpetic infection is recognised from necrotizing ulcerative gingivitis by the absence of interdental ulceration and necrosis (Kerr, 1952b).

Treatment.

Treatment of primary herpetic infection is essentially symptomatic and supportive. According to Reade (1961), general treatment should include rest, maintenance of fluid balance, provision of

adequate nutrients and the control of pain and fever.

Local treatment of oral lesions is designed to combat secondary infection and alleviate pain. Scott et al (1941), and Cheraskin and Langley (1957), note that, since the disease is self-limiting, efficacy of treatment is difficult to assess. Alkaline mouthwashes are generally agreed to be helpful for the relief of acute symptoms and removal of debris. Burket (1958), believes that the effect of mild antimicrobial agents such as 1% crystal violet and 2% acriflavine is over-estimated. However, Cooke (1961), and Reade (1961), find such agents useful for preventing infection of the ulcerative lesions.

Reade (1961), claims that a 2% aureomycin mouthwash used 6-hourly for 3-4 days reduces pain and limits secondary infection. Kerr (1952b), and Scales (1953), agree that aureomycin, given in adequate dosage at the onset of the disease, may reduce its duration. On the other hand, Burket (1961), is positive that antibiotics do not alter the course of herpetic infections. I believe they should be administered only when systemic symptoms are severe.

Cauterization of the ulcerative lesions with such caustics as 10% silver nitrate, chromic acid, trichloroacetic acid and alum is still popular with some investigators (notably Schaffer, 1951; Burket, 1961; Shafer et al, 1963). However, Scales (1953), is adamant that there is no advantage in damaging surrounding healthy tissue and, as an alternative, advocates the application of benzoin tincture to dried lesions.

The literature contains recent reports of the use of corticosteroid preparations for ulcerative lesions of the oral cavity. Hall-Smith et al (1962), found iododeoxyuridine successful for the relief of acute symptoms. This compound is believed to act by blocking metabolic pathways of virus synthesis. Zegarelli et al (1959), and Smith (1963a), claim that triamcinolone acetonide promotes rapid healing and lessens the duration of painful oral symptoms.

No form of treatment has been discovered which prevents recurrence of herpetic lesions. Suggested treatments for remission of recurrent attacks include snake venom (Fisher, 1941), multiple smallpox vaccinations (Woodburns, 1941; Savitt and Ayers in Bernier, 1959; Rosenthal, 1960; Schaffer, 1960), massive doses of vitamin B complex (Burket and Hickman, 1942), and gamma-globulin (Ramjford, 1960). Kerr (1952b), sums up the situation by stating that the lack of uniformly good results with numerous forms of therapy indicates the need for further controlled investigation.

HERPES ZOSTER

(Shingles)

Herpes Zoster is an acute infection of one or more dorsal root ganglia or extramedullary cranial nerve ganglia. It is typified by a painful vesicular eruption in the skin or mucous membrane along the course of the peripheral sensory nerve arising in the affected ganglia.

According to Jarabak (1959), and Wodak (1960), the aetiological agent is the virus of varicella (*Briareus varicellae*), which is both dermatotropic and neurotropic. Other writers, (Stokes, 1959; Burket, 1961; Shafer et al, 1963), are less positive that a single virus causes varicella and herpes zoster. Spiers (1963), notes that the virus causing herpes zoster has been serially propagated in human tissue cultures in vitro, and is morphologically and immunologically indistinguishable from the varicella virus cultured from cases of chickenpox. Stokes (1959), considers that varicella and herpes zoster are two phases of a single disease and Theodore (1952), believes that varicella is caused by the dermatotropic strain of the same virus. In my opinion the literature has not yet revealed positive substantiation for the theory that herpes zoster and varicella are caused by the same virus.

The trigeminal nerve was affected in 16% of 2,010 cases of herpes zoster seen by Bergreen and Schuller (cited by Chaconas, 1960). Chaconas lists the most frequently involved intraoral sites as the anterior portion of the tongue, soft palate and cheek. However,

Cooke (1960), believes that the tongue is rarely affected. Skin lesions do not always accompany the oral manifestations of herpes zoster.

Pain and tenderness precede the eruption of vesicles which are distributed along the periphery of the second or third division of the trigeminal nerve. These vesicles develop on a broad and slightly elevated, erythematous base and are accompanied by neuralgic or acute, deep, burning pain (Chaconas, 1960). They are considered by Chaconas and Burket (1961), to be indistinguishable from the lesions of herpes simplex. They are usually associated with fever and general malaise. Cooke (1960), classifies the vesicle of herpes zoster as the intra-epithelial type because epithelium forms the floor, roof and sides of the lesion. He states that intraoral vesicles are more profuse when the second division of the nerve is affected.

The vesicle quickly ruptures to leave a painful ulcer surrounded by an erythematous areola. The ragged remnants of the ruptured walls of the vesicle are attached to the periphery of the ulcer (Chaconas, 1960). According to Burket (1961), while the ulcers are healing they have a yellowish-grey coating which is cheese-like in appearance. The neural ulcers are considered to be of shorter duration than the corresponding cutaneous lesions.

Gardner and Hanft (1961^a), point out that the histological appearance of the vesicles of herpes zoster and herpes simplex is identical. Cooke (1958), reports that the small eosinophilic bodies

of Lipschutz, situated in the epithelium around the vesicle, are rarely seen. However, Pinkerton (1957), states that these inclusion bodies differ from those of herpes simplex in that they fill the nuclei less completely than the latter.

Cooke (1960), considers the diagnosis of a well-developed case of oral herpes zoster should include the following:-

1. Lesions preceded by facial pain.
2. Skin vesicles prominent on the upper lip with involvement of the second division, and in the region of the mental foramen with involvement of the third division.
3. Oral lesions strictly unilateral and confined to the area supplied by the nerve concerned.

Gardner and Hanft (196^a), describe herpes zoster in an elderly female whose mouth exhibited multiple, yellowish ulcers on the left buccal mucosa. These were associated with a unilateral vesicular eruption on the skin overlying the symphysis, body and ramus of the mandible.

Burtschi (1962), reports an instance of this condition in a young man who showed no cutaneous lesions. Trauma from the surgical removal of a lower third molar probably provided an entrance for the virus. In a case diagnosed by Stones (1962), the patient was the father of several children who had recently had chickenpox.

An interesting case is described by Wodak (1962), in which endoscopic findings revealed vesicles on a thick, oedematous antral

mucosa in addition to lesions on the oral and external epithelium.

There is no specific treatment for herpes zoster. Tiecke et al (1959), recommend analgesics and mouthwashes for relieving pain of the oral lesions and controlling secondary infection. Jarabak (1959), considers that hospitalization and good nursing care are required in treating one of the most painful of neuralgic complaints.

RAMSEY-HUNT SYNDROME

(Herpes zoster - meningo - encephelitis)

This syndrome occurs when the geniculate ganglion of the seventh cranial nerve is involved, and is characterized by the presence of herpes zoster, otic pain, vertigo, gustatory disturbances and diminished hearing (Chaconas, 1960; Swoope, 1963). Despite the fact that Cooke (1960), states that most of the reported cases of herpes zoster have been accompanied by zoster of the geniculate ganglion, I could only find 4 cases reported in dental literature in the last 8 years.

Sweeney (1960), describes a characteristic Ramsey-Hunt syndrome in which the typical oral vesicles and ulcerations of herpes zoster appeared on the right palate and buccal mucosa.

GRANULOMA INGUINALE

This is a slightly contagious, granulomatous disease chiefly occurring in tropical regions. It is characterized by deep, purulent, cutaneous ulcers on the external genitalia and occasionally on the oral mucous membrane. The disease was originally thought by Donovan to be caused by a protozoan, but now many consider it to be due to the virus *Klebsiella granulomatis* (Cheraskin and Langley, 1956; Thoma and Goldman, 1960; Burket, 1961; Stones, 1962). However Shafer et al (1963) note that it is probably caused by a bacillus which they designate as *Donovania granulomatis*.

The frequency of occurrence of the lesions on the genitalia has led some authors (Cheraskin and Langley, 1956; Stones, 1962; Shafer et al, 1963), to believe that the condition is venereal in origin, but Bernier (1959), and Burket (1961), state that a venereal origin has yet to be proven.

Cheraskin and Langley (1956), claim that oral manifestations occur in 2-4% of cases of granuloma inguinale when localized or diffuse lesions may occur at any site on the oral mucous membrane. Thoma and Goldman (1960), Stones (1962), and Shafer et al (1963), describe three types of oral lesions:-

- (a) An ulcerative type with a rough surface.
- (b) An exuberant type - raised, oedematous lesions which break down into ulcers.
- (c) A cicatricial type which is a result of healing of the ulcerative and exuberant types.

Diagnosis of granuloma inguinale is based on the histological recognition of small, elongated rods known as Donovan bodies. These are present in profuse numbers in the large, mononuclear phagocytes. Shafer et al (1963), consider that Donovan bodies are associated with the bacilli which they believe to be the probable causative agents. This relationship has not been supported by other writers.

Bernier (1959), describes granuloma inguinale in a young Negro. A large ulcer on the lower lip presented a centre of loose, necrotic tissue with a slimy surface. Healing took place with marked scarring. Ferro and Richter (1946), report three cases in which severe oral ulceration in the vestibular region was secondary to active genital lesions. Muckenfuss and Brown (1932), note an instance in which ulcers at the angles of the mouth had hard, rolled edges and resembled carcinomatous lesions.

Aureomycin has been used successfully in treating granuloma inguinale. Bernier (1959), emphasises that care of oral lesions is important and should consist of removal of necrotic tissue, prolonged cleansing and application of mild antiseptics.

FOOT AND MOUTH DISEASE

(Aphthous Fever)

This virus disease of animals affects chiefly cattle and is only rarely seen in man. It is transmitted to man by direct contact with infected animals, or by ingestion of contaminated milk or other animal products. The disease is typified by fever, malaise and the appearance of ulcerative lesions on the skin and oral mucous membrane. According to Burnett and Scherp (1957), lesions occur most frequently on the hands and feet but numerous small vesicles may develop at any site in the mouth. Shafer et al (1963), state that the lips, tongue, palate and oro-pharynx are chiefly affected.

The vesicles are yellowish-white in colour and are filled with a turbid fluid containing the virus. According to van Rooyen and Rhodes (1940), these vesicles may attain considerable size before breaking down. The ulcers formed are red, painful and measure 3-10 μ in diameter, (Sutton and Sutton, 1948). Before becoming secondarily infected they discharge a clear, watery fluid. Such ulcers are usually associated with excessive salivation, a foetid breath and sometimes difficulty in swallowing and masticating (van Rooyen and Rhodes, 1940; Bernier, 1959; Tiecke et al, 1959; Stones, 1962). The disease runs a self-limited course and the ulcers usually heal rapidly.

PSITTACOSIS
(Ornithosis).

This acute infection is caused by a filterable virus transmitted to man from diseased birds. Comroe et al (1954), and Pinkerton (1959), believe that it cannot be transmitted from man to man. In parrots and related birds the disease is "psittacosis" and when it occurs in other birds is termed "ornithosis". In man the infection produces a form of broncho-pneumonia.

No instances of psittacosis with oral manifestations have been reported in Australia. Day (1939), suggests that oral lesions may occur and pass unrecognised because of their mild form.

Severe palatal ulceration was the only oral manifestation in a severe infection seen by Day (1939), in a young woman who had made a habit of kissing her pet love-bird. This ulcer was extremely painful, elevated and sharply-defined. Its unusual feature was the formation of creamy-white, stalactite projections from the surface. These tended to recur after removal.

Horsfall (1959), recommends the tetracyclines for the treatment of psittacosis.

THE EXANTHEMAS.

These comprise a group of eruptive fevers in which there is a lowering of body resistance. They are important because of the complications which may ensue. Oral ulceration is not considered to be an outstanding or characteristic clinical feature of these infections.

(a) German Measles. (Rubella).

This is a mild, contagious, viral disease manifested by a pale pink rash and posterior cervical lymphadenitis. Rake (1948), Kilbourne (1959), Thoma and Goldman (1960), state that tiny red macules may appear on the soft palate. Bernier (1959), considers that they may ulcerate.

(b) Measles. (Rubeola).

An extremely contagious infection, measles primarily affects children and usually occurs in epidemic form. The most important oral lesions are the characteristic Koplik's spots which are visible on the buccal mucosa 2-3 days before the generalized cutaneous eruption. These are small bluish-white specks surrounded by a bright red areola. Shafer et al (1963), claim that a generalized ulcerative condition of the oral mucous membrane may take place.

(c) Chickenpox. (Variola).

Chickenpox is caused by a virus which closely resembles that of herpes zoster. Pinkerton (1959), notes that the infection usually causes only a cutaneous eruption. However, Krugman and Ward (1958), state that when adults are affected severe constitutional symptoms

and complications are more likely to occur.

According to Tiecke et al (1959), oral vesicles usually precede the cutaneous eruptions by 12-24 hours. They may appear at any site in the mouth but Bernier (1959), states that they occur most frequently on the palate and lingual gingivae. When the pharynx is affected swallowing may be difficult.

The vesicles quickly rupture to form small, greyish-white erosions surrounded by an inflammatory areola (Banks, 1953). These ulcers are usually painless and heal rapidly unless secondary infection intervenes.

Tiecke et al (1959), find it noteworthy that the histological changes seen in variola are indistinguishable from those seen in herpes simplex. Prior to ulceration the swollen epithelial cells undergo "ballooning degeneration" and exhibit eosinophilic intranuclear inclusion bodies. The submucosa may show a mild inflammatory reaction.

