CHAPTER 12 - SMOKING AND APHTHOUS ULCERATION:

Weinmann appears to have initiated cytological investigations of the oral mucosa in 1940 when, using Gram's and Wright's staining techniques, he distinguished six cell types, differing in degree of keratinization. The lowest degree of keratinization was found in the cheek with a progressive increase through tongue, gingivae and palate. The most advanced cell types were anucleated cells.

Subsequent investigators have adopted the staining method of Papanicolau and his classification of vaginal smears. Among them may be mentioned Ziskin and Moulton (1948), Lewis (1955), Peters (1958), Sandler and Stahl (1958), Sandler et al. (1959), Umiker et al. (1960), Calonius (1961), Camilleri and Lange (1966), and Banoczy and Sallay (1969). Depending on the degree of cytoplasmic staining and the shape and size of both nucleus and cytoplasm, three cell types (basal, intermediate and superficial) are distinguished. Blue staining cells are nonkeratinized, while keratinized cells may appear red, orange or yellow, depending upon the degree of keratinization.

Rubinstein and co-workers (1970) devised 17 cell types on the basis of the colour of the cytoplasm (blue, blue-pink, pink, pink-orange and orange) in combination with the size of the nucleus (large, pyknotic, or none) to obtain a more sensitive judgement of the oral mucosal reaction to smoking. They found a marked shift in the incidence of many cell types and suggested that a study of the surface cytology of smokers before they developed any clinical signs of change might provide a valuable means for the early identification of sensitive persons. The percentage of subjects affected by heavy smoking was highest in the posterior part of the palate and smallest in the floor of the mouth.
Many reports have been received to the effect that aphthous ulceration is less common in subjects who smoke. Schaffer (1951) reported that this observation had been made by earlier writers when presenting a case in which the patient's oral lesions were ameliorated by his beginning to smoke. Of the 120 patients analyzed by Sircus et al. (1957) 73% were non-smokers. Bookman (1960) reported four cases of aphthous ulceration which commenced with the sudden cessation of cigarette smoking and which were relieved by the resumption of smoking. Dorsey (1963) supplied two additional examples. However, none of these authors attempted an explanation of the phenomenon.

Kramer (1969) says that patients suffering from recurrent aphthae have a lower level of oral keratinization, and states that this might explain the inverse relationship between smoking (which increases keratinization) and aphthous lesions. Significantly, most authors report aphthae as occurring on the non-keratinized mucosa.

Sallay and Banoczy (1968) reported that 94.5% of their 175 patients with aphthae were non-smokers and 74% had never smoked. They found no macroscopic evidence of hyperkeratosis of the oral mucous membranes among aphthous patients, and no history of recurrent aphthae among patients with leukoplakia. In other words, there appears to be an inverse relationship between the degree of keratinization and the presence of recurrent aphthae. In the following year, Banoczy and Sallay (1969) published cytological studies of patients with recurrent aphthae and patients with leukoplakia. Their conclusions were:
1. the oral mucosa of patients with recurrent aphthae is less keratinized than that of healthy individuals.

2. the oral mucous membrane of patients with leukoplakia is more keratinized than that of healthy individuals.

3. the possibility of a decreased keratinization in patients with recurrent aphthae must be considered.

Chellemi et al. (1970) found that only two of their 36 patients with recurrent aphthae could be considered to be smokers (their criteria being 20 cigarettes or 3 cigars or three pipe bowls of tobacco per day). They regarded the results as very significant and stated that a larger-scale study is presently being conducted.

**Effect of tobacco smoke on the oral tissues:**

There have been many reports, among them the following, to the effect that smoking causes an increase in keratinization: Lewis (1955), Calonius (1961), Banoczy (1962); Pindborg and Restrup (1963), Pindborg et al. (1964), Zimmerman and Zimmerman (1965), Knychalska-Karwan (1965), Ayre (1966), Hahn (1966) and Rubinstein et al. (1966).

The oral mucosa, except for the hard palate, gingivae, and tongue, is covered by a non-keratinizing epithelium (Banoczy and Sallay, 1969; Rubinstein et al., 1970), nevertheless, it has been stated (Kuffer and Rouchon, 1967; McCarthy and Shklar, 1964) that normal buccal mucosa may also show slight keratinization in the superficial layers, and fully keratinized cells have been reported in buccal
smears (Banoczy, 1960). Smoking apparently increases the number of acidophil cells in all parts of the oral mucosa without necessarily causing macroscopic hyperkeratosis (Calonius, 1961; Banoczy, 1962; Knychalska-Karwan, 1965).

Banoczy and Sallay (1969) state that the decrease in intra-cellular and intercellular keratinization in aphthous ulcer patients may arise from a defect in metabolism and may result in an increased desquamation; both bring about a decreased resistance of the mucous membrane, i.e., an increased permeability in regard to infection or antigens. The authors conclude that possibly the decreased keratinization is not the only predisposing factor in the pathogenesis of aphthae, but it is eventually a link in the actual pathologic process.

Lewis (1955) says that the intensity of the keratotic response to the irritating stimulus of smoking seems directly proportional to the susceptibility of the patient. Lewis describes the gross response as a mild, innocent-looking whitish grey patch ranging in severity to a large, angry-looking, verrucous, papillomatous, mushroom-type growth.

Apart from the heat, tobacco contains many irritating substances. Merritt (1946) enumerates some of the ingredients and by-products of tobacco as sulphates, nitrates, chlorides, phosphates and malates of potassium, calcium and ammonium, albumin, resin, tannin, citric acid, nicotianine, nicotine, collidine, pyridine, picoline, ammonia, and carbon monoxide. Many of these are thought to act as vasoconstrictor agents.
Eichel and Shahriek (1970) state that the two most potent substances of the gas phase of cigarette combustion found to date are acrolein and cyanide. They concluded that the volatile gaseous phase of tobacco smoke (not the "tars" or nicotine) contains most of the substances which account for the observed leukocyte toxicity in their in vivo experiments.

Eichel and Shahriek report evidence of leukocyte toxicity from the inhalation of only one cigarette. Most of the cells examined appeared spherical and paralyzed. In some cases the leukocytes were rounded, and their cytoplasmic granules showed active Brownian motion. In other instances, the cells attempted to form pseudopodia, but instead showed cytoplasmic vesicles, a classical sign of cell injury. Sluggish, but atypical movement sometimes occurred. After 40 minutes incubation, inhibition of locomotion and phagocytosis were still evident.

Two other factors which influence the degree of hyperkeratinization of the oral mucosa are aging and hormones. Shklar (1966) states that a tendency to hyperkeratosis occurs with aging, and one may speculate that this fact might account, at least in part, for the decreased incidence of aphthous ulceration in old age. The hormonal effect is discussed in another chapter.

Inasmuch as smoking increases keratinization and suppresses the formation of aphthae, the degree of keratinization can be regarded as a significant factor in the pathogenesis of aphthous disease. This factor appears to be one of increased resistance to some underlying pathological process.
CHAPTER 13 - IMMUNOLOGICAL THEORY:

Because of the importance of immunological considerations in aphthous and other lesions, a brief review is presented.

In 1937 Tiselius showed that the serum globulins could be separated into three major components by their migratory activity in the electrical field. The slowest moving component, the gamma globulins, has since been shown to contain the serum antibodies.188

Two particular blood cells are associated with antibodies, plasma cells and lymphocytes. It is generally accepted that plasma cells appear to be responsible for the synthesis of the antibody components of gamma globulins. 188

The role of lymphocytes has not been precisely determined, although a good deal of experimental evidence supports a cytotoxic role. Some of this evidence is as follows:

1. lymphocyte proliferation occurs in autoimmune disease, delayed hypersensitivity and homograft rejection. 312

2. cytotoxic effects of sensitized lymphocytes have been demonstrated in tissue culture on colon, fibroblasts, and kidney cells. 404, 614, 578.

3. destruction by invading mononuclear cells of antigen-containing parenchymal cells has been observed by electron microscopy. 631

4. passive transfer of certain disease states has been carried out with sensitized lymphocytes. 169, 402

Lehner (1969e) observed lymphocytes and monocytes adjacent to damaged epithelial cells in aphthous lesions, and suggested that they may be responsible for epithelial destruction.
Five possible ways have been suggested for the manner in which lymphocytes may act:

1. **transformed lymphocytes may form gamma globulin antibodies**
2. **lymphocytes may give rise to plasma cells**
3. **they may act in the carriage or synthesis of high affinity antibodies present in very small quantities.**
4. **lymphocytes may be engaged in destroying antigen-containing tissue.**
5. **they may cause a surface injury which then allows cytotoxic antibodies to reach the intracellular antigen.**

Lehner (1969d) states that local lymphocyte proliferation may possibly be initiated by a number of clinically observed precipitating factors of oral ulcerations, e.g. minor trauma, emotional factors and endocrine imbalance.

Transformation into large "blast" cells results from antigenic stimulation of lymphocytes sensitized by previous contact with the particular antigen.  

Serum antibodies consist of a group of globulins having different chemical, physical and antigenic properties. The varieties of immunoglobulins so far distinguished are known as IgG, IgM, IgA, IgD and IgE, and amongst these, subclasses and allotypes have been described. Of the five types, IgG, IgM and IgA have most antibody activity. IgM appears to be the first antibody to be found in serum after antigenic stimulation, being replaced after several weeks by IgG which may persist for long periods; however, recent investigation suggests that this sequence may be more apparent than real.
The sedimentation coefficient of IgG is 7S, that of IgM 19S, and IgA 7S to 17S depending upon the degree of polymerization. The molecular weight of IgM is about 900,000, IgG about 150,000, and IgA about 180,000. The serological activity of IgD and IgE have not been elucidated, although the latter appears to be associated with human reagin.

The relative amounts of antibody produced seem to depend upon a number of factors:

1. protein antigens, viruses, bacteriophages and haptens stimulate a preponderance of IgG after the early IgM phase.
2. lipopolysaccharide somatic antigens of enterobacteria stimulate predominantly IgG after the initial IgM phase.
3. particle size - animal experiments have shown a preponderance of IgM stimulation with polymers.
4. larger doses of antigen stimulate more IgG over IgM.
5. species differences.

IgM antibodies are often the first to be detected and are most apparent in lytic and agglutination reactions. They neutralize viruses but not toxins or enzymes. Their avidity for antigen in comparison with IgG has been the subject of varied results. IgM molecules consist of polymer of five IgG units.

IgG antibodies are very effective precipitins, and usually play the major role in the complement-fixing activity of serum. They are also effective neutralizing antibodies, induce the Arthus reaction and form a stable union with antigen which increases with time.
A rise in IgG is often seen in bacterial infections, a rise of IgM in some viral and protozoal infections. \textsuperscript{307, 355, 497, 609}

IgA is found characteristically in certain secretions, such as saliva, nasal secretion and colostrum. Its presence has been demonstrated mostly by direct or passive agglutination. Its ability to neutralize viruses and its relatively high concentration in secretions make it very significant in the defense mechanism. Tokumaru (1966) produced evidence that human susceptibility to herpes virus infection is due, at least in part, to a deficiency of IgA production. Pike (1967) commented that "herpes infection, with its predilection for muco-cutaneous tissue, is a situation where the neutralizing antibody of secretions might be expected to play an important protective role."

The serum immunoglobulin pattern varies characteristically in certain diseases, showing quantitative differences in IgM, IgG and IgA levels.\textsuperscript{315} According to Tomasi (1965) a diffuse immunoglobulin defect is found in autoimmune diseases. Differential alterations in IgM, IgG and IgA levels are found in such conditions as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, ulcerative colitis, herpetiform ulceration, lichen planus and acute ulcerative gingivitis,\textsuperscript{315, 609} but Lehner (1969a) remarks that it is unlikely that these levels are specific markers characterizing the various diseases. Major and minor aphthous ulcers show a rise in serum IgG and IgA, but only in major lesions does the alteration reach statistical significance.\textsuperscript{315}
Both humoral and cell-bound antibodies to human oral mucosa have been found in recurrent aphthous ulcers 309, 311, 312 and in Behcet's syndrome. 311, 312, 393, 511 The humoral antibodies were shown to belong predominantly to the IgM and to a lesser extent IgG class. Perlman et al. (1965) had previously shown that haemagglutinating antibodies to colonic mucosa in cases of ulcerative colitis also belong predominantly to the IgM class though some are 7S gamma globulins.

**Salivary immunoglobulins:**

The immunoglobulin levels in saliva do not appear to have been studied comprehensively and no normal levels are available for comparison. 315 However, IgM does not appear in saliva and IgA is present in higher concentration than in serum. IgD and IgE levels have not been estimated. 315

A transport mechanism for IgA into saliva was proposed by Tomasi et al. (1965) and elaborated upon by South et al. (1968). South and co-workers proposed that IgA is produced by local plasma cells, for example in the mucosa and salivary glands. Two or three molecules of IgA are combined with transport protein produced by duct epithelial cells to form a molecule of salivary IgA. Tomasi et al. had previously been unable to obtain the transfer of $^{131}$I labelled IgA from serum to saliva, and produced evidence for its synthesis locally. They also showed differences in immunological specificity and degree of polymerization between salivary and serum IgA. They concluded that antibodies in secretions are derived from an immunological system separate from that of circulating antibody.
Adinolfi et al. (1966) supported this hypothesis by the findings of IgA antibodies for E. coli in human colostrum where none existed in serum. Estimation of salivary IgA presents certain technical difficulties such as loss of immunoglobulins during the process of concentration and adhesion to surfaces (Lehner, 1969a).

Parotid saliva contains predominantly IgA, but whole saliva contains IgG as well. The minor salivary glands probably contribute also to the immunoglobulin content of saliva. Salivary IgA has a higher molecular weight, sedimentation rate and resistance to proteolytic enzymes than serum IgA.

The gingival sulcus probably makes no significant contribution. Kraus and Sirisinha (1962) found that the concentration of immunoglobulins does not fall in the edentulous state. Lehner found no evidence that oral lesions permitted the passage of a globulin-rich exudate into the saliva as was once supposed.

South et al. (1968) reported depressed IgA levels in saliva in association with recurrent upper respiratory tract infection. In recurrent aphthae there was no evidence of decreased salivary IgA detected by Lehner (1969a) who concludes that the pathogenesis of this disease is unlikely therefore to be one of recurrent infection.
PART III - AETIOLOGY.

CHAPTER 14  Viral aetiology
CHAPTER 15  Bacterial infection
CHAPTER 16  Hereditary disease
CHAPTER 17  A psychosomatic disorder
CHAPTER 18  Manifestation of gastrointestinal disease
CHAPTER 19  Hypovitaminosis
CHAPTER 20  Endocrine disturbance
CHAPTER 21  Cyclical neutropenia
CHAPTER 22  Toxoplasma
CHAPTER 23  Food and other allergens
CHAPTER 24  Hypersensitivity phenomena
CHAPTER 25  Autoimmune hypothesis
CHAPTER 14 - VIRAL AETIOLOGY:

Recurrent herpetic lesions have been shown to occur in the mouth: Collings and Dukes (1952), Smith (1963), Griffin (1963, 1965), Brightman and Ship (1966), Muller (1968), Southam (1969), Greenberg et al. (1969) and Weathers and Griffin (1970). Herpetiform lesions, as described by Cooke (1960), are also probably viral in origin (Lehner, 1967c).

Many writers, however, have claimed that aphthous ulcers are also viral in origin, and most have incriminated the herpes simplex virus. The following are some who have stated that aphthous ulcers are caused by the herpes simplex virus: Cahn (1936), Steinmaurer (1940), Scott et al. (1941), Woodburne (1941), Burket and Hickman (1942), Cahn and Bartels (1942), Ziskin and Holden (1943), Burket (1946), Rivers (1948), Rooyen and Rhodes (1948), Queries and Minor Notes 426, Queries and Minor Notes 427, Cahn (1950), Dietz (1950), Robinson (1950), Gottlieb (1951), Kilbourne and Horsfall (1951), Kerr (1952a, 1952b), Scales (1953), Jawetz (1955), Colby et al. (1961), and Engelman (1963).

Some specify a viral aetiology, but exclude the herpes simplex virus: Touraine (1941), Everett (1950), Fisher and Leider (1951), Haensch (1953), Sezer (1953), Queries and Minor Notes 433, Baur (1957), Strean et al. (1958), and Claus et al. (1961).

There is abundant evidence that the virus of herpes simplex is not the cause of aphthous ulcers. Much of this evidence is summarized hereunder:
1. Biopsy and cytologic specimens are not suggestive of viral infection: Blank et al. (1950), Stark et al. (1954), Driscoll et al. (1959).

2. Failure to isolate herpes simplex virus from typical lesions: Rosenstein and Ziskin (1942), Buddingh and Ruchman 73, Dodd and Ruchman (1950), Blank et al. (1950), Farmer (1956), Dudgeon (1956), Sircus et al. (1957), Weichselbaum and Derbes (1957), Farmer (1958), Ship et al. (1961c), Ship et al. (1962), Ship (1965), and Graykowski et al. (1966).

3. Absence of antibodies to herpes virus in clinical cases of aphthous ulcers: Dodd and Ruchman (1950), Blank et al. (1950), Stark et al. (1954), Sircus et al. (1957), and Driscoll et al. (1959).

4. Studies reporting a lower incidence of herpes virus antibodies among aphthous patients than in patients without aphthae: Stark et al. (1954), Sircus et al. (1957), and Driscoll et al. (1959).

5. Studies reporting a lower titre of herpes simplex virus antibodies in aphthous patients than in patients without aphthae and patients with herpes labialis: Blank et al. (1950), Stark et al. (1954), and Robin (1966).

