THE APHTHOUS ULCER.

This critical review of the literature is submitted in partial fulfilment of the requirements for the degree of Master of Dental Surgery.

/ W. [Signature]
"Not a week passes but what some dental or medical journal, somewhere in the world, publishes an article on cold sores or canker sores. For all the thousands of reports and editorials, surprisingly little information on the diseases has been elicited."


"Neurologists define the anterior horn cell of the spinal cord as the 'final common pathway' because of the large numbers of neurons whose axon end-plates synapse at this point and thus effect a motor response. In like fashion the intraoral ulceration can be termed the final common pathway for oral medicine in that it is common to a variety of systemic diseases and may be the principal symptom in certain chronic diseases, and it represents a morphologic end-point response for mucous membranes to a variety of endogenous and exogenous noxious stimuli."

Irwin T. Ship (1963a)

"The primary and perhaps the only function of oral pathology is to aid the clinician in the diagnosis and, therefore, in the treatment of oral lesions."

S.N. Bhaskar (1965)
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INTRODUCTION AND OUTLINE OF THE WORK.

Oral ulcerations have plagued mankind since antiquity and perplexed clinicians since the beginnings of organised medicine. Particularly troublesome, though by no means the most serious, are those which are called aphthous ulcerations, or aphthae, or by another of some 75 synonyms. That so many names could have been ascribed to the one condition is ample evidence of the lack of understanding regarding this condition. A strong case could be established for the consideration of this disease as the most tantalizing for the researcher, the most painful for the patient, and the most frustrating for the clinician.

The Shorter Oxford English Dictionary defines aphtha as "the infantile disease 'thrush', and, in the plural, the small white specks on the mouth and tongue which characterize it". The three American medical and dental dictionaries consulted by Shaffer have adopted this definition, but it is certainly not correct by modern usage.

As employed in the literature, aphthous ulceration can be taken to mean one of two things:

(i) A mucosal ulcer with a regular outline, usually less than 1 cm in diameter, having a yellowish or greyish-white necrotic centre surrounded by a narrow erythematous zone, and with a pronounced tendency to recur; or

(ii) A specific disease, having the clinical features of the above, but of an uncertain aetiology now known to be not due to the herpes simplex virus.
Some confusion has resulted over this distinction. Cahn stated: "The recurrent aphthous lesion of viral origin must be distinguished from other types of aphthae, some of which are purely traumatic in origin", and Everett remarked that "the vesicles of herpetic gingivostomatitis turn quickly into 'aphthous ulcers' resembling recurrent oral aphthae." Herpetic and traumatic ulcers may be aphthous in the sense of (i), but not in the sense of (ii).

The diagnosis of aphthous lesions is a clinical one. Because details of clinical descriptions vary, it is proposed to examine the comments of the various contributors in an attempt to arrive at a general measure of agreement upon which a clinical concept can be based. This procedure will be extended to cover the statistical details pertaining to the occurrence of these lesions. The clinically similar conditions of traumatic and herpetic ulcers will also be discussed, as the differentiation among these three has been subject to confusion.

According to Sircus and co-workers recurrent mouth ulceration, with or without involvement of the genitals, has become interwoven with the triad of Behcet. Other authors have, of course, described the association of oral ulceration with extra-oral lesions, and this association, and Behcet's syndrome in particular, will be discussed separately.

The separation of aphthous from herpetic lesions has come about slowly and in some minds even grudgingly. This is not to say that the two may have little in common. Indeed, their oecological and serological similarities have been stressed in a paper by Ship and his colleagues in 1967. However, it has become accepted that the herpes simplex virus
is the cause of herpetic lesions but not aphthous ones. This move towards simplicity, even though the aetiology of aphthous ulceration remained unsettled, was blurred by the description in 1960 of Cooke's "herpetiform" ulcers, and by even later argument as to whether recurrent herpetic infections actually occur in the mouth. The definitive demonstration by Griffin in 1963 of intra-oral recurrent herpetic lesions by fluorescent antibody studies was mis-interpreted by some as a demonstration that aphthous ulcers were, after all, caused by the herpes simplex virus. 632

Because of the relevance of the herpes simplex virus to the history of aphthous ulceration, no less than for its importance as an oral pathogen, herpetic infections will be given a brief discussion.

Some simplification has been achieved in the concept of ulceration of the oral cavity by the proposing, by Truelove and Morris-Owen in 1958, and the confirming, by Lehner in subsequent studies, that periadenitis mucosa necrotica recurrens, described by Sutton Sr. in 1911, is but a more severe form of normal aphthous ulceration.

The term herpetiform is a potential source of confusion, being so similar to herpetic yet signifying, by Cooke's usage, a non-herpetic condition. It is suggested that herpetiform is better used in a wider sense to include all lesions resembling herpetic ones. According to this usage, some herpetiform lesions would be caused by the herpes simplex virus whilst others would not. This distinction is not important to the clinician as both appear to be of viral origin and lack specific therapy.
4.