(d) Varicella. (Smallpox).

This is an acute, highly contagious condition presenting a constant clinical picture. It is typified by severe constitutional symptoms and an exanthem which proceeds through macular, papular, vesicular and pustular stages in 3-10 days. Diagnosis is established by the clinical signs and symptoms, direct serological examination and isolation of the virus. Stokes (1959), reports that the Guarnieri bodies (cytoplasmic acidophilic inclusions lying close to the cell nucleus) and intranuclear inclusion bodies are visible in the pustular

cells but are not seen in a single cell. He believes that the Guarnieri body is probably a mass of variola virus embedded in a matrix.

Krugman and Ward (1958), consider that oral ulceration may precede the exanthem. The ulcers which follow the breakdown of the vesicle are described as being painful, greyish-white in colour, punched-out in shape and covered by a small amount of exudate which probably contributes to the yellowish colour, (Cohen and Weinstein, 1961; Stones, 1962). Burnett and Scherp (1957), note that they may be seen chiefly on the soft palate.

An attack of smallpox produces lasting immunity. Resistance in humans is obtained by vaccination. There is no specific treatment for the disease apart from supportive care and prevention of infection of the vesicles by the use of antibiotics.

THE ENTEROVIRUSES

The enteroviruses inhabit the human intestinal tract and consist of the polioviruses, coxsackie viruses and E.C.H.O. (Enteric - cytopathogenic - Human - Orphan) viruses. These latter were so named when they could not be linked with disease in man, although they were isolated from stools and produced cytopathogenic effects in tissue culture (Krugman and Ward, 1958). Stuart-Harris (1963), reports that the enteroviruses have a world-wide distribution. According to Sabin et al (1958), there is increasing evidence that the enteroviruses are responsible for a large proportion of the mild febrile illnesses of children which occur in summer and autumn in temperate zones.

(a) E.C.H.O. Viruses.

The role of the E.C.H.O. viruses in human disease is still obscure. Stuart-Harris (1963), describes a mild febrile condition of children in which vesicles and shallow ulcerations on the buccal mucosa and pharynx may accompany the more constant clinical findings of headache, drowsiness, vomiting, irritability and limb pains.

(b) The Coxsackie Viruses.

I. HERPANGINA. (Aphthous Pharyngitis)

Herpangina is a mild infection caused by the group A Coxsackie viruses. In 1951 Huebner et al isolated 4 strains, but in 1959 Huebner reports that 6 strains have been found to cause the disease. Herpangina is characterized by the sudden onset of fever,

sore throat, vomiting and the appearance of small, papular, vesicular and ulcerative lesions on the soft palate and faucial areas (Huebner et al, 1954; Krugman and Ward, 1958; Burket, 1961; Editorial, British Medical Journal, 1963). The disease is primarily seen in young children and occurs chiefly in the summer months (Bernier, 1959; Huebner, 1959; Burket, 1961; Shafer et al, 1963; Ship, 1963).

Within 48 hours of the appearance of systemic symptoms minute papules and vesicles appear on the soft palate. These rest on an erythematous base and may enlarge until they are 4 mms. in diameter before breaking down. According to Ship (1963), and Editorial (British Medical Journal, 1963), these greyish-yellow shallow ulcers have a hyperaemic margin, are 2-20 in number and are usually found on the soft palate, uvula and anterior pillars of the fauces. Burnett and Scherp (1957), and Shafer et al (1963), note that they may sometimes be seen on the hard palate, tongue and buccal mucosa. Occasionally the ulcers are not preceded by vesicle formation (Krugman and Ward, 1958). Complete recovery usually takes place within a week and no specific treatment is indicated.

Since both herpetic stomatitis and herpangina are ulcerative conditions primarily affecting children of the same age group, they may sometimes be confused. Parrott et al (1954), investigated 13 cases of herpangina and 12 cases of herpetic stomatitis and in each instance found that the clinical diagnosis was confirmed by laboratory isolation of the respective viruses. They emphasise the characteristic sites

of the herpangina lesions in a differential diagnosis between the two infections. Curnen and Godenne (1952), were successful in isolating the herpes simplex virus in all months of the year but found that 89% of the Coxsackie strains could be recognised only in the July-November period (North American Summer-Autumn).

II. "HAND-FOOT AND MOUTH DISEASE"

Stewart (1961), reports an outbreak in Sydney in the summer of 1960-1961 of a clinical syndrome in small children characterized by fever, ulcerative lesions of the mouth and fauces, and a cutaneous eruption on the hands and feet. No causative organism was isolated. Alsop et al (1960), examined 83 British children with similar lesions and concluded that Coxsackie group A type 16 virus was the causative agent. Extensive summer outbreaks of the same condition are reported by Magoffin et al (1961) and Robinson and Rhodes (quoted by Stewart, 1961), in the United States.

Alsop et al (1959), describe the oral ulcers as shallow and painful, irregular in outline with a yellowish-grey base and a hyperaemic margin. They usually number 3-10 and occur most frequently on the tongue and buccal mucosa. A 3 year old girl seen by Stewart (1961), exhibited bulbous lesions on the hands and feet and a lesion on the tongue which measured approximately 7 x 10 mms.

An Editorial (British Medical Journal, 1963), states that the lesions in "Hand-Foot and Mouth Disease" are more diffuse than those of herpangina, and that they resemble herpes simplex in their distribution except that they are not commonly found on the face.

RICKETTSIALPOX

This is a mild, self-limiting fever characterized by an initial skin lesion at the site of infection and a generalized papulovesicular rash. It is caused by *Rickettsia akari* and is transmitted to man by a parasite of the common house mouse (Smadel, 1959; Stones, 1962).

No reports of rickettsialpox with oral manifestations could be found in Australian medical literature. Cherashin and Langley (1956), state that vesicles with erythematous margins may be seen in the mouth, particularly on the palate. Colman (1950), considers that these rapidly disintegrate to form shallow ulcers which heal within a few days.

CHAPTER 5.

BACTERIAL INFECTIONS

Tuberculosis

Syphilis

Yaws

Leprosy

Noma

Gonorrhea

Tularaemia

Anthrax

Glanders

Scarlet Fever

Typhoid Fever.

TUBERCULOSIS.

Tuberculosis is an inflammatory granulomatous disease caused by *Mycobacterium tuberculosis*. The disease is widespread among men and animals and may be acute and generalized, or chronic and localized. Any tissue of the body may be affected but the lungs are most frequently involved. Pathologically, tuberculosis is characterized by inflammatory infiltration, tubercles, abscesses, caseous necrosis, fibrosis and calcification (Burnett and Scherp, 1957; Amberson, 1959). Diagnosis is confirmed by animal inoculation and histological demonstration of the micro-organisms by bacteriological culture.

Oral manifestations of tuberculosis, as contrasted with those in other parts of the body, are not common (Brodsky, 1942; Oppenheim et al, 1951; Cheraskin and Langley, 1956; Burket, 1961; Stones, 1962; Shafer et al, 1963). Reports of the prevalence of oral tuberculous lesions vary considerably. Farber et al (cited by Shafer et al, 1963), claim that it is less than 0.1% of cases diagnosed by them. Katz (cited by Schaffer, 1952; and Oppenheim et al, 1951), claims an incidence of 19.9% from 200 autopsies.

Miller (1953), believes that "chances of infection in the mouth must be great, and it seems strange that we do not see tuberculous lesions in the mouth more often." Several reasons for this have been postulated. Kanter and Appleton (1940), demonstrated the bacteriostatic effect of saliva on the tubercle bacilli. Shengold and Sheingold (1951), attach importance to the fact that there is relatively little lymphoid tissue in the mouth. These authors note

that such tissue is particularly susceptible to infection by tubercle bacilli. Bernier (1959), and Cohen (1959), refer to the poor inherent penetrating ability of the organism and the excellent resistance of the oral tissues.

The ulcer is the commonest clinical manifestation of oral tuberculosis (Brodsky, 1942; Thilander and Wennstrom, 1956; Cohen, 1959; Shafer et al, 1963; and others), but other mucosal lesions include the granuloma, tuberculoma and extension of lupus vulgaris. On the tongue there may be also glossitis and fissuring. Writers agree that the tuberculous ulcer occurs most frequently on the tongue. Nathanson (1941), considers the dorsum and tip to be the sites most frequently affected, but Schaffer (1952), believes that the lateral borders are most susceptible to tubercular infection.

Prinz and Greenbaum (1939), describe three clinical types of tuberculous ulcers:-

- (a) The simple, superficial type which is the most frequently occurring. Usually oval or irregular in shape, such an ulcer has a rough, granular soft base and undermined or perpendicular edges.
- (b) The nodulo-fissured type, usually characterized by a single, elevated lesion with indurated edges.
- (c) The papillomatous or "ulcero-vegetative" type resembles the simple ulcer but shows peripheral papillomatous growths. This type is rarely seen.

Zellner (1955), Cawson (1960), and Thoma and Goldman (1960), agree that the variability of the clinical features of oral tuberculosis make the disease difficult to diagnose. However, most writers present a uniform description of the tuberculous ulcer as follows:-

The ulcer is most frequently the result of rapid breakdown of small, painless, yellow tubercles situated in the submucosa and lamina propria. Cohen (1959), claims that some oral ulcers may be preceded by opalescent, vesicles which later become indurated. The ulcer is usually superficial and irregular in outline. The edges are undermined and slightly everted, and the pale, uneven floor exhibits granulomatous projections. The ulcer may be covered by a greyish or white exudate which sometimes appears as a muddy-brown encrustation, (Brodsky, 1942). According to Bryant (cited by Thilander and Wennstrom, 1956), this variation in colour is due to congested and cyanotic vessels near the surface of the lesion. As the ulcer spreads the base may become thickened and the surrounding tissues oedematous. Thilander and Wennstrom (1956), note that on the tongue ulcerations may be fissured. The ulcers are commonly associated with a foetid odour and excessive salivation.

Common opinion is that oral tuberculous ulcers are very painful. Burket (1961), declares that they are accompanied by intense, unremitting pain, which seriously interferes with correct nutrition. However, Finney and Finney (cited by Radden, 1957), maintain that pain is not a diagnostic feature except in advanced cases.

Ulceration of the mucous membrane may also occur as an extension of lupus vulgaris, the cutaneous manifestation of tuberculosis

(Prinz and Greenbaum, 1939; Tiecke et al, 1959). Cohen (1959), reports that this lesion is rarely seen. Initially it commences as a slowly-growing nodule which may coalesce with adjacent lesions prior to ulceration.

Orban and Wentz (1960), describe oral ulcerations associated with disseminated miliary tuberculosis as multiple and shallow but sometimes associated with deeper structures.

Glandular enlargement does not necessarily accompany oral tuberculous ulceration. Cohen (1959), states that it depends on the degree of secondary infection of the oral lesion. Galloway and Horne (1953), consider such an enlargement to be relatively painless and an Annotation (British Medical Journal, 1956) warns that an oral tuberculous ulcer should be looked for when a patient presents with painless enlargement of the submandibular lymph nodes.

The ulcerated epithelium is covered by a dense inflammatory infiltrate. The base of the ulcer and the surrounding tissues contain tubercles which resemble those found in other tissues of the body (Thoma and Goldman, 1960). According to Muir (1958), these comprise:-

- (a) A central zone of multinucleated giant cells which may contain a focus of necrosis.
- (b) A zone of spindle-shaped epithelioid cells.
- (c) Outer zone of round lymphocytes which is infiltrated with the tubercle bacilli.

Oral tuberculous ulcers may arise from primary infection, or by secondary extension from lesions elsewhere in the body. Oral secondary

lesions are considered to occur more frequently than primary lesions (Collins and Cook, 1940; Galloway and Horne, 1953; Annotation in British Medical Journal, 1956; Thilander and Wennstrom, 1956; Cohen, 1959; Milodrowska, 1959; Gardner and Hanft, 1961; Orban and Wentz, 1960; Shafer et al, 1963). Primary oral tuberculous ulcerations have been reported by Collins and Cook (1940), Brand and Ballard (1951), Galloway and Horne (1953), Miller (1953), Boyes et al (1956). Annotation (British Medical Journal, 1956), declares primary oral lesions are not so rare and that more instances would be confirmed if they were more thoroughly investigated. However, Thilander and Wennstrom, (1956), doubt the accurate diagnosis of reported primary oral lesions.

There has been much speculation as to the possible route of infection in secondary oral tuberculosis. Abbott et al (1951), showed the presence of tubercle bacilli in 44.9% of 292 salivary specimens collected from patients with proven pulmonary tuberculosis. Thoma and Goldman (1960), and Shafer et al (1963), think it most likely that organisms in the sputum infect the oral tissues through a mucosal defect. Burket (1961), points out that patients with oral tuberculous lesions often have a history of oral trauma and suggests that any area of chronic irritation favours invasion by the tubercle bacilli. Miller (1953), reported two cases of tuberculous oral ulceration in children with no history of contact with other infected persons, and in whom the lesions were first noticed following trauma. Brodsky (1942), and Cohen (1959), state that infection is usually the result of

haematogenous spread. This theory appears to be supported by the fact that tubercle bacilli are not always found in the saliva of patients with oral tuberculosis.

Radden and Reade (1961), report the occurrence of a painless ulcer in the lower molar region of a 21 year old male with proven pulmonary lesions. This ulcer measured 4 cms x 1 cm, had caused some bone erosion and was associated with the painless enlargement of draining lymph nodes. The second molar had been extracted two years previously and it seems likely that infection took place through the socket.