6. Failure to demonstrate viral activity by cytopathic effects: Ship et al. (1961c).

7. It is also likely, Savitt (1949) states, that failure of intradermal smallpox vaccinations would be presumptive evidence that the lesions were not caused by the herpes simplex virus, or that other factors are present.
There seems little doubt that recurrent herpetic infections can occur on the oral mucosa and clinically resemble aphthous lesions. Griffin (1963, 1965) identified four cases of intraoral recurrent herpes simplex virus disease, the aetiology being verified by cytologic and fluorescent antibody techniques. This fact alone explains some of the confusion regarding the role of herpes virus in aphthous lesions. Scott and Steigman (1941) had long before isolated herpes virus from the saliva of two patients with aphthous disease who also showed high antibody titres. Kilbourne and Horsfall (1951) isolated herpes virus from some ulcers in a particular patient but not from other ulcers. Collings and Dukes (1952) described a case which reads very much like one of aphthous lesions, except that intranuclear inclusion bodies, characteristic of herpes simplex virus, were recovered from the base of the ulcer. Weathers and Griffin (1970) claim that interpretation of the reports of isolation of herpes simplex virus from "aphthae" by authors such as Dodd and Ruchman (1950) and Kilbourne and Horsfall (1951) convinces them that the lesions were in reality recurrent intra-oral herpetic ulcers and not aphthous ulcers, the respective authors having failed to make the distinction.

Another factor making for confusion, mentioned by Stark et al (1954), is that the recovery of herpes simplex virus from aphthous lesions may simply be fortuitous, as the virus can be recovered from healthy mouths. Dodd and Ruchman (1950) agree that in cases where the herpes virus has been recovered from the mouths of aphthous patients, or the antibody titre has risen following infection, these were probably chance findings not related to the aetiology of the disease. Everett (1950) states that saliva contains
the herpes virus at odd intervals and that transmissibility to the rabbit cornea from aphthous lesions does not prove causation.

Inapparent herpetic infection, according to Stark et al. (1954), may explain the occasional reported recovery of herpes simplex from aphthous lesions. Brightman and Ship (1966) state that since recurrences of aphthous lesions may follow upper respiratory tract infections and gastrointestinal upsets, attempts at virus isolation from aphthous ulcers may occasionally reveal viruses aetiologically related to prior infection with herpes simplex virus. Furthermore, these authors continue, if the patient had had prior herpetic infection he will possess antibodies to this virus.

There is agreement, therefore, that the random isolation of herpes virus from mouths containing aphthous ulcers does not prove an aetiological relationship. One must agree further, with Kilbourne and Horsfall (1951) and Ship et al. (1967), that neither the occurrence of antibody to this virus nor the simultaneous appearance in a patient of aphthae and herpes labialis should be taken as evidence that Herpes simplex is related to aphthous lesions. Rovin (1966) stated that, considering the clinical similarities between herpetic and aphthous lesions, one might question the diagnosis of recurrent aphthae in a patient who had recurrent intraoral ulcers and also demonstrated antibodies to the herpes virus. However, he continues, the presence of antibodies does not preclude a nonviral aetiology of recurring ulcers if, in addition, no culture or cytologic evidence of the virus is procured.
Diagnostic procedures have also been handicapped by technical difficulties with regard to isolation of the herpes virus. Rizzo and Ashe (1964) claim that isolation of the virus may be impossible if herpetic lesions attain full development before a sample is taken. Kilbourne and Horsfall (1951) suggest that optimal conditions are necessary for the successful recovery of the virus. Nevertheless, as Rovin (1966) observed, nearly all attempts to recover the virus from recurrent aphthae are unsuccessful while the virus is regularly recovered from lesions of herpes labialis.

Rizzo and Ashe further state that biopsies taken from fully developed lesions may not reveal the characteristic signs of viral investion (inclusion bodies, multinucleated giant cells, and ballooning degeneration). Evidently the lesion must be an early one.

Another difficulty is that complement fixation techniques may give false negative results, especially at lower titres - Dodd and Ruchman (1950), Stark et al. (1954), Sircus et al. (1957) used only complement-fixation techniques although most studies use the more sensitive neutralization tests. But even with the neutralization test many aphthous patients do not show herpes virus antibodies (Rovin, 1966).

It would seem that because of conditions not being optimal, false negative results might conceivably result from laboratory investigations of herpetic infections. However, a definitive diagnosis can be achieved by the use of fluorescent antibody techniques, which are accepted as reliable methods for herpes simplex virus identification (Biegeleisen et al., 1959; Lebrun, 1956).
A point still at issue is the stability of antibody titres. Some workers believe that antibody titres remain high after initial infection: Burnet and Williams (1939), Burnet (1945), Baldridge (1959), and Driscoll et al. (1959). Others feel they may drop (Sircus et al., 1957), or are variable: Dodd and Ruchman (1950), Kilbourne and Horsfall (1951), Jawetz et al. (1952), Buddingh et al. (1953) and Stark et al. (1954). An increase in antibody titre after recurrent infection is reported by some who believe that there is a drop or variability in titre following initial infection: Dodd and Ruchman (1950), Kilbourne and Horsfall (1951), Jawetz et al. (1952), and Stark et al. (1954).

Relationship between recurrent aphthous lesions and recurrent herpetic lesions:

There is no doubt that the precise aetiological mechanisms are different, although the distinction has been subjected to much confusion. Brightman and Ship (1966) state that the use of the term "herpetic stomatitis" as a synonym for "canker sores" or recurrent aphthous ulcerations has led to the erroneous belief that the aphthae were caused by the herpes virus. Recurrent oral herpetic lesions can be identified only where careful cytologic, serologic and virus isolation procedures are adopted and where there is no possibility that the lesion may be a mild episode of aphthous ulceration in conjunction with subclinical reactivation of latent herpes virus in the tissues. Similarly, Ship et al. (1961c) say that the recurrent nature of aphthous ulceration, its grossly similar appearance to cold sores, its apparent provocation by a variety of factors, its lack of response to a variety of therapeutic agents, and the lack of a more suitable
explanation have contributed to the view that recurrent aphthae are manifestations of herpes infection.

Ship et al. (1960b) reported that there did not appear to be any relationship between aphthous lesions and herpes labialis in the 1133 professional school students in their study. Nevertheless, Ship and other workers stated that such a relationship may exist after all, and despite the different aetiologies.

Graykowski et al. (1966) found that 40% of their 62 patients with aphthous ulcers had a history of recurrent herpetic infection. This is not a surprising result considering the prevalence of herpes in the community. Other authors, however, have suggested that the antibody titre for herpes virus is high in aphthous patients. Thus Claus et al. (1961) state that the antibody titre in the presence of either condition is high. Rapoport (1965) agrees that the antibody titre for herpes virus is raised in aphthous ulceration, even though the herpes virus is not the cause. Specific figures supplied earlier by Stark et al. (1954) for the presence of herpes virus antibodies were 55% for aphthous patients and 85% for controls.

Following a statistical analysis of 343 professional school students and 242 hospitalized patients, Ship et al. (1967) postulated that similar mechanisms may be involved in both herpetic and aphthous lesions. The authors found a 3:2 chance that a person with aphthae would also have herpes (and vice versa), and this chance was only secondarily related to the presence of herpes virus antibodies.
They see more than a superficial similarity between the person who suffers from aphthae and the person who suffers from herpes: "RHL (recurrent herpes labialis) results from prior herpes simplex virus infection, but such lesions occur only in a few persons who have been infected with this virus. It is these persons who also have a predisposition to the development of RAU (recurrent aphthous ulcers), a syndrome that does not result from infection with this virus." Ship and his colleagues feel that recurrences in both diseases may be based on a similar immunological mechanism.

Aphthous ulcers are not caused by the virus of herpes simplex, but may appear clinically similar to herpetic lesions (which may recur intra-orally as well as on the lips) and the herpetiform ulcers described by Cooke. Because of this clinical similarity and because of certain technical difficulties in the isolation of the herpes simplex virus (by which false negative results might eventuate) as well as the presence of the virus as a concomitant invader (leading to false positives) a clear-cut difference between herpetic and non-herpetic conditions has been slow to come about. Even serological methods have not always given precisely accurate results. However, the use of fluorescent antibody techniques are regarded as reliable indications of herpetic infection.

Ship et al. (1967) and other workers have suggested that people prone to aphthous ulceration are more likely to be prone also to herpetic infection and vice versa. This of course does not imply a similar aetiology, but merely points to an underlying factor in all disease processes: the resistance of the host.
CHAPTER 15 - BACTERIAL INFECTION

Not unnaturally, the early literature makes reference to a possible bacterial aetiology. Loblowitz (1911) recovered pyogenic bacteria from aphthous lesions but considered them to be secondary invaders. Goadby (1925) isolated a streptococcus similar to streptococcus faecalis from 6 out of 10 patients. The majority of Jordan's (1933) patients yielded diplococci and streptococci. Jordan considered that these organisms were pathogenic only under conditions favourable to them. Lemke (1941) expressed similar feelings to Jordan, but considered fusiform bacilli and spirochaetes to be the significant organisms. More recently, Tuft and Girsh (1958) mention bacterial infection as a possible cause, since diplococci and streptococci are found in cultures from the lesions.

The lack of consistency of findings, even within most reports, is apparent, as is the failure to incriminate a likely pathogen. Vest (1957), Weichselbaum and Derbes (1957) and Theron (1959) could find only normal oral flora.

Indirect evidence of an infectious aetiology would be pyrexia, regional lymphadenopathy and an increased erythrocyte sedimentation rate. In this matter the results are somewhat contentious. One reason may be the failure to separate major and minor aphthous lesions. Another is that bacterial invasion may occur secondarily.

Sibley (1899) found no temperature elevation in his cases. Jordan (1933) found neither pyrexia nor lymph node involvement, and negative findings were reported also by Kochs (1940), Kumer (1942), and Strean et al. (1958).
Hirsekorh (1935), on the other hand, found instances of a high temperature (often in excess of 40 C.) and, in one case, submaxillary lymphadenopathy. Greither (1955) and Schuermann (1958) also reported instances of lymph node involvement. Lorkick (1935) stated that painful and swollen lymph nodes were often encountered in cases of aphthous lesions, but that this was the result of secondary infection.

Amongst the early reports the most commonly incriminated organism was Bacillus crassus: Whitwell (1934), Sircus et al. (1957), Farmer (1958), Ship et al. (1962), and Shafer et al. (1963).

B. crassus, isolated by Lipschutz (1912) from cases of ulcus vulvae acutum, has been postulated as the cause of oral lesions by Lipschutz (1923), McDonagh (1924), Carol and Ruys (1928), Samek and Fischer (1929), Kumer (1930), and Matras (1932).

Despite the Continental vogue for this organism from 1923 to 1932, there is little cause to regard it as the aetiological agent, although it may be present as a secondary invader. Whitwell (1934) was unable to isolate it from many instances of aphthous lesions, and claimed that the pathogenicity of the organism is not altogether acceptable. He was unable to isolate an abundance of any one particular organism. Farmer (1958) mentions the close relationship of B. crassus to Lactobacillus acidophilus which indicates, he feels, that it is likely to be a secondary invader.
Fleming (1968) considers that the role of specific organisms in the production of ulcers has been over-emphasized, having generally isolated only common mouth organisms and few likely pathogens. Ship et al. (1962) state that bacterial agents have not been found consistently in aphthous lesions and there has been no apparent cross infection within family groups.

Relevant to the last point is the low incidence among consorts. In the study of Sircus et al. (1957) the incidence of the disease among consorts was only 4.1%. No husband or wife was "infected" in Cooke's (1961) study, and amongst Farmer's (1958) patients, 62 were married but only two consorts started having the ulcers after marriage.

Brody and Silverman (1969) state that different species of bacteria have been indicated as the causative agent, only to be disproved by subsequent studies.

The immunological investigations of Lehner (1969a) offer no support for the pathogenesis of the disorder being one of recurrent infection. Lehner found no reduction in salivary IgA in aphthous disease, whereas South et al. (1968) had previously shown a reduction in salivary IgA in cases of recurrent upper respiratory tract infections.

The role of bacteria in the aetiology of recurrent aphthae was given renewed emphasis in later years by two events:
1. the L form hypothesis
2. the suggestion of bacteria being involved in a delayed hypersensitivity mechanism (Kramer, 1965), thereby associating the work on L form organisms carried out by Stanley, Barile, Graykowski, etc., with the immunological investigations of Lehner.

The L form hypothesis

During the mid-1960's a group of American workers postulated that aphthous ulcers were caused by an infectious agent, an L form of a bacterium, probably an alpha haemolytic streptococcus, Str. sanguis.

In 1960 Barile and Sheingorn isolated L forms of bacteria from the dental pulp of a patient with serous pulpitis and suggested that L forms of bacteria may play a role in dental pathology.

Burnett and Scherp (1962) define L forms as essentially bacterial cells without rigid cell walls. According to Barile et al. (1963) L forms are variants which may exist together with the original bacterium or independently, and may revert to the original bacterium or transform to another variant. Stable L forms, which have temporarily lost their ability to transform, resemble the classic PPLO.

PPLO (pleuropneumonia-like organisms), now referred to as mycoplasmas (Jawetz et al., 1968) are organisms similar to those isolated in 1898 by Nocard and Roux from a type of bovine pleuropneumonia. They are small, highly pleomorphic, very fragile micro-organisms cultivable in a cell-free medium (Burnett and Scherp, 1962).
McDermott (1958) suggested that microbial persistence in antibiotic treated animals may come about by alteration of the pathogen to the refractory L form or PPLO. Barile and others (1959) postulated that L formation would explain the failure of penicillin therapy to eradicate gonorrhoeal urethritis and the disappearance of Treponema pallidum from lesions, with its maintenance in the host for extended periods of time (Barile et al., 1962).

In 1963 Barile and co-workers isolated pure cultures of a transitional L form of a bacterium from the lesions of three patients with aphthous ulcers. Blood obtained for culture during exacerbations was found to be positive for the same organism, whereas blood examined during quiescence was sterile. The authors concluded that the findings suggested an aetiological relationship between the L form group of bacteria and the aphthous ulcers, and that at least some cases of aphthous ulceration are infectious.

Barile et al. postulated a mechanism of action to explain recurrences of the disease, similar in principle to that advanced by Burnet in regard to herpes virus infections. They stated that the stable L form could be maintained in the tissues, probably intracellularly, in a latent state without causing damages to the host. Under appropriate conditions, such as trauma and endocrine changes, the dormant organism could transform to a transitional L form or to the original bacterium and thus become pathogenic.

Stanley et al. (1964) searched for these forms of bacteria in biopsy specimens of aphthous lesions and
located them in 14 out of 15 cases, as against 4 out of 10 non-aphthous lesions and 15 of 32 oral mucosal specimens obtained at autopsy. They considered that these findings offered support for the causal relationship between organisms and aphthous ulcers, and suggested that the presence of micro-organisms in histopathologic sections may be some aid in diagnosis.

Graykowski et al. (1964) applied Koch's postulates to the association between the transitional L forms and aphthous ulcers. They isolated the organism from a major aphthous lesion, formed a culture with which they inoculated rabbits intradermally, and produced ulcers clinically and histopathologically identical to those in the original patient. From the rabbit lesions they were able to culture the original type of organism.

This work found immediate acceptance, Bhaskar (1965) for example, stating that aphthous ulcers "are now considered to be caused by a L form of the alpha haemolytic streptococcus." However, it soon became obvious that the theory did not meet all requirements.

Burnett and Gilmore in 1959 had shown that 100% of the oral cavities tested contained PPLO or bacteria capable of transforming to L form organisms, either in the saliva or in tooth scrapings. Stanley and co-workers (1964) had themselves detected transitional L forms in only 93.3% of aphthous lesions, 40% of non-aphthous lesions, and 47% of oral mucosa specimens obtained at autopsy. Kenny (1965) also isolated these micro-organisms, or others closely related to them, from the oropharynx of healthy patients.
Lehner and Sagebiel (1966) found that electron microscopic investigation of recurrent oral ulcerations failed to show recognizable mycoplasma or L form organisms.

Several workers cast doubts about the laboratory methods employed in cultivation. Rovin (1966) stated that in the inoculation studies no other micro-organisms were used as controls. "In other words", he states, "inoculation of several different micro-organisms might produce the same findings." Cooke (1969) stated that the media employed for the isolation of the organisms are capable of transforming streptococci into L forms.

It seems likely that if these organisms have a role to play in the pathogenesis of aphthous ulcers, it will be in an immunological capacity: Lehner (1964, 1965, 1967c), Kramer (1965), Brody and Silverman (1969), and Cooke (1969).

In 1966 Graykowski et al. gave intradermal injections of a streptococcal vaccine to 40 patients, 30 of whom had recurrent aphthae, 4 lichen planus, and 6 with no history of either. Each of the 30 aphthous patients gave a positive delayed-type hypersensitivity skin reaction, with the severity of the reaction tending to parallel the clinical severity of the oral lesions. A severe exacerbation of the disease occurred in 5 patients and 3 patients had an immediate-type reaction prior to the delayed reaction. The only really positive result amongst the other patients occurred in one with a long history of "sore throats". Control injections of saline in each case were without reaction. These results lend support to the role of streptococcal organisms in the aetiology of aphthous ulcers, but more strongly suggest the likely role of a delayed hypersensitivity phenomenon.
Francis and Oppenheim, using lymphocyte transformation as an in vitro model of delayed hypersensitivity, found a reduced responsiveness to the uptake of tritium-labelled thymidine by peripheral lymphocytes from aphthous ulcer patients compared to normal controls following exposure to killed Str. sanguis. This hyporesponsiveness did not occur when other streptococcal strains were used, and paralleled the situation in which lymphocyte cultures from rheumatic heart patients demonstrated hyporesponsiveness following exposure to Lancefield Group A, types 12 and 24 heat-killed streptococci.
CHAPTER 16 - HEREDITARY DISEASE

The influence of heredity is implied in many reported cases in which the disease has involved several members of the same family, but this assumption must be guarded inasmuch as family members are subject to similar environmental influences which may have aetiological significance.