It is important, however, for the clinician to differentiate between aphthous and herpetiform ulcerations because of their different responses to tetracycline and corticosteroid medications, and so this seems to be a more useful separation.

The clinical features of aphthous ulcers will be reproduced from as wide a source as possible as the diagnosis is, to all intents and purposes, a clinical one. These lesions (as well as herpetiform lesions not caused by the herpes simplex virus) may be focal or a part of Behcet's syndrome, and so the presence of aphthous ulcers may necessitate a thorough physical examination of the patient.

A simple classification of aphthous-like lesions which is directed towards the appropriate therapy can now be suggested:

1. Behcet's syndrome (partial or complete)
2. Focal oral ulcers
   (a) Aphthous ulcers
      i. major
      ii. minor
   (b) Herpetiform ulcers
      i. caused by the herpes simplex virus
      ii. probably caused by another virus
   (c) Traumatic ulcers.

Many aetiologies have been proposed and many forms of treatment advocated. These will be discussed separately. The most recent and most sophisticated studies are of an immunological nature, and for the sake of completion a chapter on immunological theory has been included.
5.

An historical account of the use of the word aphthae is given, and the many synonyms by which the condition has been known are presented; certain of the latter are discussed in an attempt to find the most satisfactory.

Aphthous lesions have been known to undergo remission during pregnancy and with smoking. The effect of pregnancy is discussed in relation to endocrine aetiology and oestrogen therapy. A special chapter has been included on the effects of smoking.

Because this is a review of the literature, the term herpetiform will be used to imply the lesions described by Cooke, as this is the meaning which has gained acceptance in the literature by those who have used the term.
6.

PART 1. THE APHTHOUS LESION

Chapter 1. Historical account.
Chapter 2. Terminology
Chapter 3. Clinical features. (a) Prodromal symptoms.
          (b) Early macular stage.
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          (e) Nature of the central necrotic area.
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          (a) Size of individual lesions.
          (b) Duration of the disease.
          (c) Site of occurrence.
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          (e) Sexual incidence.
          (f) Age incidence.
7.

(g) Number of lesions per attack.
(h) Frequency of occurrence.
(i) Time lag between onset of the ulcers and their becoming severe.
(j) Geographical and racial incidence.
(k) Seasonal incidence.
(l) Religious difference.
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(n) Summary.
CHAPTER 1 - HISTORICAL ACCOUNT:

The word aphtha appears in the writings of Hippocrates of Cos (460-370 B.C.) in relation to thrush, but appears later to have acquired a wider meaning. Thus Celsus (c.A.D.178) states that "by far the most dangerous ulcers are those which the Greeks call aphthae; especially in children, for these they often destroy; there is not the same danger in men and women." Obviously a more serious condition than thrush is implied, probably diphtheria. According to Ship the condition we call aphthous ulceration was actually named by Hippocrates.

Etymologically, the term has a significance which suggests the idea of burning, used, doubtless, to convey the sensation of superficial pain which the lesions provoke. According to Skinner aphtha is derived from a Greek verb meaning "I inflame"; Liddle et al. give the sense of the original verb as "to kindle" or "to touch". Theron regards the exact meaning as still unresolved.

Fleming states that aphtha means a small ulcer and only later came to be applied to cases of moniliasis. Black, however, as if to illustrate the confusion pervading this topic, had earlier stated the opposite.

Interestingly, the word sprue (ulcerations of the mouth have been associated with gastro-intestinal disease) is derived from the Dutch "spruw" meaning aphthous disease.

Two derivatives of the word aphtha are aphthoid and aphthosis. The so-called aphthoid of Pospischill was a severe form of herpetic stomatitis occurring in debilitated children and described by Pospischill in 1921.
Aphthosis was applied by Neumann in 1895 to a condition which featured the simultaneous appearance of aphthae on the genitals and in the mouth of certain of his female patients, some of whom also exhibited skin lesions. The term was popularized by Touraine and adopted by Thoma who used it to imply a chronic state of oral aphthous ulceration.

Jourdain-Berchillet discusses aphthae in his treatise "Diseases and Surgical Operations of the Mouth" in 1778, but the condition described is thrush.

According to Ship recurrent aphthous ulceration was carefully described by English and Spanish physicians of the eighteenth and nineteenth centuries. Ship states that the condition was initially described as characteristic of foot-and-mouth disease. (Shafer et al., Cheraskin and Langley and others list aphthous fever as a synonym for foot-and-mouth disease). More recently, says Ship, French writers have employed the term aphthae to describe thrush. Herpangina is sometimes referred to as aphthous fever.

"Aphthous stomatitis" was described by Billard (1828), Bohn (1880) and others, but the first valid account of recurrent aphthous ulceration, according to Sircus et al., was by von Mikulicz and Kummel in 1888.

Bednar, in 1850, applied the term aphthae to lesions found only in infants, and consisting of a group of small irregular ulcers occurring on the palate in the approximate shape of a butterfly and considered to result from pressure. These lesions are still referred to as Bednar's aphthae.
10.