A gingival tuberculous ulcer examined by Bruce (1954), had a base of raw, pebbly granulation tissue, an undermined edge and a greyish-yellow exudate.

Treatment for traumatic ulceration was given for 7 weeks in a patient seen by Cohen (1959). When there was no evidence of healing a biopsy was performed, and a provisional diagnosis of tuberculosis was later confirmed by a general physical examination.

Treatment of oral tuberculous ulcers should be supplemental to the treatment of the systemic disease. Cheraskin and Langley (1956), suggest irrigation of the oral tissues, application of mild antiseptics and frequent mouthwashes. Schaffer (1952), cautions against local surgical excision or radiation therapy. Investigators agree that in tuberculous patients all sources of oral irritation must be eliminated, since they may serve as predisposing factors for oral infection (Shengold and Sheingold, 1951; Cheraskin and Langley, 1956; Bernier, 1959; Cohen, 1959; Burket, 1961). Despite the warning by

Amberson (1959), that oral ulceration accompanying pulmonary tuberculosis has a poor prognosis, the introduction of drugs such as streptomycin, dihydrostreptomycin, para - amino - salicylic acid and iso - nicotinic acid hydrazide has vastly improved the outlook for these patients. Unfortunately Gerszten et al (1963), announce a dramatic increase in the resistance of tubercle bacilli to these drugs.

SYPHILIS

"Syphilis remains one of the greatest problems of medicine, despite the amazing progress in its diagnosis and treatment during the past three decades" (Comroe et al, 1954). The most important of the venereal diseases, syphilis is caused by a delicate spirochaete, *Treponema pallidum*, which normally only affects humans. Because of the variety of lesions which syphilis may produce in any tissue of the body and the frequent confusion in its diagnosis, Sir William Osler once remarked that it was "the great imitator of all other diseases".

Sexual transmission of *Treponema pallidum* accounts for approximately 90% of syphilitic infections but the overwhelming proportion of extra-genital infection occurs about the mouth. According to Burnett and Scherp (1957), and Muir (1958), the organism has a marked predilection for squamous epithelium and once it has penetrated a breach in the epithelium encounters little or no resistance in the oral tissues.

When the infection is transmitted by direct contact it is termed "acquired" syphilis, in contradistinction to "prenatal" syphilis which is passed to the foetus by an infected mother. If untreated, acquired syphilis manifests three stages which are customarily referred to as the primary, secondary and tertiary lesions. Ulceration of the oral mucous membrane may occur in each of these stages.

1. Primary Syphilis.

The primary lesion or "chancre" develops at the site of infection.

after an incubation period of 10-30 days (Dubos (1944), and McDermott (1959), specify 10-90 days) in which time the bloodstream is invaded with micro-organisms. At this stage Burnett and Scherp (1957), declare that a generalized syphilitic infection may occur without the appearance of a chancre.

It is generally agreed that the lip is the most frequent site of a chancre, (Curtis and Slaughter (1947), report an incidence of 46-77% of oral lesions occurring at this site) followed by the tongue, gingivae and tonsils. Fish (1948), and McDermott (1959), emphasise that there is nothing characteristic about the appearance of a chancre.

The chancre usually commences as a small, solitary papule or vesicle which rapidly breaks down into a crater-like erosion (Tiecke et al, 1959; Orban and Wentz, 1960; Stones, 1962). This enlarges and is finally seen as a large, depressed ulcer with an elevated, indurated base and well-demarcated edges. The floor produces a serosanguinous discharge, and is usually covered by a greyish-white adherent membrane (Lloyd, 1951; Burket, 1961; Ship, 1963). Induration is present to a degree largely determined by its location. Bernier (1959), Burket (1961), and Shafer et al (1963), agree that pain is not a prominent feature unless secondary infection supervenes. Lymph nodes adjacent to a chancre rapidly enlarge and Cahn (1941), McDermott (1959), and Burket (1961), consider this an important diagnostic feature. The chancre regresses spontaneously in 2-8 weeks.

In an excellent contribution to the literature Lloyd (1951),

states that a chancre may develop as an indurated mass within the substance of the tongue. He diagnosed such a lesion in a 48 year old man who complained of a sore and enlarged tongue. Examination revealed an ulcer near the tip, 0.5 cms in diameter, with marked induration and a central grey slough.

Chancres may be mistaken for carcinomatous lesions, particularly on the tongue where, because of exposure to air, they are covered by a dry crust. Lloyd (1951), considers that chancres of the tonsil may be incorrectly diagnosed as diphtheria, Vincent's Angina or a malignancy. He suggests that primary syphilitic lesions in this site are more common than is generally believed.

Histopathologically a chancre is seen as a superficial ulcer surrounded by an extensive zone of inflammatory infiltrate. Invasion of the perivascular lymphatics results in obliterative endarteritis. As the lesion subsides a fibroblastic proliferation progresses to fibrosis and subsequent healing.

Diagnosis of a chancre depends on the dark-field identification of *Treponema pallidum*, since serological tests are not positive until the sixth week after infection. Lucas and Kramer (1959), Tiecke et al (1959), Burket (1961), Colby et al (1961), Gardner (1961), and Shafer et al (1963), warn that recognition of the micro-organism may be difficult because of its similarity to other oral spirochaetes, particularly *Treponema microdentium*.

2. Secondary Syphilis.

Secondary lesions are evident approximately six weeks after the primary lesion has healed. They usually consist of a generalized cutaneous eruption, lymph gland enlargement and mild to moderate constitutional symptoms.

Curtis and Slaughter (1947), consider that nearly all patients with secondary syphilis demonstrate cutaneous cervico-facial or oral mucous membrane lesions. The principal oral lesion, "the mucous patch", teems with micro-organisms and is considered to be the most infective lesion of acute syphilis. Comroe et al (1954), state that they may occur at any intraoral site but Burket (1961), and Ship (1963), report that the tongue, tonsils and pharyngeal and labial mucosa are most frequently involved.

All writers describe the "mucous patch" as an ulcer covered by a slightly elevated, well-circumscribed, smooth, glistening plaque. The lesions are usually multiple and according to Tiecke et al (1959), Burket (1961), and Ship (1963), are moderately painful when they occur on mobile tissues. A raw, bleeding surface is exposed when the macerated surface epithelium is traumatised. The "mucous patches" tend to coalesce to form extensive, superficial ulcerations which are serpiginous in outline and commonly referred to as "snail-track ulcers" (Lloyd, 1951; Muir, 1958; Lucas and Kramer, 1959; Stones, 1962). Lloyd notes that these frequently occur on the fauces and soft palate.

The "mucous patch" may be mistaken for a healing herpetic, traumatic or bullous lesion. Positive serological tests are the

principal means of diagnosis. Secondary syphilitic lesions tend to recur for 2-3 years, and eruptions have been reported as late as 9 years after initial infection.

Lloyd (1951), describes oral lesions known as "precocious tertiaries" which may occur in the second to fifth year of infection. These exhibit some of the chronicity of the tertiary lesions such as greater depth of ulceration and a slower response to therapy.

3. Tertiary Lesions.

The oral lesions of tertiary syphilis are usually confined to the tongue and palate (Tiecke et al, 1959; Burket, 1961; Shafer et al, 1963). The characteristic lesion, the "gumma", is prone to rapid and deep ulceration and may be responsible for considerable tissue destruction.

All writers give a uniform description of a gummatous ulcer. It commences as a nodular mass of rubbery consistency which, because of central necrosis, breaks down to form a large indolent lesion. This is serpiginous in outline with soft edges and a depressed base. Surface sloughing may mask the typical yellowish discharge. Lloyd (1951), notes that less frequently the oral tertiary syphilitic lesion is seen as a smooth, rounded mass of dull, red colour which slowly softens and ulcerates to form a punched-out lesion with a central adherent slough resembling "wash leather".

When a gumma arises in the periosteum of the palate, perforation commonly ensues. In 81 cases of palatal ulceration seen by Lloyd (1951) 28% had progressed to perforation. In some cases tissue destruction

was so extensive that the turbinate bones were exposed.

Histopathologically the gummatous lesion is typified by a central, avascular area of necrosis surrounded by an infiltration of lymphocytes, plasma cells and epithelioid cells. Muir (1958), and Lucas and Kramer (1959), favour the view that necrosis is partly due to an increased tissue sensitivity or allergy which has developed in the course of the infection.

Stones (1962), states that the tongue may contain numerous small gummas, or a large single gumma which forms in muscular tissue and finally breaks down into an extensive lesion. Leukoplakia is frequently associated with syphilitic lesions of the tongue and malignant degeneration of these areas is not infrequent (Erich, 1959; Lucas and Kramer, 1959; Tiecke et al, 1959; Burket, 1961; Colby et al, 1961; Gardner, 1961; Stones, 1962; Shafer et al, 1963).

Taylor and Hipple (1961), report a gummatous lesion on the palate of a 43 year old male. An extensive ulcer was present with raised edges, a central area of necrosis and a base of exposed bone. Standard laboratory tests were negative, but the lesion responded rapidly to a trial course of penicillin. Lloyd(1951), deploras the use of antibiotics for differential therapeutic tests for oral ulcers since temporary regression of the lesion may mask the presence of an underlying malignancy.

4. Prenatal Syphilis.

Infection of the foetus by an infected mother may occur during

gestation via the placenta. Oral lesions resemble those of acquired syphilis although Cherskin and Langley (1956), Burket (1961), Colby et al (1961), and Stones (1962), consider that primary syphilitic lesions may be absent. Other oral manifestations include aberrant tooth development, malocclusion and radiographic abnormalities.

Morison and Saint (1948), Burket (1961), and Stones (1962), state that ulceration of the permanent rhagadic syphilitic scars about the mouth may occur.

Although the incidence of syphilis has markedly decreased since the use of antibiotics, Taylor and Hipple (1961), report that the decrease has occurred primarily in the early stages and that the proportion of latent to early syphilis has increased. Massive doses of penicillin are used in conjunction with preparations of mercury and bismuth (Sutton and Sutton, 1949; Tiecke et al, 1959; Orban and Wentz, 1960). Successful treatment can only be gauged by consistently negative serological tests.

Attention to oral syphilitic lesions should include application of antiseptics, careful irrigation and mouthwashes.

YAWS.
(Framboesia)

Treponema pertenue, the causative agent of yaws, is a spirochaete considered to be morphologically indistinguishable from *Treponema pallidum*. Like syphilis, yaws manifests three clinical stages and writers emphasise the striking resemblance of the lesions to those of syphilis in their clinical course, pathology and response to penicillin therapy (Manson-Bahr, 1954; Burnett and Scherp, 1957; Pund and von Haam, 1957; Turner, 1959; Hunter et al, 1960). Primarily a disease of tropical countries Hunter et al are the only authors in the literature reviewed to state definitely that it may occur in Australia.

Osler (1944), is adamant that the mucous membranes are not involved in yaws. However, Mazumder (1953), states that the primary chancre, or ulcerative "mother yaw", may occur intra-orally in children, and Manson-Bahr (1954), illustrates a primary yaw on the lower lip of a young Australian aboriginal.

Hunter et al (1960), state that in the tertiary stage, usually evident after an interval of several years, a small membranous lesion may appear on the soft palate. This assumes a honeycombed appearance in 3-4 days and a deep ulcer with marked hyperaemic edges is exposed (Burnett and Scherp, 1957; Pund and von Haam, 1957; Turner, 1959). Mazumder (1953), describes how this ulceration may enlarge until the hard and soft tissues of the palate and nose may be destroyed. This gross destruction of tissue is known as "gangosa".

LEPROSY.

(Hansen's Disease)

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*. It is seen principally in tropical climates and is characterized by the slow, progressive destruction of tissue by granulomatous infiltration (Osler, 1944; Burket, 1961). There are two broad clinical divisions : (a) cutaneous (tubercular or nodular), and (b) neural (maculo-anaesthetic). The latter is marked by degeneration of peripheral nerves (Mead, 1940; Dubos, 1948; Mathis, 1956; Thoma and Goldman, 1960). According to Dubos (1948), the cutaneous form is the most common.

Oral lepromatous ulceration is rarely seen in this country. In 1929 Vignes (cited by Prinz and Greenbaum, 1939), found that it occurred in 41.5% of 372 patients examined by him in a United States Leprosarium.

Ulceration of the oral mucous membrane is a result of breakdown of the typical lepromatous nodule, the leproma, by trauma or secondary infection. The leproma, considered by Comroe et al (1954), Mathis (1956), and Hunter et al (1960), to be the only distinctive lesion found in all clinical forms of leprosy, is firm in texture, reddish-yellow in colour and has a wax-like appearance. It consists of lymphocytes, epithelioid cells and macrophages in a well-vascularized fibrous stroma. Lepromas may be found on the hard palate, lips and tongue (Burnett and Scherp, 1957; Thoma and Goldman, 1960; Burket, 1961) but Prinz and Greenbaum (1939), consider the base of the uvula to be their most common site.

An infiltrative, lepromatous ulcer of the free margin of the upper lip was reported by Sala and de Zamora (1957). This lesion was unusual since it was unaccompanied by manifestations in other parts of the body.

According to Prinz and Greenbaum (1939), the treatment of oral lepromatous lesions is restricted to careful sanitation of the mouth, frequent mild mouthwashes and the application of suitable antiseptics. The sulphonamides and their derivatives have revolutionized the treatment of leprosy.