Loblowitz (1910) described the occurrence of aphthous ulceration in a man and seven of his children. The man's sister and two of her daughters had further more been afflicted with the disease since childhood.

Other family histories, less striking perhaps, were reported by Strandberg (1918), with eight cases in the one family (one had scrotal ulcers also), Ullman (1927), Pappworth (1941), Forbes and Robson (1960), and Getz and Bader (1967). Figures relating to family incidence of the disease were published by Sircus et al. (1957), Farmer (1958), Theron (1959), Cooke (1961), Ship et al. (1962), Ship (1965a), and Graykowskii et al. (1966).

Lorkick (1935) was able to find a positive family history in some of his patients, but there was a strong psychogenic influence involved. Of a family numbering 36, aphthae were found in 11. However 19 of the 36 were psychotic and of these 9 had oral ulcers.

Kochs (1940) detected aphthae in 17 members of a family of 49. In no case, however, was the disease transmitted from father to son and of the 17 with aphthae 13 were females. Kochs suggested the possibility of the disease being a sex-linked dominant one. In Queries and Minor Notes a case was reported whose grand mother, mother and two sisters were affected, but no male members of the family.
Theron (1959) also supports the idea of a sex-linked dominant inheritance on the basis of his finding a 52% occurrence of aphthae in a close relative of his patients. A mother-child relationship was seen in two instances of the 24 positive results, but no father-son relationship.

Schmidt (1940,1958) reported the occurrence of aphthous lesions in five generations and regarded the condition as a superficial constitutionally-linked mucosal infection of a neurotrophic nature.

Sircus et al. (1957) found that of their 120 cases, 55 (45.8%) gave a family history of the disorder. In 22 cases (18.3%) one or both parents were affected, in 18 cases (15%) one or more siblings. In only 7 instances were more than one family member concerned. Inasmuch as only 4.1% of consorts were affected, the family incidence does not seem to be due to contact infection. Low incidence rates among consorts were also found by Farmer (1958) and Cooke (1961).

In several instances in Sircus and co-workers' study in which children of aphthous patients were also affected, the disorder appeared to commence at an earlier age than it did in the parent. A similar finding was noted by Cooke (1961).

The conclusion reached by Sircus et al. was that the family incidence of the disease, in relation to the incidence in the community, was too low to suggest that heredity plays more than a minor role in the aetiology. Farmer (1958) stated, likewise, that his family incidence of 39% may be a chance distribution where the incidence in the general population is 20%.
Cooke (1961) found that only 24% of his 90 patients gave a history of either a parent or sibling having the disease and agreed with the conclusion stated by Sircus and others.

Graykowski et al. (1966) found that of their 62 patients, 51 (82%) had an additional member or members of their family with a history of the disease. This figure was broken down into husband (44%), wife (16%), sons (43%), daughters (39%), father (14%), mother (38%), siblings (62%), brothers (46%), and sisters (49%). These figures are certainly much higher than those of Sircus, Farmer and Cooke and it is a pity that they were not commented upon. No attempt was evidently made to check the accuracy of what were presumably questionnaire findings, despite Ship et al. in 1960 stating that such findings proved unreliable when checked. The figure of 82% is much higher than the incidence in the general population and warrants further confirmation.

Perhaps the greatest contributor to the statistical analysis of aphthous ulcer distribution has been Ship, whose contributions suggest a change in viewpoint. In their first 1960 publication Ship and others (Ship et al., 1960a) noted that knowledge of the disease in members of the immediate family was unreliable and proved to be paradoxical when checked. Both the positive and negative groups had little information regarding the presence or absence of the disease in parents or siblings. In 1962 Ship et al. stated that while it is not unusual to find a history of the disease among members of the same family, "the over-all incidence of approximately 50% in the absence of a definite segregation ratio is evidently against genetic factors of etiological significance."
In 1964 Ship undertook a study of 815 families with and without aphthous disease to determine whether susceptibility to recurrent ulceration in the mouth may be inherited. The disparities between observed and expected values for dominant inheritance were highly significant while conflicting results were obtained for recessive inheritance. The observed segregation ratios were higher than expected when one parent is affected and when neither parent is affected, while the values for both parents affected are in agreement with a recessive inheritance hypothesis. Ship concluded that a genetic hypothesis for aphthous ulceration had not been disproven by the study, the pattern of autosomal inheritance deserving more detailed examination.

In 1965 Ship (1965b) stated that although susceptibility to aphthous ulcers, where a family history of the disease exists, had been noted previously, the genetic factors had not been examined prior to his 1964 study. Although he was not able, on the basis of his results, to make a definite statement as to the validity of a genetic hypothesis of dominant or recessive inheritance, he could not rule out a genetic predisposition. He suggested the possibility of multiple gene combinations resulting in the manifestation of this disease.

In their 1967 study, Ship and his colleagues found that the frequency of positive family histories of the disease increased with the severity of the disease. Unfortunately specific data on pedigrees were not available to determine possible genetic factors.
The influence of heredity in the aetiology of aphthous ulcers has not been fully elucidated, partly because of the inherent difficulties involved in the study of genetics and partly because of the environmental influence. Emotional factors may result from environmental ones and, as noted by many investigators such as Sircus et al. (1957), Ship et al. (1961c), and Barile et al. (1963), may be significant in the occurrence of aphthous lesions. Another difficulty mentioned by Francis (1970) is the lack of a simple but precise diagnostic tool with which to measure the disease.

Shafer et al. (1963) stated that although several members of a family often manifest the disease, no evidence of genetic origin has been established. Perhaps at this stage of our understanding we will have to be content with the application of probability theory to the occurrence of this, as well as many other, diseases. The situation in regard to aphthous ulcers was expressed by Brightman and Ship (1966) on the basis of Ship's earlier data:

"... where both parents had the syndrome, the probability of recurrent mouth ulcers in the children was 90%; if only one parent was affected, the probability was 63%, while among families with neither parent affected, the probability was 23%. It was also shown that individuals with more frequent attacks of mouth ulcers were more likely to have clearly defined familial patterns of disease. However, conclusive evidence of a genetic basis for this syndrome has not yet been found."
CHAPTER 17 - A PSYCHOSOMATIC DISORDER:

Jacobi (1894) appears to have been the first to report a relationship between aphthous ulcers and mental disturbance, and called the condition stomatitis neurotica chronica.

Sibley, who gave the first account of aphthous ulcers in the English language in 1899 entitled his paper "Neurotic ulcers of the mouth".

Loblowitz (1910) described similar lesions in a neurotic family and offered an explanation based on the so-called neurotic skin gangrene of Kreibich. Kreibich had postulated that diseases of the central nervous system, both functional and organic, affect the vasodilator centre which then reacts to central or peripheral stimuli by a sudden hyperaemia and transudation. This causes pressure on the blood vessels at the site of the stimulus with resulting anaemia, necrosis and exudation.

Wolff (1952), a sufferer himself from the disease, considered that oral aphthae were analogous to gastric ulcers. Wolff stated that oral lesions are usually found in patients with a labile vegetative nervous system such as constitutionally-linked neurodystrophic mucosal damage. Fleming (1968) also saw a relationship between oral and gastric ulcers, the underlying factor in each being mental stress.

A writer in Queries and Minor Notes 426 offers an explanation of the manner by which an emotional problem can produce an oral lesion:
"It has been reported that the lysozyme content of various secretions rises in some persons during mental stress and that these persons are then susceptible to upper and lower intestinal ulceration. The lysozyme is mucolytic and reduces the protection of the mucosa." Brody and Noble (1969) found that total lysozyme secretion (submaxillary plus parotid) did not change significantly between aphthous and control patients. However, the change is S/P ratio from 1.58 in control subjects to 0.91 in aphthous patients indicates that in this disease the submaxillary and parotid glands come closer to secreting equal amounts of lysozyme. The significance of this finding was not discussed.

Truelove and Morris-Owen (1958) claimed that the mental disturbance often reported may be a result rather than the cause of aphthous ulceration. This opinion had been previously expressed by Hirsekorn (1933) and Lempke (1941). Kingsley (1964) described the case of a man whose repeated and frequent attacks of aphthae drove him to the contemplation of suicide, until the condition was relieved by steroid therapy. A somewhat similar case was reported by Schaffer in 1960.

Bennee (1954) claimed prolonged benefit in some cases following the intravenous injection of 2% procaine which he stated acted by suppression of the sympathetic nervous system.

A different explanation was offered by Sulke and Yardeni (1955) who stated that emotionally disturbed patients or those suffering from chronic illness or nutritional deficiency usually possess hypoactive adrenal
glands. As a result there is a lack of hydrocortisone to control oral inflammation, and aphthous ulcers, cheilosis, lichen planus and geographic tongue are said to occur.

The most comprehensive analysis of this aspect of the disease appears to have been undertaken by Sircus et al. (1957), one of whom was a psychiatrist. These workers obtained a useful and definite statement about precipitating factors from only 90 of their 120 patients. The outstanding feature was a preceding period of mental stress associated with domestic, including financial or sexual, problems in marriage. This was indicated by 21% of the patients. Fifty-five cases were closely investigated and established mental illness was recognizable in eighteen (33%). There was a close association between life experiences, individual personality and recurrent ulceration, especially where the disorder was severe.

Besides Sircus et al. (1957), many others have noted the significance of emotional stress as a precipitating factor. Amongst them may be mentioned the following: "J.A.M.A." 250, Farmer (1958), Fleming (1958), Therón (1959), Sircus (1959), Sutherland (1959), Ship et al. (1960b), Ship et al. (1961b), Ship et al. (1961c), Dalmau et al. (1961), Cooke (1961), Burket (1961), Ship et al. (1962), Shafer et al. (1963), Huebsch (1965), Kramer (1965), Scott (1965), Graykowski et al. (1966), Brightman and Ship (1966), Sametz and Dana (1967), Getz and Bader (1967), Pindborg (1968), and Brody and Silverman (1969).

Sircus (1959) considered that the interest of the physician, sedation where necessary, and the resolution of emotional and social problems are the most effective therapeutic procedures where the chronic anxiety, tension or depression that is present is exogenous in nature.
In an analysis of the medical histories of 1133 students, Ship et al. (1960b) found the strongest relationship reported was between emotional factors and recurrent aphthae, and that the extent of this association increased with the severity of the disease. Both McCarthy and Shklar (1964) and Fleming (1968) spoke of an anxiety factor among students and this may account for the high incidence of aphthous lesions that Ship and his colleagues found among students.

Insufficient research has been carried out in the oral manifestations of emotional disturbances, although Moulton et al. (1952) have written on the emotional factors in periodontal disease, and Mellors and Herms as far back as 1946 and 1947 described the rapid breakdown of oral tissues, primarily the gingivae, during emotional crises in mental institutions. Moulton (1955) states that guilt may be expressed by oral symbols when sexual conflicts exist. She says that the mouth "is highly charged emotionally and that it is likely to be neglected, not because it is unimportant, but because it is too significant."

The importance of emotional factors in oral aphthae prompted Chalmers and Sircus (1964) to a trial of hypnosis, but it was without effect.

McCarthy and Shklar (1964) seem to favour a psychosomatic aetiology for the disease, but most workers stop short of accepting that as an explanation. The general consensus of opinion among the many who have mentioned emotional factors in connection with recurrent aphthae appears to coincide with the view point of Sircus et al. (1957) who spoke of them as "aggravating or precipitating mechanisms, though not the cause of the disease."
Dalmau et al. (1961) regard oral aphthae and orolingual paraesthesia as possible isolated components of a major constellation that spells a serious emotional disturbance. These clinical entities form part of an impressive list which includes gastritis, gastric ulcer, colitis, gall bladder disturbance, diabetes, hypertension, asthma, hay fever, and migraine, all of which the authors claim to have a psychosomatic origin. They further claim that successful drug or other therapy for one disease may serve merely to precipitate another. This displacement of symptomatology is mentioned, the authors advise, not to deter the clinician, but to help him in total patient assessment. They recommend an interest in the patient as a person, the use of sedation if considered helpful and the involvement of the patient, as far as possible, in his total problem.

Francis (1970) states that whereas both physical and mental stress appear to precipitate the formation of lesions, the operational mechanism remains obscure. He noted that patients who were hospitalized for observation usually showed marked improvement even without active therapy "most probably because the patients were given a vacation from their stressful environments."
CHAPTER 18 - MANIFESTATION OF GASTROINTESTINAL DISEASE:

From the time of Sibley (1899) who stated that aphthous lesions were often classed as dyspeptic ulcers, various authors have mentioned gastrointestinal disturbances in connection with oral aphthae. Theron (1959) cites Tiscornia (1927), Pusey (1930), Lombard and Rochette (1935) and Silcox (1956) who considered gastrointestinal disturbances of great importance in the aetiology of oral aphthae; and Kochs (1940) and Wolff (1952) who considered the oral lesions to be analogous in formation to that of gastric ulcers. Chevallier and Moutier (1936) and Moutier and Cornet (1949) detected aphthae on the gastric mucosa following endoscopical examination.

Other associations between gastrointestinal disease and aphthous lesions of the mouth were made by Goadby (1923), "J.A.M.A."250, Queries and minor notes 433, Thoma and Goldman (1960), Brightman and Ship (1966), and Gold (1967).

Specific gastrointestinal diseases associated with oral aphthae have included steatorrhoea (Cooke, 1953; Truelove and Morris-Owen, 1958; Sircus et al. 1957; Burrows, 1966), ulcerative colitis (Jensen, 1944; Brooke, 1953; Todd, 1954; Truelove and Morris-Owen, 1958; Scott, 1965) and ileitis (Bechgaard, 1941). It is interesting that the term sprue is derived from the Dutch word "spruw" which means aphthous disease.618 In 1953 Cooke made the very significant claim that 100% of patients with non-tropical sprue had oral aphthae. This finding, however, does not appear to have been confirmed.
Sircus and associates (1957) investigated 120 cases of recurrent aphthous ulcer patients and found a history of dyspepsia in 31%; 9% had peptic ulcers, but the frequency of such findings was similar to that for the population from which the patients were drawn. Steatorrhoea was found in a single case, distal proctocolitis in another. Graykowski et al. (1966) found that 6% of their 62 patients had ulcerative colitis, 5% duodenal ulcers, and one patient had a peptic ulcer.

The study conducted by Ship et al. (1962) found no clinical pattern of gastric or peptic ulcers in their aphthous patients. One patient had mild intermittent diarrhoea and radiographic evidence of "mucous colitis". No ulcerative colitis or regional enteritis was detected. A later study by Ship et al. (1967) reported that oral aphthae were specifically associated with increased frequencies of other ulcerative gastrointestinal disorders.

Samitz and Dana (1967) claim that aphthous ulcers belong to a group of cutaneous vasculitides, including erythema multiforme, erythema nodosum and pyoderma gangrenosum which may complicate ulcerative colitis, and which tend to subside with control of the intestinal symptoms. However, Warren and Sommers (1949) studied 180 cases of ulcerative colitis but made no mention of oral lesions.

McCarthy and Shklar (1964) regard the association of aphthous ulceration of the mouth with gastro-intestinal disturbances as understandable, since both the oral and gastric mucosae are highly susceptible to psychosomatic influences, but state that either oral or gastric ulceration occurs as a response to emotional disturbances,
rarely both. Nevertheless, several factors seem to link oral and peptic ulcers: their occurrence in the alimentary tract, their similar clinical appearance, their undetermined aetiology and (therefore) their non-specific treatment.

There is an important environmental difference between the oral and gastric mucosae, however. The theory that gastric ulcers are a self-digestion process, expressed in the so-called "gastric equation" of acid + pepsin vs. mucosal resistance, could not be held to apply to the oral cavity although the "mucosal resistance" of aphthous ulcer patients may well hold the explanation of the occurrence of lesions in certain subjects.

Quite apart from the psychosomatic factor of McCarthy and Shklar, which may be the link between oral aphthae and gastro-intestinal disease, certain experimental studies appear relevant. Speransky (1943) and his associates were able to produce characteristic gastric ulcers and oral ulcerations in dogs by using a glass bead placed so as to exert slight pressure on the hypothalamus. This work was corroborated by Schachter and Schachter (1949) and Quintarelli and Chauncey (1959). Characteristic oral aphthous ulceration appeared in many of these animals in addition to gastric and duodenal ulcerations.

Theron (1959) found no history of gastro-intestinal disease among his patients and opined that its presence in other cases was either fortuitous or a manifestation of an aphthosis. Cooke (1961) states that the presence of another disease seems no more than a chance finding.
The combined evidence does not appear strong enough to associate oral aphthae and gastro-intestinal disease in an aetiological relationship, although a statistical relationship is not so easily denied. It is doubtful whether the incidence of gastro-intestinal disease among aphthous patients is significantly increased, although one wonders whether there may not be a higher incidence of oral aphthae among patients with certain gastro-intestinal complaints. A survey along these lines does not appear to have been undertaken.
CHAPTER 19 - HYPOVITAMINOSIS:

A vitamin deficiency can arise in a variety of ways (Theron, 1959):
1. deficient intake
2. disturbed absorption
3. defective storage in the body
4. deficiency as a result of increased requirements
5. deficiency due to abnormal loss from the body
6. deficiency as a result of antagonistic enzymes in the diet
7. deficiency as a result of disturbed tissue utilization.

Gerstenberger (1923) considered that a disturbance of metabolism or nutrition was the prime factor involved in the aetiology of oral ulcers, and that any part that bacteria or similar agents may play is of a secondary nature. He reported a remarkable therapeutic effect in aphthous patients from the administration of the B vitamins. Gerstenberger believed that the vitamin deficiency was not an absolute one, but resulted indirectly, from the intake of a diet which speeded up metabolism. As an example he cited "the common occurrence of herpes labialis in women whose metabolism, as a result of pregnancy, lactation, menstruation and thyroid disease, is so much more frequently operated at a higher rate than is that of men."