In 1892 Mikulicz and Michelson separated the commonly occurring mouth ulcers into an acute variety seen mainly in children, and a chronic, recurrent type occurring mostly in adults. The former they described under the name of acute aphthous stomatitis, and the latter they called chronic recurrent aphthae. These authors were, of course, unaware of the herpetic origin of the acute lesions they described, but recognized the condition as a separate entity.

Notwithstanding the distinction drawn by Mikulicz and Michelson, the two varieties of ulcers were considered by many authors to be the same disease showing different characteristics in childhood and adulthood. An infectious agent was commonly suspected to be the cause, especially of the acute childhood variety, and it was observed by various authors that diseases like pneumonia, diphtheria, whooping cough and catarrhal inflammation of the mouth, nose and throat often accompanied the lesions. Primary herpetic lesions in adults were late to be recognized as a clinical entity.

Confusion between herpetic and non-herpetic conditions is still perpetuated. Thus Jawetz et al. list the terms aphthous stomatitis and Vincent's stomatitis as synonyms for acute herpetic gingivostomatitis.

Sibley appears to have given the first account of aphthous ulceration in the English language. Writing in the British Medical Journal of 1899, he called his paper "Neurotic ulcers of the mouth".
11.

Following Sibley, some outstanding contributions have been written in English. Sircus and co-workers published an authoritative and comprehensive treatment of the topic in 1957. Other British writers with impressive contributions have been Farmer, Cooke and Kramer in the clinical details, while Lehner has produced a good deal of imposing material on the immunological aspects of the disease, and its light, electron, and fluorescent microscopy. Dolby has also produced distinguished articles on aphthous lesions, especially from an experimental viewpoint.

Across the Atlantic, the Americans Ship and Graykowski and their respective co-workers must be mentioned. Ship has concentrated most on a statistical treatment, while Graykowski and his colleagues have postulated an L form bacterial theory, carried out a detailed histological investigation, and initiated hypersensitivity studies.

A most comprehensive review of the literature was carried out by Theron in the Netherlands, and this included some original work with a detailed histopathological investigation. Theron's thesis is the more valuable in that it draws largely on Continental sources not generally available beyond Europe. Finally, a fluent summary of the rather detailed recent research publications has been presented by Francis.
CHAPTER 2 — TERMINOLOGY

Hurt states that under the heading "aphthous" one may find practically all recorded pathological lesions that would result in an ulcer of the oral mucosa.

The following terms have all been applied to the one condition:
apthae, aphthous ulcers, aphthous ulceration, habitual aphthae, chronic aphthae, recurrent aphthae, solitary aphthae, recurrent painful aphthae, recurrent habitual aphthae, habitual solitary aphthous ulcer, chronic intermittent recurrent aphthae, recurrent oral ulcers, cyclical habitual aphthous stomatitis, recurrent non-febrile aphthous stomatitis, recurrent mouth ulcers, recurrent aphthous stomatitis, recurring ulcers of the mouth, recurrent ulcerative stomatitis, Mikulicz's aphthae, Mikulicz's ulcers, Mikulicz's recurrent oral aphthae, chronic recurrent ulcer of Mikulicz, minor aphthous ulcers, chronic recurrent aphthae, dyspeptic ulcers, dyspeptic mouth ulcers, ulcus neuroticum, ulcus neuroticans mucosae oris, ulcus neuroticum mucosae oris, neurotic ulcers, stomatitis neurotica chronica, ulcus aphthosum chronicum, ulcus negroticum mucosae oris, maculofibrinous stomatitis, stomatitis maculofibrinosa, recurrent maculofibrinous stomatitis, recurrent aphthous ulceration of the mouth, ulcus necroticans, mucosae oris, gangrenous stomatitis, noma, aphthae resistiae, chronic scarring aphthous ulcers, stomatitis aphthosa recurrens cicatricicans, recurrent scarring painful aphthae, periadenitis aphthae, major aphthous ulcers, periadenitis mucosa necrotica recurrens, Sutton's disease, aphthous stomatitis, acute aphthous stomatitis, ulcerative aphthous stomatitis, secondary aphthous stomatitis, habitual aphthous stomatitis, habitual aphthosis, chronic recurrent aphthosis,
13.
Touraine's aphthosis, aphthose monoplaire, recurrent aphthosis multiplex mucosae oris, familial recurrent orogenital ulceration, Behcet's syndrome (complete and partial), fragmentary Behcet's symptom-complex, canker sores, herpetic stomatitis, herpetic gingivostomatitis, recurrent herpetic gingivostomatitis, secondary herpetic stomatitis, herpes simplex (with or without the addenda of facialis, labialis, buccalis, lingua, etc.) recurrent herpes, cold sores, recurrent herpetic ulcers, recurrent gingivostomatitis, vesicular stomatitis, herpetiform lesions, herpetiform ulcers, recurrent herpetiform lesions.

A recitation of the above expressions virtually narrates the modern history of the disease and its clinical features. Some of the terms are only marginally different, others are the results of faulty diagnoses and mistaken aetiologies. Some are eponyms, others clinically descriptive terms. Judged as a whole they illustrate very well much of the general confusion surrounding this topic.