NOMA.
(Gangrenous Stomatitis)

Noma, a rapidly spreading gangrenous condition of the mucous membrane of mucocutaneous orifices, most frequently involves the oral cavity where it is known as "cancrum oris" (Agnew, 1947; Burket, 1961). Now rarely seen, noma occurs chiefly in young children and elderly persons. Diagnosis presents little difficulty because of the well-defined clinical picture.

Agnew (1947), and Shafer et al (1963), consider noma a secondary complication of a systemic disease rather than a primary disease. Cheraskin and Langley (1956), state that it is the result of a combination of exciting and predisposing factors. The most common exciting factor is the extraction of a tooth or an abrasion of the mucous membrane, (d'Agostino, 1951; Cheraskin and Langley, 1956; Thoma and Goldman, 1960). Dawson (1945), reports 10 cases of noma among prisoners-of-war in whom the local predisposing causes appeared to be ill-fitting restorations, retained root fragments and unerupted teeth. Predisposing causes include malnutrition and debilitating diseases such as scarlet fever, dysentery, syphilis, tuberculosis and leukaemia. Eckstein (1940), found a high incidence of noma in patients with malaria and Sung and Sung (1947), note that 18 of the 30 cases of noma examined by them were preceded by measles.

The principle clinical feature of noma is necrosis of tissue. The lesion usually commences as a small ulcer, particularly of the buccal mucosa opposite the third molars, or as an area of stagnation around an ill-fitting bridge or crown (Masuda, 1946; Agnew, 1947; Stark, 1956; Brauer et al, 1959; Thoma and Goldman, 1960). Cheraskin

and Langley, (1956), note that the necrosis spreads rapidly because of thrombosis of small vessels adjacent to the ulcer. The skin overlying the cheek becomes oedematous, discoloured and finally breaks down forming a perforation of the cheek which exposes the jaws and teeth (d'Agostino, 1951; Mazumder, 1953; Shafer et al, 1963). The commencement of the gangrene is visible as a black discolouring of the tissues.

Agnew (1947), recognises three histopathologic zones:-

- (a) a gangrenous zone in which all cells have lost their morphological characteristics. Their walls are disintegrating and numerous micro-organisms are present.
- (b) an intermediate area, or "zone of reaction", in which there is some polymorphonuclear leucocyte infiltration. Numerous micro-organisms may be seen invading the walls of vessels which show evidence of coagulation necrosis.
- (c) there may be abrupt transition to a zone of viable tissue. Numerous micro-organisms are present. In this area apparently little tissue response has been aroused.

Bacteriological studies reveal that no single organism is the immediate aetiological agent of noma. Cheraskin and Langley (1956), and Stark (1956), report that Vincent's organisms are always present. Other writers (Agnew, 1947; d'Agostino, 1951; Shafer et al, 1963), believe that noma is a fuso-spirochaetal infection probably complicated by the invasion of other micro-organisms such as haemolytic and non-haemolytic streptococci, Gram-negative and positive cocci,

diphtheria bacilli and Gram-negative bacilli. Stark (1956), notes that in advanced cases of noma the organisms typical of necrotizing ulcerative gingivitis are found only in the deeper layers after separation of the slough.

Cases of noma arising from ulcerations adjacent to extraction sockets have been reported by Asbell (1939), Masuda (1946), and d'Agostino (1951). Stark (1956), describes an instance of noma in a 74 year old woman who was suffering from malnutrition and a malignancy. Poor oral hygiene probably predisposed to a recurrence of the gangrenous condition. Hitzelburger (1940), refers to a fatal condition in a 48 year old male who had myelogenous leukaemia.

Early diagnosis and treatment is essential. Despite the statement by d'Agostino (1951), that management of noma is difficult because of the absence of a specific micro-organism upon which treatment can be based, the early use of broad spectrum antibiotics has considerably improved the prognosis for this condition. As well as decreasing the mortality rate by as much as 95%, new chemotherapeutic agents have eliminated much of the need for deforming surgery.

GONORRHOEA

Gonorrhoea, the commonest of the venereal diseases, is caused by the Gram-negative *Neisseria gonorrhoeae*. Primarily an infection of the genito-urinary tract, manifestations in the mouth are rare. They may be the result of autoinoculation from infected hands, and in the newborn, from passage through an infected birth canal (Colyer and Sprawson, 1953; Cheraskin and Langley, 1956; Burnett and Scherp, 1957; Cohen and Weinstein, 1961). Cheraskin and Langley (1956), (1959), and Stones (1962), consider that the gonococcus cannot easily penetrate stratified squamous epithelium.

In gonococcal stomatitis the oral mucous membrane is markedly erythematous and lesions range from yellowish-white plaques surrounded by an inflammatory zone to a more extensive erosion covered by a greyish membrane (Osler, 1944; Copping, 1954; Burnett and Scherp, 1957). When this membrane separates off, raw areas of ulceration are exposed. According to Mead (1940), and Burnett and Scherp (1957), the gingivae, tongue and fauces are most frequently affected.

Colyer and Sprawson (1953), and Stones (1962), refer to a gonococcal stomatitis reported by Frazer and Menton in which a greyish adherent membrane covered the anterior half of the tongue, buccal mucosa, gingivae and tonsils. In some areas this had sloughed to produce numerous, painful superficial ulcers.

TULARAEMIA.

(Rabbit Fever)

Tularaemia is an infectious and highly contagious disease of rodents and other small animals that is transmitted to man directly by contact with infected animals, or indirectly by insect vectors and contaminated food or drinking-water. The disease is caused by a Gram-negative bacillus, *Pasteurella tularensis*, and is characterized by swelling and suppuration of lymph nodes adjacent to the site of primary infection, fever and other severe constitutional symptoms (Cheraskin and Langley, 1956; Hopps, 1957; Meyer, 1959; Hunter et al, 1960).

Oral manifestations of tularaemia are rarely seen. Most cases reported are from the United States and this writer could find no reports in this country of tularaemia with oral involvement.

When the primary papular lesion occurs in the mouth it quickly breaks down to form a punched-out ulcer with a raised edge.

Dubos (1944), and Burnett and Scherp, (1957), point out that this ulcer may resemble a syphilitic chancre. Secondary lesions may be multiple and usually commence as greyish-white areas on the tongue, buccal mucosa, gingivae and pharynx, which ulcerate causing severe pain.

Superficial necrosis is present and the ulcers are coated with a thin layer of fibrin, (Burnett and Scherp, 1957; Shafer et al, 1963).

When they affect the gingivae these ulcers may resemble those of necrotizing ulcerative gingivitis.

Pessin (1936), reports a case of tularaemia with severe ulceration of the buccal mucosa and tongue.

Prior to the introduction of antibiotics tularaemia was considered a serious disease.

ANTHRAX.

Anthrax is an uncommon disease in man. It is caused by *Bacillus anthracis* and is usually occupational in origin. The micro-organism may be transmitted to man by exposure to infected animals or their products. According to Meyer (1959), the disease may take a cutaneous form known as the "malignant pustule", or more rarely an internal pulmonary form commonly referred to as "woolsorter's disease".

The oral mucous membrane is rarely the site of anthrax infection. Briggs (1947), reports an instance of oral infection in which the infectious agent was a cheap toothbrush.

The "malignant pustule" commences as a small painful papule which becomes inflamed and quickly develops into a vesicle containing blood-stained fluid. Rupture of the vesicle produces an ulcer with a characteristic black central slough (Mead, 1940; Lucas and Kramer, 1959). The surrounding tissues are oedematous, the regional lymph nodes are enlarged and there is usually an accompanying general toxæmia. Hopps (1957), notes that in the majority of cases the disease remains localized and in a week or two the small ulcer heals.

GLANDERS.

(Farcy; Equinia)

Glanders is an infectious disease caused by *Malleomyces mallei* which may be transmitted to man from equines. It may follow an acute or chronic course and, since the introduction of sulphonamides, is rarely seen.

Prinz and Greenbaum (1939), note that the micro-organism may be introduced through an abrasion in the nasal fossa or oral mucous membrane. A small red nodule develops and soon breaks down to form a deep ulcer with an irregular edge and a necrotic, yellow-grey base, (Mead, 1940; Meyer, 1959). Mead (1940), states that these ulcers usually occur on the hard and soft palates but any part of the oral cavity may be affected (Cheraskin and Langley, 1956). Prinz and Greenbaum (1939), consider that the final soft tissue destruction of the mouth and nose may result in "chronic mutilating glanders of the face". The ulcerative lesions are accompanied by a foetid odour and enlargement of the local lymph glands.

Walters et al (1952), (cited by Norman, 1959), describe a fatal case of glanders in which there was involvement of the tonsils, loss of portion of the soft palate and extension of the ulcerative process to the hard palate, buccal mucosa and gingivae.

SCARLET FEVER

— (Scarlatina)

Scarlet fever is an acute, contagious disease typified by a scarlet cutaneous eruption. Occurring chiefly in children it is caused by a special strain of group A haemolytic streptococci, "streptococci scarlatinae", (Cheraskin and Langley, 1956; Rantz, 1959; Thoma and Goldman, 1960). Diagnosis is usually made on clinical symptoms and confirmed by the Schultz-Charlton laboratory test.

The skin rash is generally preceded by a sore throat, fever, vomiting and headache. Characteristic oral lesions include a fiery red mucosa, a greyish exudate covering the tonsils and a "strawberry tongue".

Cheraskin and Langley (1956), Thoma and Goldman (1960) and Shafer et al (1963), consider that oral ulcers occur in severe cases of scarlet fever. Thoma and Goldman (1960), state that the tongue may exhibit extensive areas of ulceration owing to confluence of small multiple lesions. Bernier (1959), notes that oral lesions usually proceed to ulceration, probably as a result of secondary infection.

In 7 cases of scarlet fever reported by Berndt (1936), and quoted by Thoma and Goldman (1960), oral necrosis was evident.

Scarlet fever readily responds to antibiotics. Ulceration in the mouth should be treated by eliminating abrasive foods from the diet and using bland mouthwashes frequently (Cheraskin and Langley, 1956).

TYPHOID FEVER.

Typhoid fever is an acute illness caused by *Salmonella typhosa* and transmitted to man by contaminated food and drinking water. Because of rigorous public health measures it is now rarely seen. The disease is characterized by sustained fever with headache, vomiting, splenomegaly and a sparse maculopapular eruption, (Comroe et al, 1954; Burnett and Scherp, 1957; Beeson, 1959). Typhoid fever runs a course of about 3 weeks and Dubos (1948), and Burket (1961), note that, if death occurs, it is principally due to complications of intestinal haemorrhage and perforation.

According to Burket (1961), ulceration of the mucosa is the commonest oral manifestation of typhoid fever. The ulcers are shallow and may occur at any site in the mouth but particularly on the lips and tongue. Prinz and Greenbaum (1939), report that such ulcers are sometimes seen during the most serious febrile state and that they may be severe in character.

Comroe et al (1954), stress the importance of maintaining adequate oral hygiene when these ulcers occur. Chloramphenicol is the antibiotic of choice in treating typhoid fever.

CHAPTER 6.

MYCOTIC INFECTIONS

Histoplasmosis

Blastomycosis

Sporotrichosis

Cryptococcosis.

HISTOPLASMOSIS

This infection is caused by the yeast-like fungus *Histoplasma capsulatum* which is thought to be transmitted to man by inhalation. Although most reports of its occurrence come from the United States, Weed and Parkhill (1948), Burnett and Scherp (1957), and Smith (1959), confirm that its incidence is world-wide. The disease may affect any body tissue, and occurs in (a) a localized, benign asymptomatic form commonly affecting the lungs, or (b) a progressive disseminated form which is invariably fatal and is characterized by splenomegaly, hepatomegaly, emaciation, irregular pyrexia, leukopenia and anaemia (Kemper and Bloom, 1944; Levy, 1945; Sutton and Sutton, 1948; Burnett and Scherp, 1957; Smith, 1959; Shafer et al, 1963).

The incidence of histoplasmosis in the United States is generally considered to be increasing (Kemper and Bloom, 1944; Plotnick and Cerri, 1957; Burket, 1961; Stiff, 1963; Tiecke et al, 1963). However, this could be the result of more accurate diagnosis due to improved laboratory techniques.

In the disseminated form of histoplasmosis oral manifestations are common. Levy (1945), estimated that 20% of 70 cases seen by him showed oral lesions. Weed and Parkhill (1948), and Keddie (cited by Curtis and Grekin, 1947), claim a prevalence of 33% and 32% respectively. Oral ulcers may occur as primary lesions or as an extension of infection from an extra-oral site.

Orban and Wentz (1960), state that the ulcer initially appears as an indurated plaque which breaks down, and may be surrounded by a

purplish discolouration of the tissues. The surface is covered with a nonspecific yellow or grey membrane which Levy (1945), feels may resemble that found in other oral conditions. The lesions are very painful and are usually accompanied by a foetid odour. According to Levy the ulcers most frequently occur on the buccal mucosa and may extend to the gingivae.

The resemblance of histoplasmosis to other disorders such as tuberculosis and sarcoidosis may confuse its diagnosis and delay treatment. That histoplasmosis should be considered in cases of obscure infection is emphasised by Levy (1945), and Smith (1959). Identification of the micro-organisms from cutaneous lesions, bone-marrow or the bloodstream is the only conclusive means of diagnosis of this disease.