Strauss (1947) claimed that a certain vitamin B₁ level is necessary for proper function of the anterior pituitary gland. In the absence of sufficient of this vitamin, various symptoms develop, including disturbances of the female sexual cycle, and aphthous ulcers. (Strauss
considered that these lesions rarely appeared in men). Strauss concluded, after clinical trials of vitamin B complex therapy, that aphthous ulcers were a symptom of vitamin $B_1$ deficiency, the latter being induced by certain stages of the menstrual cycle, probably by ovulation. Interestingly, Biskind et al (1944) postulated a relationship between vitamin B complex and oestrogens. They said that women with nutritional deficiency often give a history of menstrual disorders which can be relieved with vitamin B complex.

Other contributors to the literature have incriminated the various B vitamins: Stepp (1936) vitamin $B_2$; Prinz and Greenbaum (1936) vitamin B; Griebel (1939) vitamin B; Burket and Hickman (1942) vitamin B complex; Burket (1946) vitamin B complex; Leemans (1951) folic acid; and Mann (1954) vitamin $B_{12}$.

Stepp (1936), who considered that the deficiency of a number of vitamins viz., A, $B_2$ and C, predispose to aphthous lesions, stated that when the disease is due to $B_2$ deficiency the oral lesions are accompanied by a colitis. Griebel (1939) felt that vitamin B deficiency may result either from inadequate intake or defective absorption, as in gastro-intestinal disease.

Danziger (1934) and Roller (1939) were more impressed with the aetiological possibilities of vitamin A deficiency, and Stepp (1936), as mentioned above, also considered aphthae to result from vitamin A deficiency. Danziger (1934) said that a deficiency of vitamin A renders the oral mucosa less resistant to otherwise nonpathogenic oral flora.
Vitamin C deficiency was held responsible for aphthous lesions in cases reported by Muller (1938), and Marti (1940, 1941). These lesions subsequently came and went as vitamin C therapy was withdrawn and re-administered.

Rosenstein and Ziskin (1942) claimed to have ruled out vitamin B deficiency by dietary analyses and by the failure of vitamin therapy in treatment. However, Tuft and Girsh (1958) consider avitaminosis as a cause of aphthous lesions because improvement at times follows vitamin B or C therapy. Distelheim and Sulzberger (1949) and Afonsky (1950) reported unsuccessful results following vitamin B therapy. Theron (1959) could not incriminate vitamin deficiency as a cause of aphthae.

Durocher (1966) says that although acceptable documentation is lacking, there is a widespread clinical impression that use of the B and C vitamins are of benefit, especially in those cases associated with the menses and when high therapeutic doses are prescribed. However, he concludes that disappointments may be expected. Bishop et al. (1967) say much the same.

Of 37 patients reported by Ship (1963b) with anaemia and alcoholic cirrhosis and clinical and biochemical evidence of nutritional deficiencies, none had a history of mouth ulcers.

Although the evidence is not strong, it is difficult to properly evaluate vitamin deficiency as a cause of this disease, for several reasons:
1. a possible placebo effect following administration of vitamin preparations.
2. a possibility that the full scope of vitamin activity has not been elucidated.
3. the possibility that the presence of ulcers may preclude the patient from eating certain vitamin-rich foods, so that the ulcers cause a vitamin deficiency rather than result from one
4. the absence of proper controls in the cases reported.
5. the possibility that a nutritionally depleted state may simply predispose the patient to the development of aphthae by lowering of resistance.
6. the natural history of the disease, which is subject to lengthy remissions at times.
7. the lack of accurate measurement of vitamin utilization at the tissue level.
CHAPTER 20 - ENDOCRINE DISTURBANCE

Although several authors have referred to endocrine influences of various sorts, most references are to the relationship between aphthae and the menstrual cycle. Ullmann (1927) referred merely to endocrine influences without being any more specific. Ship et al. (1962) found no evidence of endocrinopathy, but from the experiences of some of their female patients favoured a relationship between aphthous lesions and the female sex hormones.

Kirk (1899) considered that thyrotoxicosis was an important aetiological factor, but this statement does not appear to have received additional support, except that two cases of the sixty-two reported by Graykowski et al. (1966) associated hyperthyroidism with recurrences of aphthae. Theron (1959) found no symptoms or signs of thyroid dysfunction in his aphthous ulcer patients.

Sircus et al. (1957) performed gastric function tests on some of their aphthous ulcer patients but the output of free acid and uropepsinogen were normal. These results, the authors state, also dispose of the possibility of over-activity of the adrenal glands, or of the autonomic nervous system.

Sohr (1961) states that a relationship between oral aphthae and dysfunction or hypofunction of the endocrine system (mainly involving the adrenal glands) has been suggested by Denker-Albrecht (1952), Griebel (1954), Burger (1953) and Fischer (1955) but has not met with general acceptance. Sohr presented two cases in which persistent aphthous lesions of the mouth appeared to herald
the appearance of Addison's disease. Following diagnosis and ACTH therapy the oral lesions disappeared. Theron (1959) had earlier investigated adrenal and pituitary function in an aphthous patient who 20 years earlier had been diagnosed as suffering from Cushing's syndrome, but found no evidence of disturbed pituitary or adrenal activity. By the use of intravenous ACTH in five other patients, no disturbed function of the adrenal glands could be demonstrated.

Liver function tests were also carried out by Theron on ten patients with aphthous ulceration, but the values obtained were normal.

Among the earlier writers, an association between the appearance of aphthous lesions and the menstrual cycle was observed by Port and Euler (1920), Tiscornia (1927), Klein (1934, Hirsekorn (1935), Prinz and Greenbaum (1939), Kochs (1940, Schmidt (1940) and Strauss (1947).

Port and Euler (1920), Tiscornia (1927), Klein (1934) and Schmidt (1940) found the lesions occurred at the beginning of the cycle, so that the patients could predict, in some cases, the onset of the cycle from the appearance of the lesions. Two patients of Kochs (1940) were able to tell exactly when they were pregnant, even before cessation of the menses, from the fact that their normal premenstrual aphthae did not occur. A similar case was reported by Ship et al. (1962).

A different chronological relationship was reported by Strauss (1947). In 43 of his 45 cases the lesions began within 16 days before the commencement of cycle.
(In the two exceptions the lesions began 18 and 23 days before the cycle). The timing suggested to Strauss that ovulation may precipitate the oral lesions. Strauss postulated that aphthous lesions resulted from deficiency of vitamin B<sub>1</sub> which was induced by certain stages of the menstrual cycle, probably by ovulation.

Theron (1959) found that 15 out of 27 female patients with aphthous lesions had completely normal cycles, and regarded any effect of gonadal origin to be therefore of secondary importance. Theron cites Andermatt (1950), Schreus et al. (1953), Scholdgen (1955), Boorsma (1956), and Zeiser (1957) in attesting to the alteration of the oral mucosa under the influence of the female sex hormones:

"These authors found that the mucosal epithelium is characterized by marked 'keratinization' and the presence of many pyknotic nuclei during the follicular phase of the menstrual cycle. In the luteal phase, exfoliation of the epithelial cells dominates. The cells are clumped together in irregular groups while their edges show curling and folding. During the menstrual periods, the cells are pale and stain basophilic with the presence of large nuclei, while leukocytosis may be a prominent feature. From these findings we may infer that a diminished production of oestrogen leads to an increased exfoliation in the premenstrual and menstrual phases. This decreased 'keratinization' then leaves the mucosa subject to injurious influences. In this way, it may be possible to explain the ease with which lesions of chronic recurrent aphthae appear in these phases (premenstrual and menstrual) of the cycle. To this one can add the observation of Muhlemann (1952) that a diminished production of oestrogenic hormone leads to a disturbed peripheral circulation which in turn leaves the gingiva
more susceptible to infection. In this respect it should be remembered that skin and mucosal infections, such as labial herpes and acne vulgaris, are often found in conjunction with the menstrual period."

Theron adds that the mental stress accompanying menstruation may be a factor in the development of aphthous ulceration at this time. Bishop et al. (1967) state that aphthous ulceration occurring in relation to the menstrual cycle may be related to declining levels of blood oestrogen which results in a failure of keratinization of the oral mucosa and a tendency for ulcers to develop.

Carruthers (1967b) reported that neutrophils are more prominent in a cytology smear as the cornification index falls. He believes both the cornification of the mucosa and the presence of neutrophils are controlled by oestrogen and protect against ulcer formation; when both are depressed, the ulcers form. According to Bishop et al. (1967) it is generally agreed that premenstrually there is withdrawal of both oestrogen and progesterone.

Another possible interpretation was offered by Zondek and Bromberg (1947) who suggested that many disorders which become severe during the premenstrual period may be caused by an allergy to endogenous progesterone or to the degradation products of progesterone, estradiol and testosterone.

Dolby (1968b) found that ulceration was highest in the post-ovulation phase of the cycle and parallels the urinary output of pregnanediol. This is thought in turn to reflect the output of endogenous progesterone (Dolby, 1968).
It has been suggested by Main and Ritchie (1967) that changes occurring in the oral mucosa at this stage result from the action of progesterone upon a tissue previously subjected to considerable oestrogen activity.

Some authors state an association of aphthae with the menstrual cycle, without attempting to define the association more precisely in time. Among them may be mentioned Prinzip and Greenbaum (1926), Thoma (1941), Thoma (1944, 1950, 1954), Cahn (1950), Stark et al. (1954), Strean et al. (1958), Driscoll et al. (1959), Thoma and Goldman (1960), Ship et al. (1960b), Engelman (1963), The Lancet 303, Huebsch (1965), Graykowski et al. (1966), Review Article 452, and Gardner (1970).

Stark et al. (1954) found that ulcers appeared during all stages of the menstrual cycle, and were neither influenced by nor specifically associated with menstruation.

Many, however, state, and some of the above may be said to imply, that the ulcers coincide with the process of menstruation or the beginning of the cycle: Collyer and Sprawson (1942), Everett (1950), Queries and Minor Notes 409, Editorial J.A.M.A. 154, Shafer et al. (1963).

McDearth and Shklar (1964) noted the appearance of the lesions several days prior to the onset of the menstrual cycle, and considered that emotional factors and premenstrual tension are probably significant factors in the aetiology. Ship (1965a) spoke of exacerbations during the premenstrual week. Samitz and Dana (1967) claim that many women relate their recurrent ulcers to the onset of premenstrual symptoms, such as tension, irritability, oedema, bloating, cramps, etc.
These authors further state that women with severe ulcers often have their highest ulcer activity 7 days before menstruation and the lowest activity during the two weeks following the menstrual period.

Collings (1952) reported a case in which ulceration began consistently approximately 10 days prior to menstruation and healed approximately 1 day after.

Dolby (1968b) found that the incidence of ulceration was highest in the post-ovulation phase of the cycle, and similar findings were mentioned by Francis (1970). This increase commenced at approximately the presumed time of ovulation and ceased during menstruation. Most lesions appeared to begin in the week preceding menstruation, but ulcers did appear at other times. Sircus et al. (1957) also showed peak activity in the premenstrual week when the lesions were related to the cycle. The appearance of lesions at this time seems reasonable, on the basis of findings by Main and Ritchie (1967) and Banoczy and Sallay (1969), reported in the chapters on oestrogen therapy and smoking effects respectively. Main and Ritchie found that premenstrually, in the stage of low oestrogen production, the oral mucosa has a low degree of cornification, and would presumably be less resistant to insult. Banoczy and Sallay demonstrated that the degree of keratinization in aphthous patients was lower than in normal controls.

Other investigations have failed to show a correspondence with the menstrual cycle. Sircus et al. (1957), Farmer (1958) and Cooke (1961) all found that females are affected twice as commonly as males and that there is more of a tendency for either continuous or irregular ulcer
formation in males, with a more rhythmical periodicity in females. Cooke (1961) found no consistent relationship between the periodicity of the ulcers and the menstrual cycle. Sircus et al. (1958) stated that over 50% of women in his study had lesions every third to eighth week, but with no traceable relationship to the menses. Farmer (1958) reported no findings with regard to the menstrual cycle. Ship et al. (1960a) found that the relationship to the menstrual cycle was more frequently observed in women with severe ulcerations than in women with mild lesions. In a later publication (1961a) they amplify this statement to the effect that their female students with more than one ulcer each month showed a distinct pattern characterized by exacerbations during the premenstrual week and relative remission during the post-menstrual weeks, with the weeks of menstruation and ovulation intermediate and essentially equal. When less than one new lesion was experienced each month, the menstrual and premenstrual weeks were both relatively high in ulcer activity, while there was considerably less activity in the post-menstrual and ovulatory weeks. Ship and co-workers' findings are mainly negative with regard to the influence of the cycle, however, as only 18% of their female students with a history of severe ulceration and 3.8% of those with mild ulceration associated their lesions with the cycle. Ship and associates state that a temperature-regulated rather than a chronological estimation of ovulation may give more precise information, but conclude that "premenstrual tension" and "the complex psychologic relationships" involved with the menstrual cycle, especially in young adult females, may be the explanation of their results. Specific endocrine relationships would not be expected to have primary aetiological significance.
It has been many times mentioned that regular lesions may fail to occur during pregnancy: Misch (1914), Ziserman (1934), Kochs (1940), Stark et al. (1954), Sircus et al. (1957), Farmer (1958), Driscoll et al. (1959), Ship et al. (1962), Graykowski et al. (1966), Carruthers (1967a and b), Christensen (1967), Samitz and Dana (1967), and Bishop et al (1967). Farmer (1958) reported that some of his female patients considered that the ulcers were reduced in severity during pregnancy.

Others have reported no remission during pregnancy: Prinz and Greenbaum (1939), Colyer and Sprawson (1942), Cooke (1961) and Engelman (1963).

There have been cases of ulceration beginning or exacerbating after the menopause: Colyer and Sprawson (1942), Sircus et al. (1957), Farmer (1958), Shafer et al. (1963), Dent. Abstr. 670, Ship (1965a), and Graykowski et al. (1966).

Sircus et al. (1957) reported no findings associated with the male climacteric in any way comparable with the increase in incidence after the menopause.

Cooke (1961, 1969) states that the peak onset of ulceration is between 10 and 14 years, probably as a result of hormonal changes of the menstrual cycle.

There is insufficient evidence to implicate any endocrinological factors except those related to the menstrual cycle, and even here there is a great measure of confusion. There can be no doubt that many women find that their oral lesions are specifically related to a certain period of their menstrual cycle and the success
of oestrogen therapy (q.v.) in these cases tends to confirm this. Many women, however, show no correlation between the appearance of ulcers and the menstrual cycle, and the lesions, despite the opinion of Strauss (1947), are commonly found in men. The psychological factor, as reported by several authors, may be significant.

The evidence in favour of oestrogenic levels affecting the keratinization of the oral mucosa appears convincing, and the appearance of ulcers at certain stages of the cycle may be due to this factor and perhaps, as suggested by Carruthers, to the diminution in neutrophils, but the effect appears to be merely secondary to some deeper predisposition to aphthous ulceration.
CHAPTER 21 - CYCLICAL NEUTROPENIA

Several recent reports have associated cyclical neutropenia with recurring oral ulceration: Becker et al. (1959), Telsey et al. (1962), Wade and Stafford (1963), Smith (1964), Scott (1969), Baikie et al. (1967), and Gates (1969).

Baikie and co-workers described a study of 20 patients with cyclical neutropenia, 9 of whom had recurring oral ulceration; of these, 4 had oral ulceration as the only symptomatic manifestation of the underlying blood condition. The authors state that the oral ulceration tends to occur at the time of most severe neutropenia and then heals spontaneously. In 8 of the 9 cases with oral ulcers, the neutropenia was familial and in the ninth it was associated with lymphosarcoma.

Cyclical neutropenia is characterized by episodes of neutropenia every 14 to 30 days, commonly at intervals of 20-21 days (Morley, 1966). Most cases are inherited (Morley, 1966) but some are associated with other diseases such as lymphosarcoma (Natelson, 1953; Morley et al., 1966; Baikie et al., 1967) and agammaglobulinaemia (Good and Varco, 1955). The condition leaves the patient relatively defenseless against bacterial infections (Gates, 1969).

Morley (1966) demonstrated the existence of a neutrophil cycle in healthy individuals, both male and female, and conjectured that the cycle seen in males may exist in similar fashion in females and be superimposed upon the more obvious neutrophil cycle associated with the menstrual cycle. The separation of these two postulated neutrophil cycles in females was not attempted, however, because
of the number of observations and length of time it would involve. In 8 of the 11 males studied a neutrophil cycle with a period of 14 to 23 days was observed.

Carruthers (1967b) states that Papanicolaou stained oral smears reveal white cell peaks at times of poor maturation of oral cells. Carruthers believes that the neutrophils are a defense mechanism of the oral mucosa at times of poor cell maturation, becoming more plentiful in the smear as the cornification index falls. The diminution in the number of neutrophils accounts for the aphthous ulceration associated with neutropenia, and occurs in women mainly premenstrually. (At this time, the other defense mechanism of the oral mucosa, the cornification index, is at its lowest level). Pregnant women, and those on oestrogen therapy, demonstrate more neutrophils in oral smears and less reduction in the cornification index (Carruthers, 1967b).

Cyclical neutropenia is best diagnosed by serial study of total and differential white cell counts carried out twice weekly over three or four weeks (Baikie et al., 1967). Baikie et al. suggest that the condition often remains undiagnosed. It has been proposed that repeated bouts of severe periodontal diseases, especially in a young patient, may be one of the first signs of the condition (Gates, 1969).

Scott (1965) states that whereas only a minute proportion of patients with aphthous ulcers will be found to have neutropenia, in the two rare conditions cyclical and chronic hypoplastic neutropenia, recurrent aphthous ulceration is common. He states that several cases of profound recurrent neutropenia have been recorded with
a regular 28 day cycle in which an outbreak of aphthous ulcers always coincided with the virtually complete disappearance of neutrophils from the peripheral blood. In the more common chronic hypoplastic variety, Scott continues, the peripheral neutrophil count, though always below normal, exhibits variations of an irregular nature, and when the count is lowest aphthous ulcers often appear.