The question arises as to which term is the most suitable. Perhaps the best approach to this question is by a process of elimination.

All references to an herpetic cause must be discarded, as should terms like noma and gangenous stomatitis which clearly signify a different condition. It is not generally agreed that oral ulcers are an aborted Behcet's syndrome, nor do they occur with sufficient regularity in conjunction with genital lesions to warrant their inclusion in some overall concept, and therefore references to the various syndromes should also be discarded.
Descriptive terms like vesicular stomatitis are obviously unsatisfactory, and other possibilities such as neurotic and dyspeptic ulcers imply a false aetiology. As Stark et al. comment, the expression stomatitis has little to recommend it, as it implies a diffuse inflammatory condition, whereas this disease usually has lesions which are quite localized.

The terms chronic and secondary no doubt arose when the condition was considered to be related to herpetic stomatitis, the so-called acute form of the disease.

Theron used the term chronic recurrent aphthae, and, like Hirsekorern (1935), Marti (1941), Kummer (1942), Frech (1945), Thoma (1944; 1950; 1954), Schaffer (1951) and Thoma and Goldman (1960), was forced to elevate the solitary lesion to one of special consideration. The distinction between an isolated, solitary lesion and a recurrent and/or multiple variety does not appear to be justified.

Truelove and Morris-Owen's division of aphthous lesions into major and minor types appears to have been confirmed, and there is thus no need to establish a separate entity of periadenitis ulcers, nor retain any term applicable to them.

Cooke used the term Mikułcz's aphthae for the minor variety, whereas Shafer et al. used it for the major type. Although the British writers, Kramer, Lehner, and Dolby have followed Cooke's usage, the term is neither widely used nor is it necessary. The Americans Brody and Silverman appear hesitant about using Cooke's terminology.
The British writers also employ the term recurrent oral ulcers and divide it into major ("periadenitis") aphthae, minor ("Mikulicz's") aphthae, and herpetiform lesions. Logically they should also include the lesions caused by the herpes simplex virus, which, it has been shown, can be recurrent intra-orally. Recurrent oral ulcers as a term is, therefore, inexact.

The expression canker sores appears mostly in American publications. Its only objection appears to be its implication of carcinoma.

The obvious term aphthae, or aphthous ulcers, is well established and fairly definite in its implications. It is suggested that the additional use of adjectives like recurrent and chronic are not required routinely, and, indeed may not apply, but could be adopted for a more precise description of an individual case.

Aphthous ulcers may be major or minor, and are usually distinguishable on clinical grounds from lesions of viral origin which can be grouped together under the title herpetiform.
CHAPTER 3 - CLINICAL FEATURES

In this chapter the various stages in the formation and resolution of aphthous lesions have been abstracted from the various clinical descriptions. Some are the results of large-scale investigations, others mentioned merely in passing and possibly are even derivative. They are presented here in chronological order so as to give an accurate overall impression of the clinical literature. At the end of each section some general comments will be made. Certain early contributions have had to be omitted as they obviously refer to herpetic lesions.

1. Prodromal symptoms.

A premonitory tingling or hyperaesthesia for up to twenty-four hours prior to lesion forming (Stark et al., 1954); prickly or burning sensation (Farmer, 1958); burning and itching (Sutherland, 1959); prodrome of from one to twenty-four hours, usually four to twelve hours during which there is a sensation of hyperaesthesia and burning in the effected mucosa (Driscoll et al., 1959); sudden burning sensation (Theron, 1959); burning sensation followed in twelve to twenty-four hours by a roughness (Cooke, 1961); hyper-aesthesia for one to twenty-five hours and burning (Ship et al., 1961c); a prickly or burning sensation (Stones, 1962); burning and tingling for one to twenty-four hours (Ship, 1963); hyperaesthesia and burning (Shafer et al., 1963); preceded by a burning sensation in the area or by gastrointestinal symptoms; vague symptoms related to an area of the oral mucosa (McCarthy & Shklar, 1964); prickling or burning sensation for up to twenty-four hours (Kramer, 1965); burning and tingling for one to twenty-four hours and usually four to twelve hours (Ship, 1965a);
17.
burning, tingling and swelling for four to twelve hours (Brightman and Ship, 1966); often they follow a one or two day prodromal period of strange sensation in the area (Getz and Bader, 1967); often begins as a raw, burning pain (Samitz and Dana, 1967); burning sensation (Finkborg, 1968); pain and burning for twenty-four to forty-eight hours prior to ulceration (Francis, 1970).

There is a distinct similarity among the descriptions. Perhaps the only comment necessary is the failure of almost all authors to separate major and minor aphthous lesions, and possibly herpetiform ones also. The more severe symptoms would obviously be related to the major form. This is perhaps best illustrated by the findings of Graykowski et al., (1966) that of their 62 patients, 32% had generalized oedema of the oral cavity, 31% paraesthesia, 18% malaise, 18% low-grade fever, and 5% localized lymphadenopathy.