Histopathologically, there is a heavy infiltration of granulomatous tissue containing large histiocytes, epithelioid cells, polymorphonuclear leucocytes and immature fibroblasts. The organisms can be recognised within the histiocytes where they are encapsulated. Bernier (1959), draws attention to their resemblance to the Donovan bodies seen in Granuloma inguinale. Curtis and Grekin (1947), and Snoke (1953), consider that growth of the micro-organisms in the reticuloid cells is the chief means by which histoplasmosis is distinguished from other fungal diseases. Weed and Parkhill (1948), caution that so few micro-organisms may be present in a biopsy specimen that the disease may be misdiagnosed. Stiff (1963), (citing Silverman), describes a skin test

using histoplasmin antigen, but warns that a negative reaction does not rule out infection by the organism.

Stiff (1963), observed histoplasmosis in a chronically ill man who initially presented with a large, fungating ulcer involving the palate and labial mucosa. Shira and Bhaskar (1963), report an elevated, superficial ulcerative mass at the junction of the hard and soft palates in a 63 year old male. It had rolled, erythematous, indurated margins and a sessile base. A diagnosis of histoplasmosis was made on the basis of a histopathological examination.

An instance of histoplasmosis is described by Kemper and Bloom (1944), in which the patient had noticed a small but extremely painful ulcer on his tongue for 4 months. This case is interesting because until the terminal stages the oral lesion remained the only significant manifestation.

Other cases of histoplasmosis associated with oral ulceration have been noted by Hansmann and Schenken, and Moore and Jorstad (both cited by Levy, 1945), Weed and Parkhill (1948), Rawson et al (1951), Colby et al (1961), and Tiecke et al (1963).

No treatment has been uniformly successful for histoplasmosis. Potassium iodide, antimony compounds, local irradiation and sulphadiazine have been used with little or no success. Plotnick and Cerri (1957), demonstrated in vitro and in experimental animals the effective inhibitory nature of nystatin on *Histoplasma capsulatum*. They claim that in patients with oral lesions proved to be those of histoplasmosis,

local injection of the antibiotic produced complete healing. No other successful treatment with nystatin has been reported. Cheraskin and Langley (1956), state that supportive care and the use of bland mouthwashes and mild antiseptics are important for the cure of oral lesions. Tiecke et al (1963), note that surgery in selected cases has been relatively successful.

BLASTOMYCOSIS

Blastomycosis is an uncommon, chronic granulomatous infection which may involve any tissue of the body, particularly the lungs, skin and bone. Two main forms are universally recognised:-

(a) North American Blastomycosis. (Gilchrist's Disease).

This is caused by *Blastomyces dermatitidis*. Smith (1959), reports that it is prevalent in some parts of the United States. However, I could find no reports of its occurrence in recent Australian medical or dental literature.

Cheraskin and Langley (1956), and Burnett and Scherp (1957), agree that oral manifestations are rare, but Tiecke et al (1959), and Burket (1961), note that oral lesions may be present as a result of extension from cutaneous or systemic lesions. The palate, tongue, gingivae and/or buccal mucosa may be affected by a small yellow papule which enlarges, ulcerates and may erode underlying bone (Tiecke et al, 1959; Orban and Wentz, 1960).

The epithelium exhibits abscess formation and ulceration. The characteristic histopathological feature is epithelial proliferation and extensive granulation tissue formation. Numerous macrophages in this new tissue contain the micro-organisms (Muir, 1958; Orban and Wentz, 1960).

Crich (1932), saw a painless ulcer associated with hyperplasia in a 56 year old man with blastomycosis. The ulcer had developed at the site of a recent extraction, gave off a mucopurulent discharge and

showed a small central opening through which an instrument could be passed into the socket.

Thoma and Goldman (1960), believe that there is no effective treatment for the disease. However, Cheraskin and Langley (1956), Smith (1959), and Orban and Wentz (1960), report successful therapy with amphotericin B and derivatives of stilbamidine. Erich (1947), recommends surgical removal of oral lesions by electrocoagulation.

(b) South American Blastomycosis. (Lutz's Disease).

This condition is confined to the South American Continent and is caused by *Paracoccidioides brasiliensis* which closely resembles *Blastomyces dermatitidis*. Artagaveytia (1949), Perry et al (1954), Burnett and Scherp (1957), and Stones (1962), report that the oral mucous membrane is a common site of entry for the organism. According to Salmon and Sheppard (1962), oral lesions appear as erythematous ulcerations with a granular appearance. These often cause enlargement of regional lymph nodes which may, in turn, cause ulceration of the overlying skin. Ulcers of the oral mucous membrane associated with South American Blastomycosis have been reported by Bogliolo (1950), and Perry et al (1954).

SPOROTRICHOSIS

This is an infection with a world-wide distribution caused by *Sporotrichum schenckii*, which is a saprophyte or parasite primarily of plants. The disease is typified by the formation of gumma-like nodules, abscesses and ulcers (Sutton and Sutton, 1948; Burnett and Scherp, 1957; Bernier, 1959). According to Lever (1953), and Smith (1959), the lesions are usually confined to the skin and superficial lymph nodes, although Shafer et al (1963), state that a disseminated visceral involvement may occur.

A non-specific ulceration of the oro-nasal and pharyngeal mucous membrane may appear 3-14 weeks after the initial infection. Burnett and Scherp (1957), point out that this may simulate a syphilitic chancre. When abscess formation occurs a purulent discharge is evident. Lever (1953), Tiecke et al (1959), and Shafer et al (1963), agree that ulceration is usually accompanied by regional lymphadenopathy. However, Sutton and Sutton (1948), consider regional lymph node enlargement to be uncommon.

Despite the fact that antibiotics are ineffective in treating sporotrichosis Shafer et al (1963), report that the prognosis for the condition is usually good.

CRYPTOCOCCOSIS

(Torulosis; European Blastomycosis)

This is a subacute or chronic, highly fatal infection which causes chronic meningitis and lesions in the lungs, skin and other tissues of the body. The causative agent is *Cryptococcus neoformans*. Newman and Rosenbaum (1962), believe that the oral mucous membrane is rarely affected but Shafer et al (1963), state that oral lesions may appear as non-specific single or multiple ulcers.

An instance of cryptococcosis associated with chronic lymphatic leukaemia in a 33 year old man is reported by Newman and Rosenbaum (1962). An extensive, palatal ulceration was present around the upper left third molar which healed following systemic administration of amphotericin B.

CHAPTER 7.

RECURRENT APHTHOUS ULCERATION

RECURRENT APHTHOUS ULCERATION.

Greek (Aphthai + "an eruption in the mouth"
(Aphtho - "to set on fire"

Recurrent aphthous ulceration is a commonly-occurring, but poorly-defined condition of the oral mucous membrane which has been known since antiquity. Although the first valid description appeared in 1888 (von Mikulicz and Kummel), ignorance of the nature of the disease is still reflected in the confused nomenclature and the remarkable diversity of ideas concerning its aetiology and treatment.

Confusion in terminology has arisen chiefly from the tendency of earlier writers to rename the condition each time a new aetiology was proposed, and the general acceptance of the term "recurrent aphthae" as a synonym for "recurrent herpetic aphthae". In addition, Ship et al (1962), contend that the finding of ulcers in other anatomical areas similar to those seen in the mouth, should not warrant distinction as yet another disease. I consider that all terms (see Table), other than "recurrent aphthous ulceration" should be discarded.

SYNONYMS USED TO DESCRIBE CLINICAL SYMPTOMS OF RECURRENT APHTHOUS ULCERATION

(after Sircus et al, 1957; Ship et al, 1962).

Acute aphthous stomatitis
Canker sores
Dyspeptic ulcers
Behcet's syndrome (partial or complete)
Familial recurrent orogenital ulceration
Habitual solitary aphthous ulceration
Maculofibrinous stomatitis
Periadenitis Mucosa Necrotica Recurrens
Mikulicz's aphthae
Recurrent aphthous stomatitis
Recurrent aphthous ulceration of the mouth

Vesicular stomatitis
 Ulcus necroticum mucosae oris
 Ulcus neuroticum mucosae oris
 Herpetiform lesions

Aetiology

1. Virus Theory.

Ship et al (1961), in a significant contribution to the literature state: "the recurrent nature of the syndrome, its grossly similar appearance to herpetic infection, its apparent provocation by a variety of non-specific stimuli, its complete unresponsiveness to all sorts of systemic and local therapy and the lack of a more suitable explanation have contributed to the view that these ulcers are manifestations of infection with the herpes simplex virus". Without giving much supplementary evidence, this theory was supported by Dodd et al (1938), Scott et al (1941), Cahn and Bartels (1942), Cahn (1950), and has been favoured by Schaffer (1951), Collings and Dukes (1952), Kerr (1952b), Scales (1953), Kilbourne and Horsfall (in Farmer, 1958), Bhaskar (1961), and Colby et al (1961). However, in recent years sufficient evidence has accumulated to prove that there is no positive indication that herpes infections and aphthous ulcers are caused by the same agent:-

(a) Serology.

The work of Blank et al (1950), Dodd and Ruchman (1950), Stark et al (1954), and Ship et al (1961), has shown that patients suffering from recurrent aphthous ulcers do not always have specific neutralizing antibodies for the herpes simplex virus. Dodd and Ruchman (1950), found significant levels of herpes-neutralizing antibody in only 2 out of 11 patients with aphthous ulcers, as compared with high titres in

all of eight patients recovering from primary herpetic infection.

(b) Bacteriology.

Investigators have failed repeatedly in attempts to isolate the herpes simplex virus from aphthous lesions (Blank et al, 1950; Stark et al, 1954; Farmer, 1958; Ship et al, 1961). Ship et al examined specimens from aphthous lesions at various stages of development and found no evidence of any type of viral activity in four types of mammalian cell culture known to be susceptible to a wide variety of viruses.

(c) Biopsy and Cytology.

Blank et al (1950), Stark et al (1954), Farmer (1958), Cooke (1960), and Griffin (1963), were unable to demonstrate specific herpetic intranuclear inclusion bodies in smears and biopsy specimens from aphthous lesions.

Burket (1961), observes that, although many aspects of the disease suggest latent virus infection, all attempts to isolate other viral agents have been indeterminate.

Summary of Observations over a 3-year period by
Blank et al (1950).

	Recurrent Herpes Simplex of skin	Recurrent Aphthae	Primary Herpetic Gingiva stomat- itis.
Herpes simplex virus isolated	16/18	0/27	28/35
Specific inclusions in biopsy	4/4	0/14	4/5
Specific herpes simplex neutralizing antibodies during convalescence	Present at onset; no rise in titre during convalescence 19/19	Usually present at no rise in titre during convalescence 8/13	Absent at onset; rise in titre during convalescence 38/38

N.B. The numerator of the fraction indicates the number of patients

with positive findings and the denominator the number of patients in whom the test was performed.

2. Bacterial Theory.

Since 1930 this theory has been discarded, chiefly because there has been no evidence of cross-infection in families (Ship et al, 1962). However, Barile et al (1963), report the isolation of a bacterial L-form from numerous aphthous lesions in three patients. They suggest that a stable L-form variant of a pathogenic organism is the dormant carrier in recurrent aphthous stomatitis. This work remains to be confirmed.

3. Heredity.

These lesions may occasionally appear to exhibit a genetic origin (Farmer, 1958; Forbes and Robson, 1960), but no definite evidence supports heredity as an aetiological factor.

4. Trauma.

In susceptible individuals aphthous ulcers frequently arise in easily traumatised areas, such as the tip of the tongue and the buccal mucosa (Burket, 1961). Kutscher (1953), investigated this relationship and found that trauma increases the frequency of recurrent lesions but only in susceptible individuals. Ship et al (1962), observe that the taking of a biopsy specimen from a lesion promotes rapid healing.

5. Endocrine Dysfunction.

Stark et al (1954), noted that menstruation had no effect on the chronological cycle of recurrent lesions but found that in ten women

who gave a long history of severe ulceration, the ulcers disappeared in pregnancy and recurred following parturition. Administration of oestrogen did not prevent the occurrence of the lesions. Sircus et al (1957), reported onset of the disease in some women during the menopausal years. The relationship of endocrine disorders to aphthous lesions is at present ill-defined.

6. Psychosomatic Factors.

Sircus et al (1957), and Farmer (1958), found a relationship between mental stress and the development of this type of ulceration. Sircus et al reported that in 120 subjects seen by them severe environmental or emotional stress immediately preceded the onset of ulceration in 63% of the female and 59% of the male patients. They concluded that these factors are not the cause of the disease but may act as aggravating or precipitating mechanisms.

7. Allergy.

A good deal of attention has been focused on the possible relationship between recurrent aphthous ulceration and allergy to foods or drugs. Schaffer (1960), and Ryan (1963), strongly favour the view that allergy is the likeliest cause of this disease. Kutscher et al (1958), announced the importance of citric acid and acetic acid in initiating lesions. Tuft et al (1961), showed that citrus fruits and food containing acetic acid caused ulcers in six patients. Removal of these agents from the diet produced rapid healing of the lesions present and recurrent attacks were reduced in number, frequency and severity. However, in a careful study of 150

sensitive patients on hypoallergic diets during hospitalization of 3-30 weeks, Ship et al (1962), observed that allergy to foods was not associated with recurrent aphthous ulceration.

From an examination of the literature it is apparent that the aetiology of recurrent aphthous ulceration is still obscure. It is possible that exciting extrinsic factors act on intrinsic factors to initiate formation of the lesion.

Incidence.