Cyclical neutropenia cannot be regarded as the cause of aphthous lesions except in a very small number of cases, and even then it is probably not the sole cause. However, when episodes of oral lesions, including aphthae, occur with a regular periodicity of 3-4 weeks, a cyclical neutropenia should be suspected.
CHAPTER 22 - TOXOPLASMA

Toxoplasma, a common human parasite, has been stated to cause aphthous ulcers; more specifically, toxoplasma gondii has been mentioned.

Jawetz et al. (1968) describe toxoplasma gondii as a protozoan of world-wide distribution infecting a wide range of animals and birds, but not necessarily causing disease in them; it does, however, cause either neonatal or postnatal toxoplasmosis in man.

References to toxoplasma are not common in the literature on aphthous ulcers, and those which have been detected are listed below:

Sircus et al. (1957): "Toxoplasma complement fixation antibodies were not found more frequently in the patient's sera tested than in the controls. The only serum which gave a significant result was from a control subject."

Ship et al. (1962): "Toxoplasma gondii, probably a protozoan, was reported as being present by Sodalian et al. (1954)."

Shafer et al. (1963): "Although a specific protozoan at one time was suggested to be the cause of the disease, this theory has been conclusively disproved."

Bishop et al. (1967): "Toxoplasma Gondii has been mentioned as a possible cause."

There is no worthwhile evidence for the serious consideration of this organism in the aetiology of aphthous lesions.
CHAPTER 23 - FOOD AND OTHER ALLERGENS:

Allergens are usually proteins, but may be polypeptides, lipids or lipid-soluble extracts of plants or foods, or microbial constituents (Jawetz et al., 1968). Other compounds, of low molecular weight, which are not antigenic may become allergens by combination with body protein, as was first shown by Landsteiner in 1946. In the latter way an explanation is offered for the allergic properties of certain foods and drugs.

Many reports have contained the clinical observation that the occurrence of aphthous lesions followed the intake of certain foods or drugs. As far back as 1866 Bohn related the onset of recurrences in certain patients to the ingestion of fatty pastries; he regarded aphthous ulceration as analogous to urticaria.

The following is a list of authors who have reported the occurrence of aphthae in connection with the use of certain foods or drugs:

- Bohn (1866) fatty pastries
- Beecher (1928) cocoa, wheat, cabbage
- Basch (1928), Ochsenius (1931) tomatoes
- Pusey (1930), Weisshaar (1939)
- Port (1932, 1933, 1934) ethereal oils
- Haas (1936)
- Weinberger (1933)
- Haag (1935) histamine
- Rattner (1936) base plate material
- Cahn (1936) walnuts
- Alvarez (1937) chocolate, eggs, milk, wheat, prunes, apples, bananas, cantaloupe, grapes, drugs, dentures
- Ramirez (1938) drugs
Heinemann and Anderson (1945)
Zondek and Bromberg (1947)
Pereira-D'Oliveira (1948)
Kranz (1949)
Correspondent N.Y.J. of Dent. 329
Savitt (1949)
Everett (1950)
Sugarman (1950 J.A.M.A. 328
Moutier and Cornet (1951)
Bumiller (1952) N.Y.J. of Dent. 330
Archangeli (1954)
Benzuly (1956)
Tuft and Ettelson (1956)
Moskowitz (1958)
Tuft and Girsh (1958)
Sutherland (1959)
Queries and Minor Notes 435
Rosenblum (1961)

eggs
hormones
cheese
iodoform root canal paste
wheat, milk, eggs, fish, nuts, chocolate, certain fruits and vegetables, bacteria, drugs.
walnuts, hard candies, erythrosin, toothpastes, mouthwashes
walnuts, chocolates, salted foods
mint chewing gum
walnuts, spices, fruits
strawberries, melons, peaches, chocolate, bread, game
parenteral penicillin
walnuts, spices, fruits, drugs, bacteria
metal and acrylic
walnuts, oatmeal, chocolate
weak organic acids, especially citric and acetic
acids in the diet, especially ascorbic and acetic.
citric and acetic acids
milk or milk products, citrus fruits, shellfish
nuts, shellfish, pork and chocolate
chocolate, potato chips, salted nuts (stale stearates)
Ryan (1963) chocolate, oranges
Cancellieri (1964) staphylococcus toxoid
The Lancet 303 nuts, chocolate

Others have claimed or accepted an allergic aetiology in some cases, without necessarily specifying the offending agent(s). Among them are:


The list is impressive, but the experimental backing is not. To be fair, it must be pointed out that most authors do not mean to infer that allergy to ingested substances is the sole cause of aphthous ulcers, but merely that it is a precipitating factor. This attitude is specifically stated by some, such as Jawetz (1955) and Farmer (1958), and implied by many. Cahn (1950), for example, thought that allergy was a factor which serves to reactivate the herpes simplex virus which he considered the primary causative agent. Other authors, however, such as Thoma

Certain studies have rejected allergy as being the cause of this disease: Rosenstein and Ziskin (1942), Stark et al. (1954), Barbash et al. (1958), Theron (1959), Ship (1960), Ship et al. (1962), Dent. Dig. 669, and Ship (1963b). To these may be added the failure of antihistamine therapy (q.v.) Francis (1970) states that there does not appear to be any significant relationship to seasonal or drug allergies.

The occurrence of aphthae following the use of particular foods or drugs has occurred too frequently to be denied, and the elimination of offending agents is a commonsensical part of therapy. However, the histories of some patients have not stood up well to experimental procedures such as the use of elimination diets (Stark et al., 1954; Ship et al., 1962), skin tests (Stark et al., 1954) and antihistamines.

The role of an immediate hypersensitivity reaction in the aetiology of aphthous lesions has been overshadowed by the experimental evidence in favour of a delayed response. Histological findings (q.v.) favour the latter, and the failure of antihistamine therapy (q.v.) is probably significant also. Lehner showed that the titres of humoral antibodies did not correlate with ulcer remission and exacerbation, and therefore their exclusive role in the pathogenesis of recurrent lesions is doubtful (Lehner, 1967c, 1968). This is in contrast to the behaviour of cell-bound antibody as assessed by lymphocyte transformation, which is absent or diminished in a remission and increased in an exacerbation.
CHAPTER 24 - HYPERSENSITIVITY PHENOMENA:

Hypersensitivity is here used synonymously with allergy and may be defined as an altered reactivity of tissues towards a specific substance, i.e., reactivity which is different from earlier experiences of the same individual or from experiences of other individuals of the same species. Strictly speaking, the altered reactivity may be increased (hyperergy), diminished (hypoergy), or absent (anergy), although hyperreactivity is usually implied. Hypersensitivity can be looked upon as an exaggerated state of immunity.

Hypersensitivity is broadly classified into immediate and delayed types which differ not only in the timing of the response, but also in the histological details of the resulting lesion and the nature of the antibodies concerned. Thus in the immediate type the outstanding feature histologically is dilatation of capillaries and arterioles, with prominent erythema and oedema but little cellular infiltration. The main histological feature of the delayed type, however, is cellular infiltration involving predominantly mononuclear cells and tissue induration. The immediate type is associated with humoral antibodies, the delayed type with cell-bound antibodies. Immediate reactions are caused by humoral antibody bound to parenchymal cells, while the delayed reaction is thought to be mediated by cells of the lymphocyte series at the site of the reaction.

It has been shown that foreign proteins repeatedly introduced into the blood stream by any portal may effectively sensitize the mucous membrane, and that an antigen repeatedly absorbed through the mucous membrane can sensitize distant regions or other mucous membranes.
In 1969 Adams et al. produced a delayed hypersensitivity reaction in guinea-pig oral mucosa by repeated application of a chemical 2:4 dinitrochloro-benzene (DNCB) acting as a hapten. The reaction was produced also in non-sensitized animals after transfer of lymphoid cells from a sensitized donor. Histological examination of the lesions showed mononuclear cells in focal concentrations in the sub-epithelial region perivascularly, characteristic of delayed hypersensitivity.

Histamine is one of the substances released in the immediate response. Spouge and Diamond (1963) state that the clinical lesions involving the mucous membranes are usually comparatively transient and reversible, and appear rapidly following exposure to the allergen. The characteristic symptoms are localized erythema, oedema and smooth-muscle spasm.

The delayed reaction is characterized by the death of individual tissue cells. This may result, in the case of epithelium, in vesiculation or primary or secondary ulceration, and is not so easily recognized as being a direct result of hypersensitivity (Spouge and Diamond, 1963).

Many authors, listed in the previous chapter, have attributed the occurrence of oral aphthae to the eating of certain foodstuffs, and imply an immediate hypersensitivity reaction. However little experimental work apart from clinical trials appears to have been carried out despite the fact that Kraft et al. (1963) have used a type of immediate hypersensitivity reaction as a model for the way in which phlogogenic antigen-antibody complexes are localized and exert their cytotoxic effects in ulcerative colitis. (The association of ulcerative colitis and oral aphthae has been
remarked upon.\textsuperscript{618}) The type of reaction referred to was described by Auer in 1911 and is related to serum sickness. In it circulating antigen and antibody are attracted to mildly irritated tissues where they bring about a cytotoxic reaction.

It is the delayed reaction which has received so much experimental support. Oshima et al. (1963) found a significant titre of circulating antibodies capable of agglutinating tanned red cells sensitized with an extract of oral mucosa in 17 of 40 patients with aphthous lesions. This autoantibody titre increased and decreased in accordance with clinical exacerbation and remission of the disease.

Lehner, in 1964, claimed that recurrent aphthous ulceration fulfills several of Burnet's criteria\textsuperscript{342} for an immunological disorder. He pointed to the disease affecting females more often than males, the beneficial effects of corticosteroids, the greater incidence among patients with ulcerative colitis (a known immunological disorder), and the cellular characteristics of the early lesions. Lehner adopted the same technique as Oshima and co-workers, i.e. the sensitized tanned-red-cell technique introduced by Boyden in 1951, using foetal oral mucosa as the sensitizing agent. Serum specimens from 60 patients suffering from various systemic and oral (both ulcerating and non-ulcerating) diseases were serially diluted and tested against the sensitized sheep erythrocytes. The results showed that serum from subjects with aphthous ulcers caused an agglutination reaction in higher titre and greater proportion than any of the other sera. Lehner interpreted the results as implying either an autoimmune
reaction or an antigenic cross-reactivity between oral mucosa and an infective agent. Further studies by Lehner will be discussed in a later chapter.

Additional evidence for a delayed rather than an immediate type of reaction was provided by Dolby (1969) who assessed the survival of oral epithelial cells after culture with sera, lymphocytes or both sera and lymphocytes from patients with recurrent aphthous ulceration and from control subjects. The addition of lymphocytes (but not serum alone) from patients suffering from aphthous disease significantly reduced the survival level of the oral epithelial cells as compared to the controls. The significance of this finding lies, of course, in the fact that the antibodies of the immediate reaction are humoral and those of the delayed response are cell-bound. Francis (1970) commented that, although this target cell phenomenon does not seem to be serum or complement dependent, it may in fact be due to cell-bound antibody on the lymphocytes, the level of which Lehner (1969b) showed to fluctuate with clinical severity of the disease.

In a later experiment, Dolby (1970) showed that hydrocortisone inhibited the cytotoxicity of lymphocytes. The addition of hydrocortisone resulted in a significant improvement in the survival of the epithelial cells where they were accompanied by lymphocytes from aphthous patients but not when accompanied by lymphocytes from controls. This finding represents in vitro support for the often observed clinical benefit of hydrocortisone and appears to be the answer to the query of Sutherland (1959) and others as to why an anti-inflammatory agent should shorten the healing time of aphthous ulcers.
In the elucidation of a possible hypersensitivity basis for aphthous ulcers, the cellular characteristics of the early lesions deserve consideration. The predominately mononuclear character of the perivascular infiltrate shown in studies by Theron (1959), Graykowski et al. (1966), Lehner and Sagebiel (1966) and Lehner (1969e) suggests a delayed type reaction, and this is further discussed in the chapter on histopathology. However, the presence of eosinophils (Theron, 1959; Graykowski et al., 1966; Lehner and Sagebiel, 1966; Lehner, 1969e) and of mast cells (Theron, 1959; Lehner and Sagebiel, 1966; Brody and Silverman, 1969; Lehner, 1969e) have been noted.

Eosinophils do not appear to be present in significant numbers and only Theron, whose sections were almost devoid of them, seems to have given them much consideration. Although the function and behaviour of these cells are not precisely known, tissue and blood eosinophilia are often encountered in allergic states. The presence of these cells is given diagnostic significance in atopic conditions such as asthma, hay fever and vasomotor rhinitis. Their presence in excess of 4% has been stated to have confirmatory value in cases of suspected allergy. Notwithstanding their virtual absence from his sections, Theron does not rule out the possibility of an allergic aetiology, stating that in contact dermatitis, for instance, lymphocytes predominate whereas eosinophils are only occasionally seen.

It is the presence of mast cells which appears the more significant, even though Cahn and Bartels (1942) reported their presence in large numbers in normal mucosa.
These cells have been associated with the release of heparin and histamine. Riley (1953) was able to show a correlation between histamine content and mast cell numbers in a variety of normal and pathological tissues. There may be an association between mast cells and basophils inasmuch as Graham et al. (1952) showed that much of the blood histamine resides in the basophils. It has also been suggested that mast cells may be an essential requirement for the development of tissue eosinophilia. This is based on the work of Prakken and Woerdeman (1952) who reported that in all cases of tissue eosinophilia observed by them a large number of mast cells was also found. On the other hand, large numbers of mast cells could be present without tissue eosinophilia.

Theron concluded that he was unable to draw any conclusions from the presence of the considerable numbers of mast cells he observed. Lehner and Sagebiel (1966) stated that mast cells were present in their sections in about three times the number found in normal mucosa, but made no attempt to explain their presence. In a later publication, Lehner (1969e) contrasted the raised level of mast cells in aphthous ulcers with the decrease observed in non-specific ulcers. He states that although immunological stimuli such as anti-ratglobulin serum may release histamine in mast cells in rats, the role of histamine and mast cells in delayed hypersensitivity has not been clarified. Dolby (1968) states that histamine levels are not maintained in the delayed response, and other pharmacologically active agents such as lymph-node permeability factor may be responsible for the slow development and persistence of this type of response. Interestingly, Lehner (1969e) stated that increased mast cell counts have been recorded in rheumatic fever, rheumatoid arthritis, lupus erythematosus and
ulcerative colitis.

The perivascular cuffing by lymphocytes and monocytes observed in early aphthous lesions (Frech, 1945; Theron, 1969; Graykowski et al. (1966); Lehner and Sagebiel, 1966; Lehner, 1969e) resembles the early histological change in the delayed hypersensitivity response to intradermal antigen (Roitt and Doniach, 1967) and is in contrast with the neutrophil response which occurs in the Arthus reaction (Lehner, 1969e) which is an immediate type reaction depending on the precipitation of antigen-antibody complexes within the vessel wall. In aphthous lesions the neutrophil infiltration occurs subsequent to ulceration (Lehner, 1969e).

Francis and Oppenheim, using lymphocyte transformation as an in vitro model of delayed hypersensitivity, found that the uptake of tritium-labelled thymidine by peripheral lymphocytes in aphthous ulcer patients following exposure to killed Str. sanguis, was significantly lower than by lymphocytes from normal controls. This suggests a delayed hypersensitivity response to Str. sanguis as the hyporesponsiveness did not occur when other streptococcal strains were employed, and forms a link with the delayed hypersensitivity skin reactions to streptococcal vaccine reported by Graykowski et al. (1966). A similar hyporesponsiveness was found with in vitro lymphocyte cultures from rheumatic heart patients when exposed to Lancefield Group A types 12 and 24 heat-killed streptococci.

This chapter presents additional circumstantial evidence for the consideration of aphthous ulceration as a delayed hypersensitivity reaction.
It augments some of the material presented in the chapter on histopathology (q.v.) and introduces some of the investigation of Lehner which are summarized in the next chapter.
CHAPTER 25 - AUTOIMMUNE HYPOTHESIS

Most of the work in the elaboration of an immunological explanation of the pathogenesis of aphthous lesions has been carried out by Lehner, who in 1964 reported that serum from aphthous patients caused a specific agglutination of cells which had been coated with an extract of oral mucosa in higher titre and greater proportion than did serum of control subjects and patients suffering from other ulcerating and non-ulcerating oral lesions. Moreover no appreciable difference could be found between the other ulcerating and non-ulcerating conditions. Lehner concluded that more than an immunological reaction to non-specific mucosal damage was involved, and suggested either an autoimmune reaction or a situation whereby an antibody cross-reacted with an infective agent and oral mucosa.

The latter possibility is linked to the L form theory (q.v.) postulated by the Americans Barile, Stanley, Riggs, Graykowski and others. Graykowski et al. (1966) found that each of 30 aphthous patients, but not others, showed a delayed hypersensitivity reaction following an intradermal injection of a streptococcal vaccine. Kramer had suggested in 1965 that the investigations of the Americans and those of Lehner were drawing closer together.

Lehner's work can be seen as a steady unfolding of elegant supporting experimentation backing his autoimmune hypothesis. Contributions by others, such as Dolby and Adams, have also been forthcoming.
A summary of Lehner's findings subsequent to 1964 can be presented thus:

1965: 1. The detection of autoimmune haemagglutinating antibodies in aphthous patients.
       2. The detection of complement-fixing antibodies in aphthous patients.
       3. Gamma globulin binding in the prickle cell layer of the epithelium in early aphthous lesions.
       4. The production of antibodies in rabbits injected with human foetal oral mucosa.