It seems fair to generalize that the prodromal symptom of minor aphthous ulcers consists, usually, in a localized burning sensation for up to twenty-four hours prior to the development of a lesion.

2. **Early macular stage**
little red plaque (Whitwell, 1934); small, localized, oval area of redness (Stark et al., 1954); the mucosa becomes reddened (Farmer, 1958); thickening of the mucosa (Rushton and Cooke, 1959); very small erythematous macule measuring approximately 1 to 3 mm. in diameter, which grows but rarely becomes larger than 1 cm. (Driscoll et al., 1959); a small area of redness on the mucosa (Ship et al.
18.
1960a); thickening of the mucosa (Cooke and Armitage, 1960); surface feeling rough to the tongue with mucosa slightly raised and erythematous (Cooke, 1961); small erythematous macule (Ship et al., 1961c); the mucosa becomes reddened and in some cases a greyish white plaque is formed which is lost within a few hours (Stones, 1962); a small erythematous macule (Ship, 1963a); sometimes only a focal area of erythema (Shafer et al., 1963); a small circumscribed macular red lesion (McCarthy and Shklar, 1964); small area of erythema (Bhaskar, 1965); small erythematous macule 1 or 2 mm. in diameter increasing in size to 1 cm. (Ship, 1965a); slight reddening (Kramer, 1965); small erythematous macules 1-2 mm. in diameter which increase in size in several hours but rarely exceed 1 cm. in diameter (Brightman and Ship, 1966); 50% show a nodule (Graykowski et al., 1966); the lesion first appears as a macular eruption (Getz and Bader, 1967); round to oval, discrete erythematous macule 2 to 20 mm. in diameter (Samitz and Dana, 1967); small erythematous macules 1 to 2 mm. in diameter which increase in size in several hours but rarely exceed 1 cm. in diameter (Review Article, 1968452); begins as a small white spot or raised bump in the mucosa (Francis, 1970); erythematous macule or papule (Weathers and Griffin, 1970).

Once again, the larger sized macules can be taken to refer to the major form of the disease. Most authors of articles on major aphthous ulceration (q.v.) describe a nodule as preceding the ulcer stage.

In minor lesions, the earliest stage of development is an erythematous, thickened area of the oral mucosa several millimetres in diameter.
19.

3. **Secondary changes.**

Development of a superficial yellow to greyish membrane (Stark et al., 1954); a greyish white plaque is sometimes formed and is lost within a few hours (Farmer, 1958); a central blanched region appears and breaks down after several hours (Driscoll et al., 1959); central necrosis and subsequent slough (Ship et al., 1960a); following a vesicular stage which is rarely seen, a light yellow or yellow spot is seen which is generally oval. The size is rarely more than 2 by 3 mm. (Thoma and Goldman, 1960); a central blanched region forms (Ship et al., 1961c); a central ischaemic avascular region which undergoes necrosis (Ship, 1963a); macular area quickly undergoes necrosis, leaving an ulcer (McCarthy and Shklar, 1964); central necrosis or vesicle formation (Bhaskar, 1965); a central blanched region appears which is found to be avascular when examined stereomicroscopically (Ship, 1965a); a central blanched area appears in the area of engorged mucosal vessels and is found to be avascular when examined with a lens (Brightman and Ship, 1966); the macule necroses rapidly, leaving a distinct, exquisitely painful yellowish ulcer (Getz and Bader, 1967); during the next few hours (rarely more than one day) after formation of the macule, the area of redness develops a slight induration but never a vesicle. A necrotic slough soon appears, leaving a well-defined painful ulceration (Samitz and Dana, 1967); necrosis is formed and a shallow ulcer is formed (Review Article, 1968); central blanching (Weathers and Griffin, 1970).
20.

The degree of uniformity shown may be more apparent than real inasmuch as ship is involved in five of the fifteen studies cited. Nevertheless, it would appear that the central area of the erythematous plaque becomes ischaemic, as a result of which necrosis occurs and an ulcer results. This concept receives support from later sections.

4. The controversy over a vesicular stage.

Most contributions can be conveniently treated on the basis of pro et contra.