Sircus et al (1957), drew attention to the high incidence of recurrent aphthous ulceration. Using data from 1,590 individuals they found an overall prevalence of 20.1% or approximately 1 in every 5 persons; a female ratio of 1 in 4 and a male ratio of 1 in 5. They consider that in men the disorder tends to "burn out" after middle age, whereas in women this reduction of incidence is not observed.

More recently Ship et al (1960), found that 55% of 1,788 students gave a positive history (males 52.5%, females 57.2%). Analysis of the frequency in these students indicated that 14% of the students with a history of aphthous ulcers reported recurrences of lesions at intervals of one month or less, 50% had recurrences at intervals of from two months to eleven months, and 36% reported annual or less frequent recurrences.

Clinical Considerations.

All writers give consistent clinical descriptions of recurrent

aphthous ulcers (notably Farmer, 1958; Burket, 1961; Cooke, 1961; Ship et al, 1961; Stones, 1962); apart from some dissension concerning vesicle formation. Stark et al (1954), Cooke (1960), and Ship (1963), doubt that a vesicular stage can be observed clinically. On the other hand, Cahn (1950), Thoma and Goldman (1960), and Stones (1962), describe the clinical appearance of the vesicle.

Initially, there is a prodromal period lasting 1-24 hours in which a sensation of hyperaesthesia and burning is felt. A small erythematous macule appears on this site and develops a central ischaemic area which breaks down within 12 hours (Burket, 1961, specifies a few minutes), to form a shallow ulcer. This increases in size to form a lesion about one centimetre in diameter with a sharply-delineated margin and a clearly visible greyish-yellow fibrinous base.

Farmer (1958), and Cooke and Armitage (1961), state that the outline of the ulcer depends on its location; if situated on a flat surface it is round whereas, if in the sulci it is more likely to be elliptical. The lesion is surrounded by a narrow, erythematous zone. Marked pain, aggravated by speaking, eating or any movement of the facial tissues is usually associated with such ulcers. Farmer (1958), emphasises however that, even in severe cases, there is no rise in temperature and the patient feels well, apart from the inconvenience of a sore mouth.

The ulcers are most often solitary (Cooke, 1961; Ship et al, 1961) and heal slowly without scarring. Cooke reports that ulcers situated above muscle heal more slowly than lesions situated elsewhere.



Male, Aged 33 years.

RECURRENT APHTHOUS ULCERATION.

This patient had suffered from attacks of painful, recurrent ulcers approximately every two months for the past six years. The lesions, which most frequently occurred on the tongue, were usually one or two in number and persisted for about ten days. They were not associated with constitutional symptoms and healed rapidly without scar formation.

The patient was in excellent general health and his dental condition was satisfactory. He appeared free of emotional stress and allergies. Results of standard laboratory tests, including a dietary analysis, were negative.

Treatment included the use of dilute hydrogen peroxide mouthrinses and the topical application of hydrocortisone hemisuccinate sodium (in the form of "Corlan" pellets). The patient felt that this cortisone preparation gave more relief than solutions such as aqueous merthiolate and Gentian violet.

The lesions disappeared within a week. A recurrence occurred six weeks later.

Stark et al (1954), studied one hundred aphthous lesions and concluded that they most frequently occur on the buccal mucosa, lateral borders of the tongue, mucous surfaces of the lips and in the buccal sulci.

Occasionally, a severe form of aphthous lesion is observed which is characterized by deeper penetration of underlying connective tissue, rolled, raised margins and a tendency to heal slowly with the formation of a depressed, white scar. This lesion, known as Mikulicz's aphthae, or periadenitis mucosa necrotica recurrens, is larger in size and more painful than a typical aphthous lesion, is frequently accompanied by constitutional symptoms and may persist for several months.

It is described as a separate entity by Sutton and Sutton (1949), Andrews (1955), Alling (1956), Weichselbaum and Derbes (1957), Hurt (1960), Burket (1961), and Shafer et al (1963). In an article entitled "Mikulicz's Aphthae" Cooke (1961), is obviously referring to typical aphthous lesions. Since this form of aphthae cannot be distinguished on a histopathological basis (Cooke, 1960), I see no justification for its recognition as a distinct entity. On the contrary, I feel that its differentiation complicates an already confused terminology.

It should be emphasised that the clinical appearances of recurrent aphthae and herpetic lesions are frequently indistinguishable. Bataille (1961), notes that herpetic ulcers are usually grouped in a

"bouquet" arrangement. Ship (1963), observes that the vesicle preceding an aphthous lesion is never visible whereas that preceding a herpetic ulcer may occasionally be seen. I consider other clinical points of differential which have been described (such as differences in the history of onset, size, number and recurrence of the lesions), as equally worthless. The only certain means of distinguishing the two conditions have been described by Theodore (1952), Sircus et al (1957) and others as:-

1. The isolation of the herpes simplex virus from herpetic lesions.
2. The finding of herpetic inclusion bodies in biopsies from such lesions.
3. The presence of specific neutralizing antibodies for herpes simplex virus at a high level during the clinical phase.

Histopathology.

Recurrent aphthous lesions exhibit non-specific histopathological features which are non-contributory to clarification of their aetiology (Stark et al, 1954; Jawetz, 1955; Farmer, 1958; Rushton and Cooke, 1959; Ship et al, 1962). The typical ulcer has a fibrino purulent surface membrane beneath which is dense inflammatory cell infiltration. In the later stages, granulation tissue and fibrosis are prominent, but generally tissue involvement is superficial (Cahn, 1941; Stark et al, 1954; Rushton and Cooke, 1959; Shafer et al, 1963). Cooke (1960), considers that there are no apparent histopathological differences between simple aphthous ulcers and Mikulicz's aphthae. In attempts to emphasise these latter lesions



FIG. 162

A recurrent aphthous ulcer. There is slight undermining of the ulcerated epithelium, and the dense polymorphonuclear leucocytic infiltration is localised to the breach. Haematoxylin and eosin. $\times 70$.

(Rushton and Cooke, 1959)

as distinct entities, Alling (1956), Weichselbaum and Derbes (1957), and Hurst (1960), are unable to describe any specific histopathological characteristics.

Treatment.

It appears likely that a cure for recurrent aphthous ulceration will not be found until a definite aetiology is established. Meanwhile, I do not agree with Erich (1959), who advises persons suffering with this condition to "learn to live with it", for, with modern therapeutic aids, the condition in most patients can be relieved.

I consider that patients presenting with recurrent aphthous ulceration should have routine laboratory tests performed to eliminate the possibility of an underlying systemic disorder. They should then be given an efficient masticatory mechanism which exerts a minimum of trauma on the oral tissues.

Sircus (1960), observes that the interest of the clinician, sedation and the resolving of social and emotional problems do more than any other procedures to effect control in those patients in whom chronic anxiety, tension or depression of an exogenous origin is evident. No such value has been shown in patients in whom the abnormal states of mind were endogenous.

A variety of drugs has been used in an attempt to reduce the severity, duration and frequency of recurrence of attacks:-

(a) Caustics. In general, the use of caustic preparations to obtund nerve endings has lost favour (Sutherland, 1959; Ryan, 1963). However,

Schaffer (1960), recommends 8% zinc chloride for the relief of pain.

(b) Antihistamines. Sutherland (1959), has found these are useful if given during the prodromal stages when the patient first notices burning and itching of the mucous membrane. He recommends oral preparations of anthisan (50-100 mgm 4-hourly) or diparalene (50 mgm. twice daily). No support for this therapy could be found in the literature.

(c) Antibiotics. The systemic and local use of aureomycin has been investigated extensively in recent years. Everett (1950), Zegarelli et al (1952), Sircus et al (1957), and Cooke (1960), report that it is effective in slightly reducing the size and severity of lesions, and, in some instances, in reducing the frequency of recurrent attacks. However, after withdrawal of the antibiotic the number, severity and duration of recurrent lesions was found to be the same as before medication. Sutherland (1959), points out the risk of sensitization from the topical use of aureomycin and recommends neomycin cream (0.35-1%) to which allergic sensitization has not yet been shown.

(d) Vitamins - were used widely in early experiments and reports of their effectiveness were variable. In a carefully-controlled experiment Sircus et al (1957), used nicotinamide, folic acid and riboflavine and found that they caused no improvement in the ulcerative lesions.

(e) Smallpox vaccination - was suggested as a prophylaxis against recurrent aphthous ulceration when a virus, probably related to that

of variola, was considered the aetiological agent. Although it has been reported as a reliable, safe and efficient means of preventing recurrent attacks, most workers (notably van Cleve, 1949; Kutscher, 1953; Stark et al, 1954), have used it unsuccessfully.

(f) Gamma-globulin. Since this blood factor contains antibodies for several viruses, it was considered that it should be effective against the virus presumed to cause recurrent aphthous ulcers (Strean, 1957; Strean et al, 1958; Claus, 1961). Morelli and Maroczy (1963), report that it reduces the severity and frequency of attacks. However, Fraser-Moodie (1960), found that it does not influence healing of the ulcers or their recurrence.

(g) Cortisone preparations - have been used locally and systemically in recent years. In all instances they have decreased the frequency, severity and duration of lesions (notably Strean and Horton, 1953; Bergeman, 1954; Alling, 1956; Claus et al, 1957; Weichselbaum and Derbes, 1957; Farmer, 1958; Hurt, 1960). Cooke and Armitage (1960), found hydrocortisone hemisuccinate sodium ("Corlan" pellets) dissolved in the mouth four times daily during exacerbations and twice daily during remissions reduced the duration and number of lesions by 50%. Another cortisone preparation, iododeoxyuridine, has been shown by Hall-Smith et al (1962), to relieve pain from herpetic ulcerative lesions and Ryan (1963), predicts a great advance in treatment if similar results can be duplicated for aphthous ulcers.

Sircus (1960), sums up the present-day knowledge concerning cortisone preparations for the treatment of aphthous ulceration by stating that they are useful when neither exogenous stresses nor

endogenous abnormalities are associated with the disease.

CHAPTER 8.

PERIODONTAL DISEASES

The Marginal Lesion

Necrotizing Ulcerative Gingivitis.

THE MARGINAL LESION.

No consideration of ulcerative lesions of the oral mucous membrane would be complete without reference to the ulceration associated with the marginal inflammatory lesion. This is dealt with in considerable detail in periodontal literature as "gingivitis" and "periodontitis" (Notably Kerr, 1952 a; Robinson, 1952; Weinmann, 1952; Beube, 1953; Goldman and Cohen, 1957; Goldman et al, 1959; Shafer et al, 1963).

Goldman et al (1959), describe the marginal lesion as a chronic inflammation brought about by local injurious agents rather than as a systemic process. The initial lesion, which presents an ulcerated crevicular epithelium, gradually extends into deeper gingival tissues until finally the alveolar bone is involved.

1. Gingivitis.

This is a general term applied to inflammation of the gingival tissues and according to Robinson (1952), is usually a sequel of epithelial ulceration and bacterial invasion.

All writers agree that the chronic form of gingivitis is by far the most commonly seen (notably Goldman et al, 1959; Goldman et al, 1960; Shafer et al, 1963). It is the response of a low-grade irritant and may develop so gradually as to escape notice until it is well-established (Fish, 1952). The most important of these aetiological factors are calculus, overhanging margins, faulty restorations, tooth malposition and mouth breathing. Schultz-Haude et al (1954), Burnett and Scherp (1957), Lucas and Kramer (1958), Appleton (1950), and Shafer et al (1963), are positive that gingivitis

is a mixed infection and that no specific micro-organisms are the causative agents.

Ulceration of the sulcular epithelium is accompanied by a marked inflammatory infiltration of the submucosa and between the connective - tissue bundles of the periodontal membrane (Goldman and Cohen, 1958). The histopathological picture is also characterized by enlargement of blood vessels, fluid infiltration and the presence of large numbers of inflammatory cells, chiefly plasma cells and lymphocytes.

Gingivitis is usually recognized by alterations in the marginal gingivae and in the interdental papillae (Goldman et al, 1959).

These include oedema, loss of stippling, bleeding and exudate from ulceration of the sulcular lining, a change in colour from pink to red and distortion of the normally rounded gingival margin. As a rule, extension of the inflammatory process is gradual but all writers agree that eventually most of the gingival tissues exhibit some change.

2. Periodontitis.

This term designates a more severe inflammation of the gingival tissues than gingivitis. Although the division between the two conditions is arbitrary, most writers consider periodontitis to exist when the inflammation has extended into deeper tissues causing alveolar bone destruction (notably Kerr, 1952 a; Robinson, 1952; Weinmann, 1952; Goldman and Cohen, 1957; Cohen et al, 1959; Rushton and Cooke, 1959; Shafer et al, 1963).

There has been controversy in the early literature regarding the mechanism of the spread of inflammation from the initial sulcular

ulceration. Black (1936), and Fish (1939), claimed that inflammation proceeded directly into the periodontal membrane. Weinmann (1941), showed that it takes place through the crests of the interdental septa and along the vascular canals, rather than through the periodontal membrane. In 1949 Weinmann noted that, only after destruction of the bone separating the inflammatory focus from the periodontal membrane, is the latter involved. He explained this mechanism by the fact that inflammation into the alveolar bone follows the path of least resistance.

Cohen et al (1959), stress that the signs and symptoms of gingival disease in marginal periodontitis resemble those of gingivitis. However, because of crestal bone destruction, pocket formation is deeper and tooth mobility may be evident.