1967a: The demonstration of haemagglutinating, complement-fixing and precipitating antibodies to foetal oral mucosa in patients with Behcet's syndrome.

1967b: The stimulation by oral mucosa of lymphocyte transformation in patients with recurrent aphthous ulceration.

1967c: A significant incidence of haemagglutinating, complement-fixing and precipitating antibodies against foetal oral mucosa in patients with aphthous ulcers and Behcet's syndrome.

1968: The incidence and titre of haemagglutinating antibodies are unrelated to the age or sex of the patient, or to the severity or duration of the aphthous lesions.
1969a: Increased serum IgG and IgA levels in patients with recurrent aphthous ulcers; but the increase was significant only in patients with major aphthae. Salivary IgA showed little variation, and serum IgM was normal. (Francis, 1970, comments that elevated IgG and IgA levels are commonly associated with autoimmune phenomena).

1969b: Antigenic cross-reactivity between human oral mucosa and mucosa of the pharynx, larynx, oesophagus, conjunctiva, vagina and colon, and also skin. No species specificity was shown. Humoral antibodies to oral mucosa belonged predominantly to the IgM fraction and, to a lesser extent, the IgG. The lymphocyte transformation test varied with the clinical behaviour of the aphthous lesions; at the same time the haemagglutination titre remained constant.

1969d: 1. Humoral antibodies to oral mucosa showed cross-reactivity with other epithelia, lacked species specificity, and belonged to the IgG and IgM fractions.

2. Immunofluorescent binding of IgG and IgM was demonstrated in prickle cell cytoplasm of autologous epithelium.
3. Light and electron microscopy and the lymphocyte transformation test support a delayed hypersensitivity reaction.

4. The autoimmune hypothesis was strengthened by a study of lymphocyte kinetics. As reported earlier, the activity of lymphocytes, as shown by their transformation into blast cells, paralleled the clinical stages of aphthous lesions.

1969e:

1. Histological and electron microscopical investigations of recurrent aphthae support a delayed hypersensitivity reaction.

2. A significantly raised mast cell count was found in oral aphthae and Behcet's syndrome. This is in keeping with similar findings in autoimmune diseases.

3. Immunofluorescent binding of IgG and IgM was found in early aphthous lesions and Behcet's syndrome. Complement binding was detected in some cases.

Lehner's results represent the most sophisticated and best supported body of evidence on the aetiology and pathogenesis of aphthous ulcers and Behcet's syndrome. Nevertheless several points remain unsettled:

1. The positive demonstration, notwithstanding the paper by Waksman in 1961, of the cytotoxic effects of antibodies.
2. In view of the cross-reactivity of autologous antibodies, why other tissues are not more frequently involved.

3. Why positive results for haemagglutination and lymphocyte transformation tests are not obtained in all cases of aphthous ulceration.

4. The precise method by which the prickle cell cytoplasmic antigens make contact with the reticuloendothelial system and why "self-tolerance" is lost.

Lehner (1967c) presents the following account of his autoimmune hypothesis of aphthous ulcers which, he states, is equally applicable to Behcet's syndrome: "According to this, the cytoplasm of prickle cells acts as an antigen which may be phagocytosed by macrophages and passed on to plasma cells and lymphocytes. Alternatively, a common antigenic determinant shared by oral mucosa and an infective agent may equally account for this stage. Plasma cells and lymphocytes are stimulated to proliferate and the former produce humoral antibodies and the latter cell-bound antibodies. These may act jointly or independently upon the cytoplasm of prickle cells giving rise to the pathological lesion. There is certainly evidence for stage 1 of the hypothesis, from the immunofluorescent studies showing gamma globulin binding by the cytoplasm of prickle cells. Stage 2H (humoral) is supported by the presence of haemagglutinating, complement fixing and precipitating antibodies. Evidence for stage 2C (cellular) is the histopathological and electron-microscopical demonstration of lympho-monocytic infiltration of the epithelium. Moreover, lymphocytes in tissue culture from patients with aphthous ulceration
were specifically stimulated to undergo blast cell transformation by the foetal oral mucosa antigen."

Evidence of an auto-immunological basis for various diseases has been reported. Thus Hashem et al. (1963) give a similar hypothesis for infantile eczema as Lehner has advanced for aphthous ulcers: "The fact that a skin component will stimulate lymphocytes from the eczematous patient to undergo mitosis and cell transformation, and the evidence cited that similar stimulation results from an antigen-antibody reaction, indicates that the lymphocytes of the eczematous subject have become sensitized in some manner to an antigenic component of the skin cell. Apparently only a fraction of the lymphocyte population is so sensitized or conditioned."

Gustafson (1968) postulated a hypersensitivity mechanism to account for a necrotizing lesion (acute ulcerative necrotizing gingivitis) resulting from a mild, relatively innocent inflammatory process. It was considered whether this might be mediated by naturally occurring humoral antibodies against bacterial antigens. Lehner (1969d) states that the part the combined humoral and cell-bound antibodies may play in the pathogenesis of the aphthous lesion is not at present known, but suggests the possibility of a synergistic effect.
PART IV - TREATMENT

CHAPTER 26  Cauterizing agents, caustics and astringents.

CHAPTER 27  Placebo effect.

CHAPTER 28  Antibiotic therapy.

CHAPTER 29  Steroid therapy.

CHAPTER 30  Oestrogen therapy.

CHAPTER 31  Antihistamines.

CHAPTER 32  Vitamin therapy.

CHAPTER 33  Treatment with gamma globulin.

CHAPTER 34  Vaccine therapy.

CHAPTER 35  Lactobacillus acidophilus preparations.

CHAPTER 36  Miscellaneous modes of treatment.

CHAPTER 37  Supportive therapy.
CHAPTER 26 - CAUTERIZING AGENTS, CAUSTICS AND ASTRINGENTS:

Various preparations of a cauterizing, caustic or astringent nature have been employed for many years to relieve the pain of aphthous ulcers. The following is a list of authors who have advocated or commented upon the use of the preparations or techniques mentioned:

- Whitwell (1934) - silver nitrate stick
- Grace (1936) - cautery
- Strauss (1947) - silver nitrate crystal
- Everett (1950) - 10% silver nitrate, 5% chromic acid, phenol or other caustics and astringents
- Farmer (1958) - silver nitrate applied early
- King-Turner (1958) - hydrochloric acid
- Sutherland (1959) - caustics such as silver nitrate
- Regan 449 - nitric acid stick
- White 642 - 10% silver nitrate, powdered alum, chromic acid
- Schaffer (1960) - 8% zinc chloride
- Thoma and Goldman (1960) - 5% chromic acid, camphorated phenol, alum
- Ship et al. (1961b) - silver nitrate
- Cooke (1961) - alum stick
- Schmidt (1962) - electrocautery
- Stones (1962) - silver nitrate
- Ryan (1963) - nitric, chromic, trichloracetic and carabolic acids, silver nitrate, alum
- McCarthy and Shklar (1964) - phenol, silver nitrate, electrocautery
- Sagar and Faulkner (1965) - silver nitrate, phenol
- Ship (1965a) - silver nitrate
- Graykowski et al. (1966) - chemical cauterery
Brightman and Ship (1966) phenol, silver nitrate
Durocher (1966) chromic acid, phenol, silver nitrate, zinc chloride, alum, calamine
Kramer (1967) phenol, silver nitrate
Lehner (1967c) phenol, silver nitrate
Kay (1969) phenol, silver nitrate, alum stick

Not all comments, however, are favourable, although the treatment does reduce the pain of the lesions and has been employed for centuries (Ship et al., 1961b). The objection is that further tissue destruction occurs and has been raised by many, including Truelove and Morris-Owen (1958), Schaffer (1960), McCarthy and Schklar (1964), Sagar and Faulkner (1965), Durocher (1966), Kramer (1964), and Kay (1969), with the implication that healing time is increased and the possibility, according to McCarthy and Shklar (1964), of scarring in cases of excessive drug use. Ryan (1963) makes the bald statement that the use of these agents is not recommended, and Lehner (1967c) says that they are of doubtful value.

On the other hand, Stones (1962) and Ship (1965a) report a reduction in healing time following treatment with silver nitrate, although Stones specifies one application only. Cooke (1961) advises the application of an alum stick once only, and Farmer (1958) states that silver nitrate, if applied early, causes the lesions to heal more rapidly on the first few occasions. Graykowski et al. (1966) reported an analgesic effect in eight out of seventeen patients, with no effect on the healing time.
It is not necessarily correct, as implied by many authors, that traumatic therapy such as caustic agents will impose further tissue destruction upon that already present and prolong the healing time, at least if the agent be applied early. It is well known that an aphthous lesion takes much longer to heal than a traumatic one (q.v.) probably because of the delayed hypersensitivity mechanism involved. It seems quite conceivable that the application of trauma could convert the delayed hypersensitivity reaction into an acute inflammatory response and actually shorten the healing time. Much may depend upon the amount of tissue necrosis induced, and this fact may explain the insistence of Stones and Cooke of one application only.

Two possible methods of achieving the obtundent effect have been mentioned. The coagulation of the adjacent nerve endings has been advanced by Everett (1950), Ryan (1963), McCarthy and Shklar (1964) and others. Cooke (1961) employs a single application of an alum stick in order to aid the formation of a protective slough over the ulcer.

Especially in the absence of any known cure, it is difficult to condemn outright a mode of treatment which must have helped very many people, even at the possible risk of prolonging the duration of their lesions. A small isolated lesion might still occasionally be treated by this method, but generally speaking more refined methods of palliation have superseded it. One is surprised however at the lack of mention of tannic acid and glycerin.
CHAPTER 27 - PLACEBO EFFECT:

A placebo (Latin: I will please) is defined by Leslie (1945) as "a medication or preparation which has no inherent pertinent pharmacological activity but which is effective only by virtue of the factor of suggestion attendant upon its administration. The substance may be ingested, inserted, inhaled or applied."

Beecher (1955) summarized 15 studies involving over 1000 patients and showed that placebos gave satisfactory relief in $35.2 \pm 2.2\%$ of cases involving a variety of conditions including severe post-operative pain, angina pectoris, headache, cough, seasickness, mood changes and the common cold. The small standard error of the mean indicates the constancy of the effect and in such a wide variety of conditions suggests the operation of some fundamental physiological or psychological mechanism.

According to Glass (1962) the placebo effect is a complex result of many factors, the most significant of which are the state of the organism at the time of medication, the severity of the distress, the degree of psychologic set or predisposition for expectation of relief, the previously established patterns of drug reaction, and the circumstances surrounding drug administration.

Glass relates an example of the powerful effect of suggestion wherein one group of patients with bleeding ulcers was told by doctors that the preparation they were being given would undoubtedly give relief, while a second group was told by nurses that their medication was purely experimental.
Both groups were given the same placebo. Satisfactory responses were given by 70% of the first group but only 25% of the second. According to Marcus (1964) the effectiveness of the placebo lies in the action, ritual, faith and enthusiasm on the part of both doctor and patient.

It is apparent that any evaluation of therapeutic measures for aphthous ulceration must be undertaken against a background of a possible placebo effect, especially when most medications are frankly palliative only.

Thus Farmer (1958), whose results were assessed by the patient's reaction to treatment, comments that the manner in which the treatment is given is probably as important as the drug itself. Sircus et al. (1957) had previously found the results of placebo treatment almost as effective as any medication and referred to "the astonishing effect sometimes seen as the result of suggestion alone."

It is not suggested that therapeutic agents used to treat aphthous ulcers are devoid of pharmacological action (although this has been stated of some), but merely that the success claimed on behalf of any preparation be judged in relation to the known natural history of the disease where lengthy remissions have been associated with improvement in the domestic or work situation (Cooke, 1961) and the placebo effect.

Because of the significance of the placebo effect in the evaluation of drugs and the benefit of placebo therapy in treatment (Marcus, 1964), several quotations from prominent contributors to the field of aphthous ulcer-
ation will be given.

Sircus (1959): "It is notable that 6 of the 13 patients showed a remarkable response to the initial consultation, and before any therapy had been instituted; three subsequently remained totally free from lesions during the nine-months follow-up. The other three relapsed after a month or two, and then proved resistant to all therapy, including hydrocortisone. Furthermore, dummy lozenges produced a reduction of over 50% in the frequency and duration of ulcers in 6 of the 13 subjects. Therapy for this remittent disorder must be set against this backcloth before judgement is made on its efficacy. Nevertheless, local application of a steroid, prednisolone or hydrocortisone, is capable in approximately a quarter of the subjects of bringing about a sustained remission from the disease where all other measures, including suggestion, appear to fail."

McCarthy and Shklar (1964): "If the cause of aphthous stomatitis is psychosomatic, and all evidence at present points in this direction, one can understand why a variety of drugs may have some beneficial effect. The reaction to the therapeutic agent would depend upon the patient's as well as the clinician's belief in the efficacy of the agent."

Brightman and Ship (1966): "... successful management of these patients also seems to depend on the amount of emotional support that a patient can obtain during attacks. Failure to repeat an earlier successful treatment may also reflect changes in emotional relationships which the patient has developed with the dentist, physician or other individuals."
Kramer (1967): "It is true that many treatments have been found beneficial in some cases, treatments ranging from repeated smallpox vaccination to injections of distilled water into the left buttock by the light of the full moon; the placebo effect is a potent one, but there is little evidence to suggest any specific curative action."

A placebo effect undoubtedly lies behind many of the claims made on behalf of a great variety of treatments. As Kerlinger (1964), Suchman (1967) and others have pointed out, double-blind studies are necessary so that neither party knows whether an active product or a placebo is being employed. Without this safeguard, an experiment is prone to biased findings.
CHAPTER 28 - ANTIBIOTIC THERAPY

Distelheim and Sulzberger are credited with the accidental discovery in 1949 that rinsing the mouth with solutions of the broad-range antibiotics aureomycin or terramycin is exceedingly effective in the palliative treatment of oral lesions. Several writers credit the use to the recommendation of Gottlieb in 1951.

According to Collins (1968), Orban had suggested more than a decade before Collins wrote that a mixture of aureomycin powder and denture powder in an insufflator would keep the patient with aphthous ulcers comfortable. Sircus et al. (1957) found an aureomycin suspension helpful in ameliorating the lesions in 10 of 11 patients who had been treated with other drugs without success. No change was found in the number or the frequency of the lesions but the duration of the ulcers was reduced, usually from ten days to five, and each application produced an analgesic effect lasting from 30 minutes to two hours.

In a later publication, Sircus (1959), on the basis of his results in 13 cases of major aphthous ulceration concluded that antibiotics are of no value in treatment. Sircus employed lozenges containing 10 mg. of framycetin sulphate, a dummy preparation, and a combination of the antibiotic with 1 mg. of prednisolone.

Other writers have expressed opposition, disappointment or equivocation, and among these may be mentioned the following: - Queries and Minor Notes 431; Stark et al. (1954): "Antibiotics, both locally and parenterally, did little aside from controlling local secondary infection when present."
Truelove and Morris-Owen (1958): "unnecessary and potentially dangerous" - these authors refer to risk of sensitization, fungal growth, and lack of evidence that aphthous ulceration is an infective condition; Ryan (1963): "The use of antibiotics locally in the mouth is today deprecated because of the tendency for growth of fungal organisms, and also because aureomycin has no effect upon any virus that might be present"; McCarthy and Shklar (1964) and Ship (1965a).

Nevertheless, most reports are favourable, at least as far as palliation is concerned. None claim freedom from further attacks which sometimes occur even during active treatment. Favourable reports have been given by: Distelheim and Sulzberger (1949), Everett (1950), Stewart and Roth (1950), Zelman and O'Neil (1950), Rosenberg and Levy (1950), Sigel (1950), Astaff (1956), Sircus et al. (1957), Arnold et al. (1959), Thoma and Goldman (1960), Bhaskar (1965), Sagar and Faulkner (1965), Graykowski et al. (1966), Brightman and Ship (1966), Gold (1967), Guggenheimer et al. (1968), and Francis (1970).

Graykowski et al. (1966) considered aureomycin mouthwashes the most effective topical agent used. This appears to be the opinion also of Sircus et al. (1957), Sagar and Faulkner (1965) and Bishop et al. (1967). However, Graykowski and co-workers state that some of their patients became refractory to treatment with this drug.

**Mode of usage:** This has been given succintly by Lehner (1967c) as follows: "Patients are instructed to open a 250 mg. capsule of tetracycline, allow the powder to dissolve in a tablespoon of water and keep the solution
in the mouth for 2 minutes. This procedure is repeated 4 times daily for 3 to 4 days."

Whether the solution is subsequently swallowed is not stated by Lehner or by Kramer (1967) who quotes him. Graykowski et al. (1966) advised that the solution should be swallowed, while Sagar and Faulkner (1965) and Guggenheimer et al. (1968) were against the solution being swallowed. Swallowing does not appear necessary and, if the treatment were to be required frequently, undesirable.

**Other antibiotics:** Aureomycin appears to have been most frequently employed, but other antibiotics have been mentioned in the literature. Some of these references are listed below:

**Terramycin:** Kutscher et al. (1963a) reported that terramycin troche therapy brought about clinical improvement, but without prevention of new attacks. This was also the experience reported by Pedler (1953) and by Collings and Stout (1954), the latter authors, however, employing a mouthwash instead of lozenges.

**Chloramphenicol and terramycin:** "Kutscher et al. (1953b) obtained palliation and a lessening of duration of the lesions, but no cure.

**Streptomycin:** Gurney (1968) states that streptomycin has been used in the empirical treatment of aphthae, but gives no details.

**Vancomycin:** Found by Collins (1968) to give symptomatic relief ("probably due to reduction in secondary infection and protection offered by the vehicle") but no cure.
Nystatin: Recommended in Queries and Minor Notes to combat secondary infection with Candida albicans.

Systemic aureomycin: Zegarelli et al. (1952) reported a decrease in severity and discomfort without affecting a cure. These authors claim other antibiotics to be disappointing in this regard.