**PRO:** A vesicle forms and is filled with lymph and degenerate cells and contains in abundance the herpes virus (Cahn and Bartels, 1942); in early stages a vesicle forms but is rarely seen as the symptoms do not occur until the vesicle is broken (Thoma, 1944, 1950, 1954); the common canker sore follows a vesicular onset (Queries and minor notes, 1948424); the primary lesion is a vesicle, rarely seen as the oral fluid quickly macerates the epithelial covering (Everett, 1950); vesicle stage (Kerr, 1952a); aphthae are infrequently observed at their inception when they are generally seen as vesicles (Kutscher et al., 1953); infrequently observed at their inception at which time they are generally seen as vesicles (Zegarelli et al., 1953); discrete or multiple vesicles (Strean et al., 1958); the primary lesion is a vesicle (Ingersoll and Morgan, 1958); the lesion resembles a vesicle (Tuft and Girsh, 1958); vesicle forms but is rarely seen (Sutherland, 1959); vesicle stage (Erich, 1959); in the early stages a vesicle forms but is rarely seen as the symptoms do not occur until the vesicle is broken (Thoma and Goldman, 1960); the vesicle of the early stage is rarely seen, as the symptoms do not occur until the vesicle is broken (Schaffer, 1960); the syndrome is characterized in its inception by vesicles that break down into ulcerations (Dalmau et al., 1961); starts
as a vesicle in the stratum granulosum but this is rarely seen because it rapidly breaks down into an ulcer (Ryan, 1963); frequently but not invariably begins as vesicles (Shafer et al., 1963); vesicle-like formations containing mucus were seen in eleven patients (17%) (Graykowski et al., 1966); reports of vesicle formation have been noted (Getz and Bader, 1967); vesicles full of yellowish serous fluid; not often observed (Schlemmer, 1968); five of thirteen patients reported a vesicular stage. The vesicle quickly broke. This phenomenon was documented by observation and biopsy. Viruses could not be demonstrated (Brody and Silverman, 1969); a vesicular lesion develops (Gardner, 1970).

**CONTRA:** vesicle formation has not been observed (Stark et al., 1954) no vesicle (Scott and Crawford, 1958); have not observed vesicles in any patient (Driscoll et al., 1959); at no stage is a blister to be seen (Cooke, 1961); we have never been able to observe a vesicle in aphthous stomatitis and doubt its existence (McCarthy and Shklar, 1964); not observed a vesicle stage (Ship, 1965a); no vesicle observed (Brightman and Ship, 1966); never a vesicle (Samitz and Dana, 1967); these ulcers do not begin from the rupture of a vesicle but from the localized erosion of the epithelial surface (Francis, 1970).

Even though Cahn and Bartels described a vesicle containing the herpes simplex virus in profusion, they regarded aphthous and herpetic lesions as different lesions. Colby et al. (1961), however, described a vesicle but made no distinction between herpetic and aphthous lesions.
Authors such as Hall (1948), who ascribe the condition to the herpes simplex virus, probably mean to imply a vesicular stage. On the other hand, Whitwell (1934), writing at a time when the distinction between aphthous and herpetic lesions was less clear, gave a precise clinical description of aphthous lesions without mentioning a vesicle.

There can be little doubt that the presence of a vesicle was often inferred from the similarity of the ulcers to herpetic lesions; significantly, many who describe a vesicular stage also state that it is rarely seen.

It is also possible that clinical vesicles could have been inferred by the finding of microscopic ones. Cahn (1936) considered that the lesions start as the result of intra-epithelial oedema with the formation of a vesicle. Cahn (1936, 1950) described the lesions as first appearing as small, short-lived vesicles. However, he also considered the lesions as due to the herpes simplex virus, and herpetic lesions have a well recognized vesicular stage. Cahn's opinion had a wide influence, Dietz (1950), Scales (1953), and Schaffer (1960), being three authors who have quoted him directly. Farmer (1958) reported what he said was probably an intraepithelial vesicle in four out of eight microscopic examinations carried out.

Beside the differentiation from primary herpetic ulcers, it is necessary also to differentiate aphthous from herpetiform lesions (in Cooke's usage of the term) and intra-oral recurrent herpetic lesions. Failure to do this would tend to invalidate virtually all claims on behalf of a vesicular stage except that of Brody and Silverman (1969), and cast doubt upon Schaffer and co-workers' posture of vesicular "aphthous" lesions.
Interestingly, in the skin tests carried out by Graykowski et al. (1966) with a streptococcal vaccine, a vesicle developed in the centre of the skin lesions in several instances. This might suggest that a vesicle may form in severe cases, but a vesicle has not been described in connection with major aphthous ulcers.

The evidence in favour of a vesicular stage, despite the number of "witnesses", is not impressive. Bhaskar (1965) says that the small area of erythema is followed by central necrosis or by the formation of a small vesicle and its rupture. Whether two different lesions are thereby described, or whether the one lesion presumably behaves in two different ways, or whether Bhaskar had some doubt upon the subject, it is impossible to decide.

It can be taken that at least the clinical absence of a vesicular stage is an important diagnostic feature of aphthous ulceration; the condition can be regarded, in the words of Francis (1970), as a necrotizing ulceration. Thus, from the point of view of its pathogenesis, it may have more in common with Vincent's infection than with herpetic stomatitis.