ULCER IN EARLY PERIODONTITIS

(Fish, 1952)

The epithelium is completely detached from the enamel and a lymphocytic infiltration (R) is evident beneath a chronic ulcer (E) situated at the base of the detached gingiva at U. Toxins entering the tissues through the ulcerative lesion aid the destruction of the periodontal fibres and aid in the initiation of a "periodontal pocket".

NECROTIZING ULCERATIVE GINGIVITIS

(Vincent's Infection; ulcero-membranous gingivitis; trench mouth; fuso-spirillary gingivitis; fusospirochaetosis; ulceronecrotic gingivo-stomatitis; Plaut-Vincent's infection.)

Since it was described by Plaut and Vincent in the 1890's, this condition has received much attention and a multiplicity of ideas have been advanced concerning its nomenclature, predisposing factors, bacteriology and treatment. Although the condition is most commonly known as "Vincent's infection", I support the modern tendency to use terminology describing the clinical appearance - hence "necrotizing ulcerative gingivitis."

The signs and symptoms of necrotizing ulcerative gingivitis may vary in acuteness and severity. Most writers have presented a classification: Beube (1953), divides clinical types into early, moderate and advanced, according to the amount of tissue destroyed; each is further described as acute or chronic. However, the majority of writers refer to "acute" and "subacute" forms (Kronfeld, 1955; Goldman and Cohen, 1957; Kerr and Ash, 1960; Stones, 1962; Shafer et al, 1963). Wilson (1952), Burket (1961), Colby et al (1961), and Shafer et al (1963), also mention a "chronic" form. Since this classification cannot be substantiated by histopathological findings, I support Glickman (1953), who considers its differentiation unwarranted.

Acute necrotizing ulcerative gingivitis most frequently is confined to the interdental papillae and free gingival margins. Stammers (1944), found that the gingivae of the incisor teeth were involved in 80.1% of 1,020 instances, either as the site of origin or through extension of the lesion. Occasionally the inflammation may

involve the buccal mucosa ("Vincent's stomatitis") or anterior pharynx ("Vincent's angina"). According to Schaffer (1952), in severe cases it is not uncommon for the tongue to be affected. The subacute form of necrotizing ulcerative gingivitis is the result of an initial low grade infection or of an incompletely cured acute infection.

The acute condition is characterized by the rapid development of painful, hyperaemic, oedematous gingivae and congested interdental papillae. Stammers (1944), believes the first sign of the condition is a spontaneous haemorrhage from the inner aspect of the interdental papilla. Wilson (1952), claims that the initial stage can be recognised by a markedly painful gingival response to slight digital pressure. Since other gingival conditions may exhibit this symptom, I consider this criterion worthless.

As the disease progresses the tips of the papillae rapidly become necrotic and ulcerate, giving the gingivae a typically "clipped-off" appearance (Orban et al, 1958). Small "punched-out" erosions finally extend around the teeth to form a continuous gingival slough. These ulcers are covered by a grey necrotic pseudo-membrane which exposes a bleeding surface, if removed.

Acute necrotizing ulcerative gingivitis is usually accompanied by pain, difficulty in masticating and a characteristic noisome odour. Saliva appears thick and ropy, and the patient frequently complains of a metallic taste and a sensation of the teeth being "wedged apart", (Hutchinson, 1954; Kerr and Ash, 1960; Burket, 1961; Seidberg, 1963; Shafer et al, 1963). If periodontal destruction is extensive the



Male, Aged 19 years.

ACUTE NECROTIZING ULCERATIVE GINGIVITIS

The patient reported complaining of "bleeding and sore gums" when he attempted to brush his teeth.

An ulcerative condition involving the entire gingival margin was present. The lesions were only moderately painful and had caused a characteristic "clipping-off" of the interdental papillae. Foetor oris was absent and no constitutional symptoms were observed.

The patient admitted that he had suffered a similar attack twelve months previously, and that for the past three months he had been fatigued and had neglected his diet.

Treatment included removal of debris, application of Chromic acid (10%) to the necrotic tissue, warm hydrogen peroxide and saline mouthrinses, dietary advice and oral hygiene instruction. Necessary operative work was later carried out and gingival deformity was corrected by surgery.

affected teeth become mobile. In such cases Stones (1962) reports an elevated temperature, malaise and lymphadenitis. Seidberg (1963), and Shafer et al (1963), consider that more severe cases may be complicated by gastro-intestinal disorders, leucopenia and tachycardia.

In the subacute form of this condition ulceration and sloughing are usually absent. The onset is gradual and there is little discomfort. Stones (1962), points out that if the condition persists for a long period there is a gradual destruction of the periodontal tissues and pocket formation.

Necrotizing ulcerative gingivitis may occur at any age but primarily affects the 15-30 age groups. Wade et al (1961), consider that it has a markedly higher incidence in males and Stones (1962), claims that the most susceptible age is 19 years. The average age of 61 patients examined by Manson (1961), was 24.6 years. Although investigators agree that necrotizing ulcerative gingivitis is extremely rare in children (Miller and Greenhut, 1944; Cohen and Goldman, 1962; Stones, 1962; Shafer et al, 1963), Reade (1963), reports oral ulcers in a 15-month old girl which present the clinical and bacterial characteristics of this condition.

The histopathological picture is one of non-specific inflammation and resembles that caused by traumatic or chemical irritation (Glickman, 1958; Bernier, 1959; Tiecke et al, 1959; Seidberg, 1963; Shafer et al, 1963). The surface of the ulcer is covered by a thick slough consisting of fibrin, disintegrating tissue cells, bacteria, leucocytes and erythrocytes. Berke (1961), reports that the base of

the ulcer contains a dense network of spirochaetes. Walling the ulcer off from the deeper structures is a zone of intense inflammatory reaction consisting of polymorphonuclear leucocytes and engorged capillaries (Stammers, 1946; Glickman, 1958; Stones, 1962). Shafer et al (1963), state that a surface layer of keratin is absent even from the non-ulcerated epithelium. This finding is not confirmed by other writers.

Stammers (1946), examined specimens from the acutely ulcerated gingivae of 21 patients and found that surface disintegration occurred in only that part which overlay inflamed connective tissue papillae containing congested vessels. He reported that gingival hyperaemia is an unsatisfactory defence mechanism since it causes rupture and thrombosis of vessels and consequently ischaemia and necrosis of the overlying epithelium. His inability to find bacteria in the deeper structures was also the experience of Schaffer (1953), who considered that bacteria do not penetrate vital tissues, but rather infiltrate such tissues as they become necrotic. However, Berke (1961), found that the spirochaetes attack the epithelium and then penetrate the underlying connective tissue. Stones, (1962), points out that in recurrent necrotizing ulcerative gingivitis the irritated crevicular epithelium may proliferate in papillary processes into the underlying connective tissue.

The bacteriological picture varies with the acuteness and duration of the condition. In the acute phase a smear reveals a heavy

overgrowth of *Treponema vincentii* and fusiform bacilli. Other organisms present in fewer numbers are gram-negative and gram-positive cocci, bacillary forms, other spirochaetes, vibrios and spirilla. As the clinical condition subsides smears show a reduction in the overall bacterial population with little alteration in the predominance of the spirochaetes and fusiform bacilli. Hartman (1945), considers that, since the fusiform bacilli may be visible within leucocytes, they are the aggressors and the spirochaetes and other organisms are probably harmful invaders. Recent authors (Erich, 1959; Orban and Wentz, 1961), refer to these two organisms as the causative agents. Goldman et al (1959), note that these organisms and a vibrio are the aetiological micro-organisms. However, since the spirochaetes and fusiform bacilli may flourish in any healthy mouth, it is now widely agreed that diagnosis of this condition should depend primarily on the clinical picture rather than the bacteriological smear. However, Burket (1961), is adamant that a smear should be done for a final diagnosis. In my opinion a bacteriological smear is only of value in determining whether the fuso-spirochaetes are abnormally numerous.

Burket (1961), and Reade (1963), state that there is still some confusion in differentiating necrotizing ulcerative gingivitis from primary herpetic stomatitis. Unlike the former, herpetic lesions commence as vesicles which rupture to produce painful ulcers with a ragged margin. According to Burket (1961), oral manifestations of erythema multiforme, uncontrolled or unrecognized diabetes mellitus

and acute syphilis may be initially diagnosed as necrotizing ulcerative gingivitis. Erich (1959), and Kugelmass (1960), stress that a blood count is necessary to eliminate the possibility of an underlying blood dyscrasia. Rockoff et al (1955), report an instance of necrotizing ulcerative gingivitis superimposed on marked gingival enlargement with acute myeloblastic leukaemia.

Despite intensive investigation the aetiology of necrotizing ulcerative gingivitis remains in a confused state. Clinical and laboratory experiments have failed to support the earlier view that it was due to an infection with spirochaetes and fusiform bacilli. However, that these organisms are intimately concerned appears to be supported by the excellent response to antibiotics reported by Goldman et al (1949), (1950), and Orban et al (1958), and by the fact that the organisms have been used in the experimental transmission of the disease in animals (Berke, 1961).

The present consensus of opinion is that these two principal organisms multiply to pathogenic concentration as a result of lowered tissue resistance. In a detailed consideration of the aetiology Stammers (1944), declares that local conditions are of paramount importance, systemic factors contributory to the aggravation of local trauma, while fuso-spirochaetes are of secondary importance in the inception of this disease. Local factors predisposing to necrotizing ulcerative gingivitis are pericoronal flaps of erupting teeth, periodontal pockets, poor oral hygiene, irritation from calculus and

from poor margins and contours of restorations. Other factors which have been reported are nutritional deficiencies, fatigue, stress and seasonal changes. Moulton et al (1952), established that emotional factors often appear to precede the onset or recurrence of an acute phase of the disease whether local irritating factors are present or not.

Necrotizing ulcerative gingivitis was once considered to be contagious, principally because it appeared in outbreaks which seemed epidemic in nature. Recent writers attach importance to the fact that groups so affected, chiefly students and servicemen, live under conditions producing emotional stress and physical exhaustion (Beube, 1953; Glickman, 1958; Goldman et al, 1959; Fitch et al, 1963). Attempts to produce necrotizing ulcerative gingivitis in humans by laboratory transmission have been unsuccessful. However, Berke (1961), claims to have successfully transmitted the disease in dogs. Schluger (1949), in a study of 92 servicemen with the condition, was unable to find a definite pattern of spread. The existing evidence suggests that necrotizing ulcerative gingivitis is an endogenous infection rather than a communicable one.

Treatment.

The management of necrotizing ulcerative gingivitis has been the subject of controversy for the past thirty years. An American Dental Association Report (1945), concludes that treatment should be concerned with the following (a) mouth sanitation, (b) mouth medication, (c) elimination of predisposing factors, (d) post-operative treatment.

Recent investigators generally agree that scaling and prophylaxis should be commenced as soon as possible (Beube, 1953; Schaffer, 1954; Glickman, 1958; Goldman et al, 1959; Colby et al, 1960; Goldman et al, 1960; Fitch et al, 1963). Goldman et al (1960), report a dramatic tissue response to instrumentation and Rosebury et al (1950), state that the rate of healing is proportional to the amount of debris removed at the first visit. Manson (1961), found marked relief of pain following removal of gross debris and calculus. However, Burket (1961), agrees with earlier writers such as Fish (1948), who contend that instrumentation should be postponed until the acute phase has subsided lest the infection extend into the bloodstream and deeper tissues. I consider no substantial evidence has as yet been brought forward to support this latter theory.

A variety of medicaments have been recommended for the treatment of necrotizing ulcerative gingivitis. These include caustics, oxidising agents, iodine compounds, aniline dyes, antibiotics and derivatives of arsenic, mercury and silver. Many of these have lost favour because of the difficulty of application and the likelihood of undesirable side effects. Using chromic acid (10%) carefully applied to the necrotic tissues, consistently satisfactory results are obtainable. However, some investigators (Rosenthal, 1950; Oliver and Fletcher, 1959; Burket, 1961; Manson, 1961; Messing, 1962; Ryan, 1963), declare that chromic acid is too caustic for oral use. Alternatives suggested include tinctures of metaphen or merthiolate, zinc oxide protective packs (Sumner and Baer, 1961), ascorbic acid

with sodium percarbonate ("Ascoxal"), sodium peroxyborate monohydrate ("Bocasan") (Wade et al, 1961). Despite the current view of the medical and dental professions that antibiotics should not be employed if other treatment measures are effective, Fish (1952), Cheraskin and Langley (1956), Orban and Wentz (1960), and Ryan (1963), recommend the routine use of systemic penicillin for necrotizing ulcerative gingivitis. Goldman and Bloom (1950), report success with the topical application of Aureomycin but used too few patients for definite conclusions to be made. I believe that antibiotics should be used in this condition only as an adjunct to instrumentation for those patients with systemic symptoms, severe pain and extensive tissue destruction.

The tendency of many dentists to treat only the acute phase of necrotizing ulcerative gingivitis is to be condemned. Burket (1961), emphasises that the disappearance of acute, painful symptoms by no means constitutes a cure. After analysing 61 recurrent cases of this condition, Manson (1961), confirms that recurrence is caused by gingival deformity from previous attacks and failure to eliminate local and systemic predisposing factors.

CHAPTER 9.

DISEASES OF THE BLOOD.

Leukaemia

Agranulocytosis

Cyclic Neutropenia

Infectious Mononucleosis.

LEUKAEMIA.