Erythromycin: Mentioned by Sutherland (1959) as a 2% cream, but not recommended (nor was aureomycin cream) because of the possibilities of sensitization and bacterial resistance.

Neomycin: Used as a cream (0.35 - 1%) by Sutherland (1959) who reports symptomatic relief if used every two hours. An alternative preparation mentioned was one containing bacitracin and neomycin (Neotracin).

Framycetin sulphate: Considered to be of no value by Sircus (1959).

Much of the confusion encountered in this aspect of the literature seems to result from a lack of experimental protocol in a situation where the effect of suggestion is known to be high (Rovin, 1966) and a failure by most authors to separate true aphthous from herpetiform lesions, and even major from minor aphthae.

Guggenheimer et al. (1968) deplored the lack of a careful double-blind investigation of the effects of tetracycline therapy, and carried out research of their own. They found that topical tetracycline reduced the duration of lesions by about 50% whereas a placebo
preparation had no effect. Significantly, no improvement was shown in cases of severe ulceration.

Kramer (1967) stated that the results of tetracycline therapy are usually disappointing in both major and minor varieties of aphthous ulceration, but in herpetiform lesions a very satisfactory response is obtained. The response to tetracycline had previously been mentioned by Cooke (1960) virtually as a diagnostic aid in the case of herpetiform lesions. Lehner (1967c) described the effect of local tetracycline on herpetiform lesions as "dramatic", and suggested three possible modes of action:

(a) that the tetracycline is acting against a large virus,
(b) that it is counteracting mycoplasma, or
(c) that it is effective because it clears secondary infection.

The striking nature of the response, Lehner concludes, argues against the last possibility.

In conclusion, it appears that while herpetiform lesions respond rapidly to tetracycline, major and minor aphthae may give somewhat disappointing results. Nevertheless, many reports are encouraging and this form of therapy appears to have clinical value. However, no permanent cure has been claimed even by the most enthusiastic advocates, and the risks of allergic reaction and thrush infection have been reported (Guggenheimer et al., 1968).
CHAPTER 29 - STEROID THERAPY:

With the introduction by Hench, Kendall and associates in 1949 of the anti-inflammatory adrenal cortical extracts, cortisone and hydrocortisone, the treatment of various diseases, notably arthritic conditions and the dermatoses, was given a new dimension. Hydrocortisone possesses the advantage of being suitable for topical use, but both of these natural products have since given rise to more potent synthetic derivatives.

Sinkford and Harris (1964) summarize the anti-inflammatory effects of the corticosteroids thus: "Microscopically, the anti-inflammatory action of the glucocorticoids has been shown to occur through an increase in vascular tone accompanied by decreased capillary permeability and suppression of the vascular response to inflammation. It has been suggested that the cortisone effect on vascular tone is actually dependent on local catecholamine (epinephrine) potentiation. Further suppression of the inflammatory response by the corticosteroids may be related directly to an inhibition of biogenesis of the physiologically mobilizable histamine and to inhibition of binding of newly released histamine."

Corticosteroids are also immunosuppressive (Lehner, 1967c; Cooke, 1969) and an in vitro demonstration of their effect upon lymphocyte cytotoxicity was provided by Dolby in 1970. Dolby found that the survival of oral epithelial cells in association with lymphocytes from patients with recurrent aphthous ulceration was significantly enhanced by the addition of hydrocortisone.
The first use of corticosteroids on aphthous lesions appears to have been by Kenet (1951) who reported an unsuccessful attempt to treat a case of Behcet's syndrome exhibiting severe laryngeal ulcerations. Strean advocated the use of cortisone in dental practice in 1952, and in the following year Strean and Horton (1953) reported that hydrocortisone acetate ointment showed promise in the treatment of aphthous ulcers. Bergman (1954) claimed a prompt response in 15 of 17 patients following the topical application of both 1% and 2.5% hydrocortisone acetate ointment. However, Rivin and Barton (1955) and Fisher (1955) reported disappointing results. Two other reports, by Hillman (1956) and Morton (1957), were encouraging. The use of cortisone or ACTH was advised by Orban and Wentz (1955) and an article in the N.Y. Journal of Dentistry in the same year.

An advance in topical hydrocortisone therapy came about through an alteration in its method of application. Truelove, in 1957 and 1958, reported symptomatic relief in cases of ulcerative colitis by the use of a rectal drip of hydrocortisone. However, when he employed a water-soluble preparation of hydrocortisone (instead of using the active ingredient in a 5% solution of ethyl alcohol) he obtained histological improvement in biopsy specimens as well.

In 1958 Truelove and Morris-Owen used tablets containing 2.5 mg of hydrocortisone in the form of its hemisuccinate sodium salt in the treatment of both major and minor aphthous ulcerations.
The tablets (Glaxo Laboratories) had a lactose base and were designed to dissolve slowly, the hydrocortisone compound being freely soluble in saliva which was thus used as a transporting medium. The previously employed ointment had been unsuitable for use in the mouth. Of the 52 patients used in this study nearly all obtained rapid benefit.

Bull (1958) and Donaldson (1958) confirmed these early findings of Truelove and Morris-Owen, whereas King-Turner (1958) preferred to treat the ulcers with dilute hydrochloric acid "in the usual way after meals" instead of using the "highly complicated" treatment suggested by Truelove and Morris-Owen. Sircus et al., (1957) and Farmer (1958) obtained symptomatic relief without achieving an actual cure. Sircus (1959) stated that steroid hormones "have a useful but limited application", Sircus considering that the emotional aspect of treatment accounted for much of the benefit reported, as 6 of his 13 patients showed a "remarkable response" to the initial consultation alone.

Cooke and Armitage in 1960 undertook a double-blind clinical assessment of topical hydrocortisone hemisuccinate as used by Truelove and Morris-Owen and reported a reduction over the placebo of about 50% in the number of "ulcer days" and of new ulcers per patient, per eight-weeks period. This study revealed that the difference in results between hydrocortisone and the placebo was significantly less if the hydrocortisone were given before the placebo than if it were given after. This fact was interpreted by Truelove and Morris-Owen (1960) as being due to the treatment having "broken a vicious circle in
the progress of the disease." This study was undertaken with the use of 2.5 mg. pellets of hydrocortisone hemisuccinate sodium (Corlan) allowed to dissolve near the lesion. Ryan (1963) claimed this form of therapy disappointing.

Further developments in topical steroid therapy have resulted from the introduction of synthetic derivatives with increased potency and in the development of a new vehicle, Orabase (Squibb).

Orabase consists of gelatin, pectin and carboxymethylcellulose in a mineral oil polyethylene base which forms a protective film lasting for 15 to 20 minutes. The advantages of this vehicle are enumerated by Zegarelli et al. (1959) thus:

(a) it increases the potential effectiveness of the drug by means of maintaining higher concentrations at the lesion,
(b) it decreases the total amount of the drug which need be applied,
(c) it increases the duration over which the material will remain in situ,
(d) it decreases the amount of material which, following displacement from the area, would be swallowed and would hence be available for systemic activity,
(e) it provides a mechanically protective layer over the lesion.
McCarthy and Shklar (1964) however, have suggested that the vehicle may in fact keep the lesion separated from the active ingredient by preventing release of the drug. They suggest that the corticosteroid be first applied to the lesion and the adhesive base be applied subsequently.

Stoy (1966) claimed that the topical application of Orabase without the addition of corticosteroids was effective in treatment. He concluded that mechanical protection is probably the factor inducing healing.

Biobase, which resembles Orabase in that it adheres to the oral mucosa, is utilized in a product marketed under the name Bioral. Bioral gel, containing 2% carbenoxolone in Biobase, affords palliation in cases of aphthous ulcers. According to Kay (1967) Biobase is being compared with Bioral gel to determine whether the carbenoxolone contributes to the ameliorative effect. MacPhee et al. (1968) found carbenoxolone, as well as other agents, ineffective.

It is difficult to assess the value of a preparation like Orabase. It may help the patient by a physical protection of the lesion and/or it might exert a placebo effect. It may be significant that Stoy's results were assessed purely on a subjective basis. Browne et al. (1968) obtained results contradictory to those of Stoy. They reported a clear statistical preference for triamcinolone acetonide over Orabase alone, and that triamcinolone was of greater benefit when applied in Orabase than when applied in an aqueous base. Orabase alone was considered to be of no value.
These authors suggest the use of triamcinolone to treat severe episodes of aphthous ulceration and not for long-term management.

The specific effect of a placebo was illustrated by McFall (1968) who treated 50 patients in a double-blind study with fluandrenolone ointment and a placebo preparation consisting of the ointment alone. Both the drug and the placebo (there was no significant difference at the .05 level of confidence) appeared to offer relief from pain and decreased the duration of the ulcer. No side effects were observed.

Various steroid preparations have been advocated in the treatment of this condition:

Weichselbaum and Derbes (1957): cortisone followed by prednisone
Claus et al. (1957): fluorohydrocortisone
Sutherland (1959): hydrocortisone acetate
Zegarelli et al. (1959): triamcinolone acetonide
Zegarelli et al. (1960): triamcinolone
Ship et al. (1961b): fluorometholone
Mierau (1963): prednisolone
Kingsley (1964): betamethasone
McCarthy and Shklar (1964): triamcinolone, dexamethasone
Huebsch (1965): triamcinolone
Durocher (1966): triamcinolone
Ryan (1966): oxyphenbutasone and prednisolone
Graykowski et al. (1966): cortisone acetate
Holst (1966): hydrocortisone, betamethasone
Reading (1966): triamcinolone
Lehner (1967c): triamcinolone
Kramer (1967): hydrocortisone hemisuccinate or betamethasone
MacPhee et al. (1968): betamethasone
McFall (1968): fluandrenolone
Brown et al. (1968): triamcinolone
Cooke (1969): triamcinolone
Francis (1970): triamcinolone, prednisone

Kay (1969) gives the comparable potencies of many of these corticosteroids (based on clinical effect) as follows: cortisone 25 mg, hydrocortisone 20 mg, prednisolone and prednisone 5 mg, triamcinolone and methylprednisolone 4 mg, paramethasone 2.5 mg, betamethasone and dexamethasone 0.75 mg. He mentions two other preparations specifically used as topical medication: fluometholone and flucinolone acetonide. Both exert a local anti-inflammatory action which is approximately 40 times greater than that of hydrocortisone, but fluorine-containing steroids have such an intensifying effect on diabetes as to exclude them from use even on the skin of a diabetic. Kay states that the three corticosteroids in current favour as topical agents in the mouth are hydrocortisone, triamcinolone, and betamethasone. Browne et al. (1968) consider triamcinolone, a more powerful anti-inflammatory agent than hydrocortisone, no more effective in the treatment of aphthous ulcers. Cawson (1968) reported the same opinion regarding betamethasone.

Although corticosteroid treatment of aphthous lesions is mostly by topical application, systemic administration has been used in severe cases: Sircus et al. (1957), Weichselbaum and Derbes (1957), Sircus (1959),
McCarthy and Shklar (1964), Kramer (1965), Holst (1966). McCarthy and Shklar suggest approximately 24 mg. triamcinolone (or 30 mg. prednisolone) in three divided doses for the first three days followed by a careful reduction by 4 mg. daily (5 mg. for prednisolone) so as not to allow a flare-up of the inflammatory process. Sublesional injection of corticosteroids (e.g. 0.1 to 0.3 ml. of triamcinolone) offers the distinct advantage, in suitable cases, of concentrating the drug at the desired site, and avoiding significant systemic effects (McCarthy and Shklar, 1964).

Kutscher et al. (1966) reported that systemic triamcinolone in doses equivalent to those administered in topical oral usage gave equally good results in their small series of cases.

**Effect on progress of the disease:**

Natural remissions of the disease are common, and this fact must be considered in assessing the long term value of corticosteroid medication. Sulke and Yardeni (1955) state that aphthae and other oral lesions can result from hypoactive adrenal glands, there being insufficient hydrocortisone to control infection. If there were any substance in this claim, then cortisone preparations as replacement therapy should have a controlling effect on the disease. There is division of opinion as to whether or not it does. This may be illustrated by the following examples:

Zegarelli et al. (1959): failed to effect progress of the disease.

Erich (1959): Lesions recur when treatment discontinued
Sircus (1959): remission sustained in only 25% of cases
Truelove and Morris-Owen (1958): reasonably good results on a maintenance dose of 2-4 linguets (2.5 mg. ea.) daily
Cooke and Armitage (1960): reduces the number of new lesions
Ship et al. (1961b): may perhaps reduce the incidence of new lesions
MacPhee et al. (1968): no effect on incidence

MacPhee et al. (1968) found no evidence of alteration of incidence or duration of ulceration following the use of triamcinolone acetonide, Orabase, hydroxyquinoline, carbenoxolone sodium (Biobase), or betamethasone disodium phosphate (Beta-Corlan) over a four-weeks period. These results are at variance with the encouraging report by Cooke and Armitage (1960) who used a less potent agent in hydrocortisone hemisuccinate over a period of eight weeks. MacPhee and his colleagues consider that it may take some four weeks for the beneficial effects of the drug to be revealed, but this has not been the impression of other workers.

Most studies make no strong claims to this form of therapy preventing new attacks of the disease, although some claim a reduction in incidence after completion of therapy. It would be interesting to see the results of a well-controlled double-blind study involving a small maintenance dose over a long period of time.

Complications of steroid medication:

Possible complications may be local or systemic. As to local complications, Cooke (1961) and Kramer (1967) advise against the use of corticosteroids in herpetiform
lesions because of the danger of exacerbation. Durocher (1966) states that steroids have definitely been associated with exacerbations in corneal herpes and other viral diseases. However, Smith (1963) found no complications in the palliative treatment of 43 cases of herpes simplex of the oral mucous membranes, but states that the drug is contraindicated in cases involving varicella, ocular lesions, poliomyelitis, and other diseases. Kay (1969) referred to the management of herpetiform lesions with corticosteroids merely as "disappointing".

Systemic complications involve a consideration of possible effects on the hypothalamo-pituitary-adrenal system and effects on concomitant diseases.

Lehner and Lyne (1969) state that the effect of topical steroids used in the mouth on the pituitary-adrenal function have not been investigated comprehensively, but suppression was not considered likely because of the low therapeutic doses employed. McCarthy and Shklar (1964) state that with the use of topical corticosteroid preparations in the mouth some systemic absorption could occur but never enough to be of any concern.

Lehner and Lyne studied the effects of three topical oral corticosteroids on adrenal function, measuring plasma hydrocortisone levels before and after administration of a synthetic corticotropin. They found that therapeutic doses of topical oral hydrocortisone hemisuccinate and betamethasone 17-valerate may be used in adults without effect on adrenal function; however, they advised against the use of betamethasone disodium phosphate because it may cause adrenal suppression. MacPhee et al. (1968) found
that suppression of the hypothalamo-pituitary-adrenal axis can occur from the sublingual absorption of 0.4 mg. of betamethasone daily.

Kutscher et al. (1961) found that serum and urine sodium and potassium levels were within normal limits in patients treated for one week with routine dosages of orally applied triamcinolone. Smith (1963) stated that although eosinophil counts and 17-ketosteroid determinations indicate that there is little alteration in adrenal cortical activity, these tests are of limited value.

The possibility of an exogenous source of corticosteroid suppressing the feedback mechanism regulating the secretion of endogenous corticosteroids does not seem to be very real with the normal recommended doses, but if it did occur it would have the effect of rendering the patient less well equipped to tolerate stress. According to Lehner (1967c) the suppressing dose of hydrocortisone is at least 50 to 100 mg. daily; Kay (1969) states that whereas the suppressing dose varies with the individual, 50 mg. would represent a reasonable figure. Fortunately, this dosage is significantly in excess of therapeutic levels. Moreover, Lehner (1967c) states that prolonged corticosteroid administrated in amounts below that of physiological replacement (25 to 50 mg. daily) does not have a cumulative or adverse effect on the pituitary-adrenal system.

The patient's response to stress is of concern to the dentist, and additional corticosteroids have been advised in cases where the patient already receiving steroid medication is required to submit to a stressful dental procedure. The adreno-cortical response to oral
surgery has been measured by Banks (1970), by estimation of plasma levels of 11-hydroxy-corticosteroids before surgery and at various intervals after surgery. The operative adrenocortical response was often negligible, but there was a high plasma cortisol level four to seven hours post-operatively which returned to normal within 24 hours post-operatively. The author states that his results contraindicate the prolonged post-operative administration of high doses of steroid, especially in the possibility of adversely affecting wound healing. The adrenocortical response was much less than for an equivalent length abdominal operation.

Other side-effects:

Sinkford and Harris (1964) list as some of the complications of prolonged steroid therapy, adrenal cortical atrophy, stomach ulcers, hormone-induced psychosis, abnormal electrolyte metabolism, thromboembolic complications and leukocyte suppression. But these, they continue, are not of particular significance to dental practice; in the latter situation the major adverse effects are likely to be (1) inhibition of fibroblastic proliferation, which favours dissemination of micro-organisms and their products, and (2) inhibition of the cellular response (both vascular and local tissue response) to an irritant. The latter point includes diapedesis of leukocytes and migration of macrophages. These authors advise that the oral use of topical hydrocortisone preparations could be potentially dangerous to the incipient rheumatic, the individual with resistance lowered by viral infection, or to others with particularly vulnerable organs such as lungs or kidneys.
Several authors warn of possible side-effects to the treatment of aphthous lesions with corticosteroids, but no actual cases are cited: J.A.M.A. 250, Erich (1959), Zegarelli et al. (1959), Sinkford and Harris (1964), Durocher (1966), Brightman and Ship (1966), Lehner (1967c), MacPhee et al. (1968), Browne et al. (1968), Review Article 452, Cooke (1969), Kay (1969).