5. Nature of the central necrotic area.
base covered with a bright yellow fibrinous deposit, on removing which a fairly clear floor composed of the corium is seen (Whitwell, 1934); covered by a yellowish-grey surface (Cahn, 1950); covered by a false membrane (Dodd and Ruchman, 1950); covered with a necrotic membrane or exudate (Zegarelli et al., 1953), a superficial yellow to greyish membrane which, within two or three days, forms a superficial slough leaving a shallow ulcer, the base of which soon becomes
covered with greyish granulation tissue (Stark et al., 1954); greyish yellow shallow ulcer (Ingersoll and Morgan, 1958); greyish surface (Strean et al., 1958); grey-yellow base (Farmer, 1958); yellowish white sloughy floor (Sutherland, 1959); grey-yellow fibrinous base (Driscoll et al., 1959); a greyish white fibrinous base (Ship et al., 1960a); light yellow or yellow spot. Closer examination reveals a whitish membrane covering the lesion which becomes necrotic when a yellowish exudate accumulates (Thoma and Goldman, 1960); light yellow (Schaffer, 1960); greyish-yellow fibrinous base (Ship et al., 1961c); covered with a grey Slough (Cooke, 1961); greyish yellow fibrinous material adhering to the base (Ship, 1963a); an area of central necrosis with the formation of a covering greyish-white fibrinous exudate (Shafer et al., 1963); pseudomembrane ranging from grey in colour to yellow (Engelman, 1963); covered with a whitish membrane; this in turn becomes necrotic, giving off a yellowish exudate which accounts for the familiar, yellow-looking sore (Ryan, 1963); a yellow-white base representing necrotic tissue at the surface (McCarthy and Shklar, 1964); grey or yellow base (Scott, 1965); grey-yellow fibrinous base (Ship, 1965a); base covered by a yellow or grey pyogenic membrane (Kramer, 1965); yellow-white colour (Huebsch, 1965); central necrosis and subsequent slough; a greyish white fibrinous base (Levin, 1965), ulcer develops a grey-yellow, fibrinous base, and petechial haemorrhages are frequently observed in the base and on the margins (Brightman and Ship, 1966); grey membrane (Graykowski et al., 1966); distinct yellow colour (Getz and Bader, 1967);
a necrotic slough soon appears, leaving a well-defined painful ulceration with a grey-white fibrinous exudate at the base and a halo of erythema at the border, resembling a minute infarct of the mucosa (Samitz and Dana, 1967); fibrin-covered (Pindborg, 1968); a greyish-white necrotic centre (Collins, 1968); covered by a yellow to grey pseudomembrane (Brody and Silverman, 1969); yellow necrotic centre (Weathers and Griffin, 1970).

The concept of a minute infarct as proposed by Samitz and Dana (1967) is an appealing one, and no macroscopic description negates it. It receives additional support from the unanimous description of a surrounding hyperaemic zone as described in the following section. This concept is further discussed in the chapter on histopathology (q.v.).

The colour of the central necrotic area is apparently a light yellow or light grey, and there is a covering fibrinous exudate. Cooke (1961) states that the presence of a covering slough protects the ulcer, and he encourages its formation by the single application of an alum stick.

6. Nature of adjacent tissue

bright red inflammatory halo (Whitwell, 1934); marked erythematous zone (Thoma, 1944, 1950, 1954); surrounding red zone of inflammation (Strauss, 1947); surrounded by a red halo (Cahn, 1950); surrounded by a red areola (Dodd and Ruchman, 1950); surrounded by an area of inflammation (Zegarelli et al., 1953); a variable amount of induration occurs at the periphery dependent upon duration (Stark et al., 1954); red surround (Farmer, 1958); hyperaemic zone (Sutherland, 1959); surrounded by a narrow, well-marked erythematous halo; there is
little if any oedema or other local reaction (Driscoll et al., 1959); bright red areola (Ship, 1960a); often surrounded by a marked erythematous zone (Thoma and Goldman, 1960); often surrounded by a marked erythematous zone (Schaffer, 1960); narrow, well-marked erythematous areole (Ship et al., 1961c); lesions have a hyperaemic inflammatory base (Claus et al., 1961); surrounded by an area of inflammation (Dalmau et al., 1961); narrow, well-marked erythematous areole (Ship et al., 1961c); bright red areola (Shafer et al., 1963); a bright red circular inflammatory border (Engelman, 1963); the mucosa at the margins presents a surrounding zone of erythema. The marginal erythema may be extensive or slight depending upon the degree of secondary bacterial involvement in the lesion (McCarthy and Shklar, 1964); surrounding zone of hyperaemia (Scott, 1965); narrow, well-defined erythematous border (Ship, 1965a) margins of the ulcer are erythematous and indurated (Huebäch, 1965); bright areola (Levin, 1965); narrow, well-defined erythematous border (Brightman and Ship, 1966); surrounded by a bright, discrete, thin erythematous zone (Graykowski et al., 1966); dark erythematous border (Getz and Bader, 1967); a halo of erythema at the border, resembling a minute infarct of the mucosa (Samitz and Dana, 1967); surrounded by an area of oedema and hyperaemia (Bishop et al., 1967); erythematous border (Collins, 1968); surrounded by a narrow, erythematous border; oedema develops in adjacent tissues (Review Article, 1968); surrounded by an erythematous and oedematous area (Brody and Silverman, 1969); a well-defined erythematous border (Chellemi et al., 1970);
27. constant erythematous halo (Weathers and Griffin, 1970); some localized swelling and inflammation (Francis, 1970).