Leukaemia is a progressively fatal disease of the blood-forming organs characterized by uncontrollable and widespread proliferation of the leucocytes and their precursors. These immature cells circulate in the bloodstream and become deposited in fixed tissues (Kracke and Garver in Cook, 1947). Except when leukaemia follows exposure to benzene or roentgen rays, the aetiology in man is unknown. Hormonal, nutritional, viral and genetic factors have been cited as possible causes. However, the balance of evidence at present favours a neoplastic theory and Sturgis (1959), reports that in practice both treatment and prognosis are based on the assumption that the leukaemic process is malignant.

Leukaemia is classified on the basis of its cytological type, that is, myeloid, lymphatic or monocytic, each of which is subdivided into acute or chronic. The condition affects both sexes at any age. However, the various types can be linked with age. The incidence of leukaemia is highest in the first 5 years of life, with most instances to the age of 20 years being of an acute nature. From 5-50 years myelogenous leukaemia is most frequently observed and after 50 years the chronic lymphatic type predominates (Rettberg, 1953; Sinrod, 1957; Whitby and Britton, 1957; Smith, 1960). Several authors (notably Duffy and Driscoll, 1958; Smith, 1960; Burket, 1961; Vogel, 1963), report that the incidence of leukaemia has markedly increased in recent years.

Oral manifestations of leukaemia have been extensively reported

in medical and dental literature. Maloney (1940), believes oral lesions are clinically important because they occur frequently and are often the initial sign of the disease. After examining 99 leukaemic patients Sinrod (1957), found that 44% of them showed obvious oral changes. Of these 55% were of the acute and 15% of the chronic form.

According to Burket (1944), and Vogel (1963), oral lesions most frequently accompany monocytic leukaemia. Resch (1940), considers that they are caused by absence of clotting factors and protein elements in the blood and infiltration of the oral mucosa by immature leucocytes.

Lesions in the mouth and pharynx vary in severity from small necrotic ulcers to areas of marked swelling with extensive ulceration. These lesions are extremely painful and may occur at any site on the oral mucous membrane (de Gruchy, 1960), with the gingivae being most frequently affected. Sinrod (1957), and Shafer et al (1963), note that gingival haemorrhage results from ulceration and necrosis of the sulcular epithelium. Gingival hypertrophy may be so severe that the teeth appear almost buried and de Gruchy (1960), believes this occurs most commonly in acute monocytic leukaemia.

According to Whitby and Britton (1957), the acute and chronic forms of leukaemia are clinically indistinguishable. However, acute forms usually have a sudden onset with fever and prostration, a rapidly progressive anaemia and a developing tendency to general haemorrhage. In contrast to the dramatic symptoms of the acute form, chronic

leukaemia may have such an insidious onset that discovery of its presence may be made only accidentally in routine blood examinations (Rettberg, 1953; Whitby and Britton, 1957; Scopp and Quart, 1959; Shafer et al, 1963).

In a detailed histopathological examination of the gingivae in leukaemia, Wentz et al (1949), found that the acute form was characterized by a massive infiltration of the tissues by immature leucocytes. On the other hand, the chronic form exhibited no specific changes and only a few immature cells were evident.

Colebatch and Taft (1963), consider that the attempt to develop effective measures for helping leukaemia patients has brought into prominence the importance of an early diagnosis. Marrow preparations generally provide the best means of diagnosis, classification of the condition according to its cytological type, and estimation of the severity of infiltration. Whitby and Britton (1957), observe that the frequency with which oral lesions first reveal acute leukaemia is not generally recognised. Glickman (1958), cautions that such lesions are of suggestive rather than pathognomonic use. If however, the patient exhibits lassitude, pallor, loss of weight and lymphadenitis, the clinician should suspect leukaemia. Vogel (1963), advocates a haematological examination for every patient with buccal ulceration especially when haemorrhage is present. However, unless the lesion is non-healing and the patient shows constitutional symptoms this is unnecessary.

There have been numerous case reports of leukaemia which has initially exhibited oral ulceration. Cook (1947), and Matheson (1949),

report instances of gingival hyperplasia, haemorrhage and ulceration in patients whose condition was confirmed by haematological examination.

Specific chemotherapy, blood transfusions and antibiotics are employed to improve the comfort of the patient and induce temporary clinical remissions. Drugs used include a combination of antimetabolites (such as mercaptopurine), steroid hormones and alkylating agents (such as cyclophosphamide or nitrogen mustard). Colebatch and Fitch (1963), emphasise constant monitoring with blood and marrow examinations. Ostrander (1958), Robinson (1958), and Vogel (1963), point out that these recently discovered drugs may present a narrow margin of safety between the therapeutic and toxic doses. A complication of the antimetabolite group is the appearance of aphthous-like ulcers on the oral mucosa (Robinson, 1955; Duffy and Driscoll, 1958).

The treatment of oral lesions in leukaemia should be directed at control of infection and the prevention of necrotic extension. The application of mild antimicrobial agents is recommended and strict attention to oral hygiene is essential. Any surgical procedure in these patients should be avoided.

AGRANULOCYTOSIS

(Malignant neutropenia, malignant leucopenia,
agranulocytic angina, granulocytopenia.)

Agranulocytosis is a serious condition in which there is extreme diminution of cells of the myeloid series associated with necrotic ulcerations, particularly of the mouth (Whitby and Britton, 1957). This decrease in circulating neutrophil leucocytes lowers the resistance of the body to infection. Therefore the clinical manifestations are those secondary to bacterial invasion of tissue — fever, prostration, mucosal ulceration, pyoderma and septicaemia (Hanzlik, 1935; Moore, 1959).

The disease may occur suddenly, or follow as a complication from an existing illness. The exact mechanism by which agranulocytosis is produced is unknown but it is associated with a variety of agents and conditions which have been described by Whitby and Britton (1957), Tiecke et al (1959), and Shafer et al (1963), as primary and secondary causes. The clinical and laboratory findings are identical in each.

(a) Primary or idiopathic agranulocytosis.

(b) Secondary agranulocytosis may be caused by:—

- i. Agents which inhibit leucocyte production so that the marrow contains little or no leucoblastic tissue, or,
- ii. Noxious or restraining influences which prevent maturation of leucocytes or the release of mature cells into the bloodstream, or,
- iii. Absence of factors essential for maturation.

Drugs which are most commonly associated with the development of an agranulocytic condition include amidopyrine, sulphonamides, thiouracil, barbiturates, dilantin and tridione. Bacterial toxins from infections such as osteomyelitis or pneumonia may produce a similar effect. Fortunately, reports of agranulocytosis caused by antibiotic therapy are rare.

In the development of agranulocytosis the patient may first complain of chills, fever and/or a sore throat. de Gruchy (1960), emphasises that oral lesions are usually the most prominent, and occasionally the initial, symptom. Gangrenous ulceration develops rapidly and may involve serious tissue destruction. Orban and Wentz (1960), describe the ulcers as commencing as haemorrhagic spots on the gingivae, lip, soft palate, buccal mucosa or pharynx, in other words, sites where bacteria are normally numerous (Moore, 1959). The ulcers have an irregular margin and are covered by a dirty yellow or greyish membrane. Wentz (1952), suggests that this colour is a result of tissue breakdown. All writers agree in the description of oral ulcers in agranulocytosis and emphasise that, because of the underlying cause, no surrounding tissue response is evident (notably Rettberg, 1953; Robinson, 1955; Dalitsch, 1957; Moore, 1959; Bhaskar, 1961; Colby et al, 1961). Cheraskin and Langley (1957), and Shafer et al (1963), report the presence of foetor oris, increased salivation and periodontal involvement which may allow mobility of the teeth. When the ulceration extends into the pharynx, eating and swallowing are difficult. Whitby and Britton (1957), consider that

advanced ulcers may produce palatal perforation and perforation and noma of the buccal tissues is not infrequent in the terminal stages.

A constant histopathological picture is described by all writers reviewed. Because of the absence of neutrophils ulcerated areas are not surrounded by a typical inflammatory infiltration or associated with pus formation (Bernier, 1959; Bhaskar, 1961). Orban and Wentz (1960), and Shafer et al (1963), note that ulceration is deep and the surface is covered by a necrotic mass separated from viable tissue by an infiltration of lymphocytes, plasma cells and macrophages. Many of the plasma cells have two or more nuclei.

An early diagnosis of agranulocytosis is of vital importance. Cahn (1941), and Burket (1961), observe that prognosis for the condition is related to the duration of the disease before treatment is commenced and the nature of the bone marrow depressant. Diagnosis is made from the clinical history, appearance of the lesions and the typical haematological picture. At times this may be characterized by the complete absence of neutrophil leucocytes.

Screebny and McGrew (1953), report marked oral reactions in a 33-year old male in whom agranulocytosis was caused by the anticonvulsant drug tridione (trimethadione). Soon after therapy commenced the patient noticed crusted ulcers of the lips and nostrils and small ulcers on the tongue.

In a patient with Hodgkin's disease treated by Cheraskin (1961), the total leucocyte count decreased to 1,100. Four days after the administration of chlorambucil and nitrogen mustard oral ulcers

appeared and the neutrophil count dropped to 242. On withdrawal of these drugs the ulcers vanished and two weeks later the neutrophil count was 2,415.

According to Robinson (1955), and Orban and Wentz (1960), since the introduction of antibiotics, the mortality in agranulocytosis has fallen from 40-50% to 5%. Whitby and Britton (1957), observe that, if the patient can be tided over the acute phase after removal of the causative agent and before a normal neutrophil count has returned, recovery can be expected in those instances due to drugs.

To relieve discomfort and prevent extension of infection oral lesions should be treated with mild mouthwashes, medicaments and, if necessary, benzocaine lozenges.

CYCLIC NEUTROPENIA
(Periodic agranulocytosis)

This rare condition is characterized by the disappearance of neutrophil granulocytes from the circulating blood at approximately three weekly intervals. The neutropenic phase is associated with fever, malaise and the appearance of ulcerative lesions of the oral mucous membrane. At the end of approximately seven days the neutrophil count returns to within normal limits. However, Prinz and Greenbaum (1939), and Cohen and Morris (1961), state that at no time do the neutrophils represent more than half of the differential leucocyte count.

Attempts to discover a cause for this condition have so far been unsuccessful. Serial bone marrow studies have shown a suppression or maturation arrest of the granulocytic series of cells during the neutropenic phase; the basic cause of this change is still unknown.

Gorlin and Chaudhry (1960), and Cohen and Morris (1961), emphasise that oral ulceration is the most commonly observed clinical manifestation in cyclic neutropenia. The ulcers, which resemble aphthous ulcers, may involve any part of the oral mucous membrane and frequently extend into the pharynx. Wade (1963), finds it difficult to explain the pathogenesis of these ulcers since cultures from the lesions reveal only normal oral commensals.

Reimann and de Berardinis (1949), first focused attention on cyclic neutropenia with a review of sixteen cases cited in the literature. More recent reports have been presented by Page and Good (1957), Gorlin and Chaudhry (1960), and Cohen and Morris (1961).

In a girl aged 7 years seen by Cohen and Morris the ulcers had occurred at 3-4 weekly intervals since she was 16 months of age. The lesions which were usually multiple, rarely bled and persisted for approximately 10 days.

Treatment of cyclic neutropenia is aimed chiefly at preventing infection during the neutropenic phase.

INFECTIOUS MONONUCLEOSIS

(Glandular Fever)

This is an acute, self limiting disease, chiefly affecting children and young adolescents and characterized by a myriad of symptoms the most important of which are fever, generalized lymphadenopathy and the presence of atypical lymphocytes and heterophile antibodies in the circulating bloodstream (Cottrell, 1939; Stevens, 1952; Comroe et al, 1954; Lawrence, 1955; Robinson, 1955; Fraser-Moodie, 1959; Thoma and Goldman, 1960). Stevens (1952), Thoma and Goldman (1960), Stones (1962), and Shafer et al (1963), believe a virus is probably the causative agent, but no micro-organism has yet been isolated. Diagnosis is based on the Paul-Bunnell test for circulating heterophile antibodies. There is no specific treatment.

Oral ulceration is not a consistent finding in infectious mononucleosis: Fraser-Moodie (1959), reports a 3% incidence of oral ulceration in 140 patients examined by him. Stevens (1952), gives a higher estimate of 74% from a study of 109 patients with this condition. Cheraskin and Langley (1956), consider ulceration occurs less frequently than petechiae.

According to Orban and Wentz (1960), the oral ulcerative lesions in infectious mononucleosis present a severe inflammatory condition with necrosis. A fibrinous membrane covers the surface of each ulcer. The base exhibits an acute, inflammatory response and in the deeper tissues there are many mononuclear cells. This latter finding is

characteristic of the disease.

Because of associated lymphocytosis and lymph node involvement, Cahn (1950), points out that oral ulcers in infectious mononucleosis may simulate those seen in leukaemia. Other writers (Robinson, 1955; Orban and Wentz, 1960; Thoma and Goldman, 1960), note that they resemble the ulcers of necrotizing ulcerative gingivitis and herpetic stomatitis. The announcement of Nathanson and Morin (1953), that herpetic stomatitis accompanied by lymphadenopathy is an early manifestation of infectious mononucleosis requires further evidence.

Stevens (1952), draws attention to the fact that infectious mononucleosis may be associated with dental infections and extractions, but is unable to support this statement. Stafne (cited by Stevens, 1952), has frequently encountered this disease in young adults with erupting third molars and a concurrent cervical lymphadenopathy. He points out that these patients have exhibited an ulcerated gingiva over the site of the erupting tooth. The significance of this finding is not explained.