No systemic effects were noted in the trials conducted by Ship et al. (1961b) or in the treatment of 184 patients by Kutscher et al. (1966) with Kenalog in Orabase, with the exception of 5 cases of thrush and elevation of the blood sugar in two known diabetics, which were easily managed by their physicians.

Brightman and Ship (1966) advise that a careful watch should be kept for the following complications if treatment is prolonged: hyperglycaemia and glycosuria, reactivation of pulmonary tuberculosis or other chronic infections, muscular weakness, low blood pressure (especially under stress) and symptoms of gastrointestinal ulceration.

Kay (1969) states that systemic corticosteroid therapy is contraindicated in cases of peptic ulcers, tuberculosis, psychotic tendencies, osteoporosis, hypertension and diabetes mellitus. Kutscher et al. (1966) provided a similar list: active or healed tuberculosis, diabetes mellitus, hypertension under treatment, gastrointestinal ulcers, and pregnancy.
Conclusion:

It appears that, some reports notwithstanding, corticosteroids afford relief from pain and a decrease in duration of aphthous lesions, although long-term improvements are doubtful. It would appear that the more potent preparations may not offer any additional advantage, and the less potent ones would probably be safer, although with normal doses side effects should not occur. However patients should be screened for contraindications to the use of an anti-inflammatory agent and should not be subjected to excessive medication. The use of a vehicle such as Orabase is probably advantageous by virtue of its protective properties and concentration of the medication at the site. There are many points in dispute in this aspect of the literature.
CHAPTER 30 - OESTROGEN THERAPY:

The rationale of oestrogen therapy for aphthous lesions is given by Bishop et al. (1967): "Unfortunately it is still not possible to detect, by estimation of urinary oestrogens and pregnanediol, or by plasma-progesterone estimations, the relative secretion-rates, circulation, excretion, or effect on peripheral tissues of oestrogens and progestogens through the menstrual cycle. Nevertheless it is generally agreed that premenstrually there is withdrawal of both oestrogen and progesterone. The so-called premenstrual syndrome is thought to be due to inadequate progestogenic activity in the second half of the menstrual cycle and is characterized by mood changes such as irritability and depression, sometimes accompanied by mastalgia and fluid retention, and is sometimes relieved by administration of progestogens from the fifteenth to the twenty-fifth day of the cycle. But it is nevertheless possible that there may be peripheral manifestations of oestrogen deficiency which become especially evident during the period of oestrogen withdrawal a few days before menstrual bleeding takes place. Oestrogen therapy is based on the assumption that premenstrual buccal ulceration is one of these manifestations."

Vaginal cytology has long been used to determine tissue response to the sex hormones, and oestrogen is known to increase the cornification of the vaginal mucosa (Lessof et al. 1961). Other mucosal surfaces have been reported to be influenced by oestrogen, including the oral cavity. Thus Ziskin et al. (1936) induced keratinization of the gingival mucosa of ovariectomized monkeys by the administration of oestrogen.
In the following year Ziskin (1937) found that oestrogen injected into women in the treatment of menstrual disturbances induced hyperkeratinization and hyperplasia of the oral epithelium.

Bishop et al. (1967) found that oral ulceration occurred in their female patients when the cornification index of the vaginal epithelium was absent or low. This confirmed an observation made previously by Murray and Osmond-Clarke (1961).

According to Bishop et al. (1967) histological evidence of the effect of oestrogen on the oral mucosa is scanty but they quote Richman and Abarbanel (1943) who noted hyperplasia of the prickle cell layer, increased activity of the basal cells and in some cases a smooth hyperkeratinization of the corneous layer.

Bishop and co-workers postulate that premenstrual aphthae may result from a low level of circulating oestrogen which results in a failure of adequate keratinization of the oral mucosa and leaves it vulnerable. They suggest that the administration of therapeutic oestrogen might allow for the formation of a protective keratinized layer and also a diminished capillary fragility.

The British Medical Journal of 1948 had previously recommended chorionic gonadotropin 500 i.u. intramuscularly twice weekly.
Many clinicians have observed that women with histories of recurrent aphthae may gain relief from the condition during pregnancy. Among them are Ziserman (1934), Kochs (1940), Stark et al. (1954), Ship et al. (1962), Carruthers (1967a), Christensen (1967), and Samitz and Dana (1967).

A good response to oestrogen therapy has been claimed by Cahn (1950), Sutherland (1959), Bishop (1960), Harrison (1967), Bishop et al. (1967), Carruthers (1967a), and Christensen (1967). Disappointing results have been reported by Stark et al. (1954) and Sircus et al. (1957).

Bishop et al. (1967) reported a good response in 30 of 33 patients in whom the aphthae were related to the menstrual cycle and in 5 of 10 patients without this association. The effect on males receives little mention in the literature, Harrison (1967) stating that in his study no male undergoing oestrogen treatment gave a history of aphthae, although biopsy specimens from the gingival tissue of such men have shown the same histological changes as in females. Bishop and co-workers state that the treatment is well tolerated and side effects are rare, so that it may be continued for long periods if necessary.

Hirsekorn (1935) noted an association between aphthae and the various stages of female sex hormone alteration (puberty, menstruation, pregnancy). He thought that at these times women were predisposed to bacterial infection. More recent papers have mentioned three aspects of the effects of the female sex hormones: the effect on
keratinization, the effect on neutrophils, and a psychological effect.

Andermatt (1950, Schreus et al. (1953), Scholdgen (1955), Boorsma (1956) and Zeiser (1957) have shown a cyclical change in the oral mucosae in women as a result of sex hormone influence. The follicular phase of the menstrual cycle is marked by keratinization and the presence of many pyknotic nuclei. In the luteal phase the outstanding characteristic is exfoliation of the epithelial cells. Clumping of the cells in irregular groups is noted and their edges are curled and folded. In the menstrual period the cells appear pale and basophilic and with large nuclei; leukocytosis may be a prominent feature. Muhlemann (1952) reported that low levels of oestrogen lead to a disturbed peripheral circulation, and this may be another factor in the lack of resistance which the oral mucosa shows at this time. As Theron (1959) points out, skin and mucosal infections such as herpes labialis and acne vulgaris are often observed in conjunction with the menstrual period.

Main and Ritchie (1967) have shown the existence of a cornification cycle in the oral mucosae of healthy young females after puberty. Carruthers (1967a) says that aphthae are rarely seen in areas of good keratinization, and that the removal of mature epithelial cells by trauma is an important aetiological factor.

Oestrogen is effective in that it increases the degree of keratinization.
Shklar (1966) has shown that with increasing age there is an increase in keratinization, and this may be reflected in the lower incidence of aphthous lesions in old age.

Morley (1966) demonstrated the presence of a neutrophil cycle in health, and Carruthers (1967b) stated that neutrophils become more plentiful in a cytology smear as the cornification index falls. Carruthers postulates that the scarcity of neutrophils accounts for the occurrence of aphthous lesions in cyclical neutropenia (q.v.) This, he says, occurs mainly premenstrually since at this time the mucosa is most dependent upon the defensive function of the neutrophils, its cornification index being at its lowest level. Pregnant patients show more neutrophils in buccal smears, as do those on oestrogen therapy, and the cornification index is less depressed.

Christensen (1967) wrote in support of Carruthers' advocacy of oestrogen therapy, and suggested use of the contraceptive pill in this regard. Both Carruthers and Christensen reported greater success with higher doses of oestrogen. Carruthers (1967a) states that there is a noticeable increase in neutrophils in smears from patients taking the contraceptive pill. He states that whereas antimitotic drugs bring about oral ulceration by depression of both the cornification index and the neutrophil count, anovulants seem to stimulate both defence mechanisms and lead to a resistance to aphthous ulcer formation.

Some suggestions of a psychological effect have been made. Theron (1959) and others have stated that the significance of menstruation in the aetiology of aphthous lesions may be due to mental stress, and Chalmers and Sircus (1964) think that psychological as well as hormonal factors may play an important part in oestrogen therapy.
In conclusion, it appears that oestrogen therapy may be a worthwhile form of treatment in those aphthous lesions that appear to be related to the menstrual cycle. Perhaps the simplest method of administration would be per medium of the contraceptive pill.
CHAPTER 31 - ANTIHISTAMINES:

Both immediate and delayed hypersensitivity have been implicated in the aetiology of aphthous ulceration. In the immediate type histamine is believed to be one of the substances released, and antihistaminic agents have been employed in a variety of conditions to combat the pharmacological action of histamine.

Dolby (1968) quotes experimental workers to the effect that although histamine production may occur in the delayed response, the levels are not maintained: the slow development and persistence of this type of reaction is probably due to other pharmacologically active substances such as lymph-node permeability factor.

Nevertheless favourable early reports to the use of antihistamines were given by Pereira-D'Oliveira (1948), Moutier and Cornet (1949), Daniel (1951), Kremer (1952) and Owen (1957). Indeed Owen, who obtained rapid healing following the use of oral antihistamine treatment, suggested that the cure implied the cause.

Barile and Graykowski (1963) obtained symptomatic relief by the use of an antihistamine mouthwash, and Zegarelli et al. (1953) reported similar improvement following the administration of antihistamines systemically. However Zegarelli and co-workers recorded no effect on the duration of the lesions or the frequency of attacks. The long-term effect was no better than that recorded with a placebo and lesions frequently appeared during periods of active therapy. Disappointing results have also been recorded by Stark et al. (1954), Stones (1962), Graykowski et al. (1966) and Dolby (1968).
Most comments on the use of these preparations have been based on patient reaction, although Zegarelli et al. (1953) infused a note of objectivity into their results (see above) by the registration of blood eosinophil counts. They stated that eosinophils in excess of 4% are considered outside the normal range and when found in cases of suspected allergy are often cited as confirmatory evidence of allergic disease. No marked difference or deviation from normal in the eosinophil count was observed.

Some of the symptomatic relief found in conjunction with antihistamine therapy may be due to the considerable local anaesthetic activity which these preparations possess (Dolby, 1968). Indeed Lehner (1967c) has proposed four possible ways in which antihistamines may act:

1. they may counteract local histamine produced by the mast cells and thereby decrease the inflammatory reaction.
2. they have a sedative effect which is of value in emotionally disturbed patients.
3. they possess anti-allergic properties
4. they may have a local anaesthetic effect

Lehner (1967c) suggests that antihistamines are useful in some cases where other treatment has failed and where the patient tends to become agitated. He recommends promethazine (Phenergan) 10 mg. t.d.s. or mepyramine (Antisan) 50 mg. t.d.s. as two of many possible preparations.

Sutherland (1959) recommends the use of antihistamines during the prodromal stage, but warns against the local use of antihistamine cream because of the danger of sensitization.
Although the generally disappointing results associated with the use of antihistamines suggests a prima facie case against an immediate hypersensitivity aetiology, Dolby (1968) states that the role of histamine cannot be completely discounted. He states that the antihistamine level reached at the site of the lesion may not be sufficient to counteract a rapid histamine production. On the other hand, other pharmacologically active substances such as 5-hydroxytryptamine, slow reacting substance, and the plasma kinins may be aetio-logically involved.

Antihistamines must take their place amongst other medications used in the treatment of aphthous lesions, where clinical improvement in the ulcers may be expected in some cases, despite a doubtful rationale, but where the progress of the disease remains unabated.
CHAPTER 32 - VITAMIN THERAPY

As mentioned in the chapter on hypovitaminosis, various vitamin preparations have been used in the treatment of aphthous ulcers. The success or failure of this treatment has influenced many investigators to accept or reject the theory of a vitamin deficiency being the cause of the disease. Most treatment has been frankly empirical. This is most clearly illustrated in the advice of the British Medical Journal of 1948\(^{12}\) to try large doses of vitamins A, B and C in turn.

Vitamin A therapy has been advocated by Danziger (1934), Stepp (1936) and Roller (1939). Vitamin A is often employed in oral mucous membrane lesions for its "anti-hyperkeratotic" effect. The rationale of its use in cases of aphthous ulceration, where a degree of keratosis would be helpful, is difficult to see.

The various vitamins of the B group have been given most support, and one type or another has been suggested by Gerstenberger (1923), Stepp (1936), Prinz and Greenbaum (1936), Grieble (1939), Burket and Hickman (1942), Burket (1946), Strauss (1947), Cahn (1950), Tuft and Girsh (1958), Dent. Abstr.\(^{98}\), Kramer (1965), Durocher (1966) and Bishop et al. (1967).

Although most therapeutic administrations seem designed to make good a deficiency, some workers stipulate a particular member of the B group, whereas a deficiency would probably involve all members.\(^{598}\) Thus Burket and Hickman (1942) recommend thiamine chloride, Leemans (1951) folic acid, Dent. Abstr.\(^{98}\) pyridoxine, and Kramer (1965) folic acid, presumably because of some specific therapeutic benefit. Mann (1954) reported excellent results in three
cases following injections of vitamin $B_{12}$ but did not mention whether a pernicious anaemia had been ruled out.

Vitamin C therapy was suggested by Muller (1938), Marti (1940, 1941), Durocher (1966), Bishop et al. (1967), and Francis (1970).

In fairness, some of the advocates of vitamin therapy for the treatment of aphthae are knowingly reporting selected cases, or recommend the treatment only because it had proved helpful in some instances of a disease where no ideal form of therapy exists.

Sircus et al. (1957) found no significant alteration over that of a placebo in the progress of the disease following the administration of folic acid, riboflavin, nicotinamide or vitamin $B$ complex. Farmer (1958) reported no improvement from the use of aneurine hydrochloride or folic acid by themselves, but the two combined, he claims, resulted in short and/or long-term improvements in most cases.

The effects of vitamin therapy are subject to conflicting results and handicapped by the lack, in most cases, of experimental protocol, and an acceptable rationale. However no one doubts that a proper nutrition is important in general health and consequently in resistance to disease. Whether vitamin preparations can do more than rectify a deficiency has not been consistently demonstrated.
CHAPTER 33 - TREATMENT WITH GAMMA GLOBULIN:

In 1957 Strean reported on the treatment of 50 aphthous ulcer patients with doses of 3-10 ml. of gamma globulin, claiming that "in most instances prompt recovery was observed."

In the following year Strean and others (1958) reported encouraging results in the treatment of oral herpetiform lesions with gamma globulin. Significantly, these workers used the term "herpetiform" to include both herpetic and aphthous lesions, both of which they considered may have a similar, though not necessarily identical, viral cause. They explained their rationale of treatment thus:

"Human poliomyelitis immune globulin, also known as gamma globulin, contains significant concentrations of the antibodies useful in the attenuation or prevention of poliomyelitis, measles, and infectious hepatitis. Since this blood fraction taken from a large pool of blood presumably contains antibodies against other infectious agents, an attempt was made to test its effect in the treatment of herpes zoster and chickenpox. The results of treatment in eleven cases appeared highly encouraging. Because of this effort, an attempt was made to expand its usage to include the treatment of herpetiform lesions of the oral cavity."

Herpes zoster and chickenpox had been treated successfully by intramuscular gamma globulin as reported by Rodarte and Williams (1956), and its extension to other viral conditions was logical. The reported success in some cases of oral ulcerations (bearing in mind the weight of evidence against a viral aetiology for aphthous lesions) can be ascribed to:
(a) many authors failing to discriminate amongst herpetic lesions, aphthous lesions and the herpetiform ulcers of Cooke,
(b) a placebo effect, or
(c) natural remissions of the disease.

Ramfjord (1960) reported that 9 out of 10 patients with herpetic gingivostomatitis experienced various degrees of relief following the administration of gamma globulin, but the one patient with major aphthous ulceration was not improved.

Fraser-Moodie (1960) and Claus et al. (1961) applied gamma globulin therapy to patients with aphthous lesions on the supposition that the condition has a viral cause. Claus and co-workers considered their results encouraging, although they included cases of herpetic ulceration. Fraser-Moodie noted some early temporary improvement in some of his cases, but found that the improvement after one year corresponded closely to that obtained with a placebo.

Although Morelli and Maroczi (1963) claimed that patients following gamma globulin treatment showed "somewhat greater" improvement over control patients, many authors have discredited the treatment: Dent. Abstr. 98, Ship (1965a), Graykowskie et al. (1966).

Brightman and Ship (1966) state that no controlled studies are available on the efficacy of gamma globulin injections. To this may be added the lack of a logical rationale in cases of aphthous ulceration.
CHAPTER 34 - VACCINE THERAPY

A result of the supposed viral aetiology of aphthous ulcers has been the employment of vaccines, particularly smallpox vaccine (Hall, 1948; Kutscher et al., 1953c; Durocher, 1966). The thinking behind this form of treatment was expressed by Hall (1948): "Aphthous ulcers are now generally considered to be a variant of herpes simplex of the recurrent type. Repeated vaccination as for smallpox will frequently put a stop to the recurrent attacks or at least ameliorate them."

Smallpox vaccination was commonly advocated in the correspondence section of the Journal of the American Medical Association from 1948 to 1950. 226, 426, 428, 429, 431 The same treatment has also been recommended by Robinson (1950) and Huebsch (1965). Sutherland (1959) mentioned a 50% success rate.

Other vaccines have been employed also:

Whitwell (1934): tuberculin
Farmer (1958): influenza vaccine
Queries and Minor Notes 435: poliomyelitis vaccine
Ship (1965a): poliomyelitis vaccine, autovaccine

Two things have served to discredit this method of treatment of aphthous ulcers:
1. The unsound theory on which it was based; and
2. Failure to secure satisfactory results in clinical trials.
The following authors have reported unfavourably on the use of vaccination in the treatment of oral aphthae: Savitt and Ayres (1949), Kutscher et al. (1953c), Stark et al. (1954), Losch (1954), Sircus (1959), Queries and Minor Notes 435, Stones (1962), Ryan (1963), McCarthy and Shklar (1964), Sagar and Faulkner (1965), Ship (1965a), Brightman and Ship (1966), Graykowski et al. (1966), and Kramer (1967).