A narrow, surrounding hyperaemic zone is the most consistently noted feature of these lesions. The central necrosis may provoke an inflammatory response from the surrounding tissue, as in the case of an infarct. The degree of surrounding hyperaemia would doubtless depend on the size of the ulceration, and induration would occur in the case of major aphthous disease. Secondary bacterial invasion may also stimulate a greater response from the surrounding vital tissue. A diffuse erythematous background is more suggestive of a viral infection.

7. **Shape of ulcer and nature of margins.**

regular in outline, oval or round and spoonshaped; the larger ulcers become irregular in outline but not undermined at the edges (Whitwell, 1934); round, or where two coalesce, elongated (Strauss, 1947); appear as if they were punched out of the tissue (Schaffer, 1951); usually round or oval but may present irregular peripheries (Zegarelli et al., 1953); dependent upon duration, a variable amount of induration of the periphery develops (Stark et al., 1954); the form of the outline frequently depends on the site, those appearing on flatter surfaces being usually rounded while those in the buccal and labial sulci are usually more elongated. When the lesion is of long standing it frequently becomes deeper and the margin may be raised and rolled (Farmer, 1958); punched out (Rushton and Cooke, 1959); shallow crateriform ulceration which has regular, sharply delineated
margins; not undermined (Driscoll et al., 1959); the margins are regular and are not undermined (Ship et al., 1960a); raised red rampart-like margins (Cooke and Armitage, 1960); crateriform ulcer with firm inflamed borders (Thoma and Goldman, 1960); oval ulcer (Schaffer, 1960); shape largely determined by the site, being oval or round on the lips and cheeks, and linear in the buccal sulcus; crater-like, punched-out appearance, with raised red rampart-like margins (Cooke, 1961); round or oval (Ship et al., 1961b) deep and crater-like, with red-inflamatory indurated edges (Claus et al., 1961); regular, sharply delineated margin (Ship et al., 1961c); rounded or oval with irregular peripheries (Dalmau, 1961); the outline of the ulcer depends on the site of origin, those appearing on flatter surfaces usually being rounded while those in the buccal and labial sulci are usually more elongated. When the lesion is of long standing it frequently becomes deeper and the margin may be raised and rolled (Stones, 1962); lesion is round to oval and has a very regular margin which is not undermined; a very regular saucer-shaped crater is formed (Ship, 1963a); round to oval (Shafer et al., 1963); circular (Engelman, 1963); the margins of the ulcer are somewhat indurated; sharply defined rounded ulcer, relatively deep (McCarthy and Shklar, 1964); circular, oval or irregular (Scott, 1965); sharply delineated margins which are not undermined (Ship, 1965a); the margin is slightly raised but there is only a little induration; shape depends partly on site; those on lip or cheek mucosa usually
rounded or reniform, whilst on sulci or on floor of the mouth they tend to be elongated (Kramer, 1965); varying shape, margins indurated (Huebsch, 1965); round to oval crateriform lesions (Levin, 1965); round to oval superficial ulceration (Bhaskar, 1965); regular, sharply delineated margins which are not undermined (Brightman and Ship, 1966); well-defined ulceration (Samitz and Dana, 1967); rolled edges, usually symmetrical (Collins, 1968); regular, sharply defined margins; shallow ulcer (Review Article, 1968 452); usually circular and may be well circumscribed or irregularly defined (Brody and Silverman, 1969); sharply defined, rounded ulcer (Qheldemi et al., 1970); regular border, some may coalesce (Weathers and Griffin, 1970); margins are usually rolled and indurated and may or may not be inflamed (Francis, 1970)

Failure to separate major and minor aphthous ulcers may account for certain discrepancies in the above descriptions: the degree of induration, the rampart-like margins mentioned by some and not by others, and perhaps even the apparent regularity of the outline.

Despite the fact that some describe the peripheries as irregular, most state that the ulcer is of a regular outline and usually rounded, unless its location imposes a more linear shape upon it. The description of raised, rampart-like margins and surrounding induration can be assumed to apply to the major form of the disease. The edges are not undermined; there seems to be a general agreement upon a punched-out appearance.
8. Widespread and systemic effects.

evidence of sepsis is not constant; constitutional disturbance does not seem to occur in the grossly recurrent cases, but occurs in some cases two or three days before the appearance of the ulcers; except in severe attacks the regional lymph glands do not enlarge (Whitwell, 1934); none of the seven adults gave a history of fever or was found to have fever when examined; two of the four children had fever; marked gingival swelling or bleeding was not seen (Dodd and Ruchman, 1950); no associated diffuse redness of the gingivae as often seen in herpetic stomatitis (Stark et al., 1954); the associated lymph nodes may become involved (Sutherland, 1959); slight fever may be present if several ulcers occur together (Queries and Minor Notes, 1959^{435}); usually there are no systemic manifestations, but with extensive ulceration there may be a low grade fever, leukocytosis, cervical adenitis and general debility. There may or may not be evidence of secondary infection (Ship et al., 1962); there is no accompanying pyrexia (Stones, 1962); a variable amount of oedema and adjacent inflammation may be seen (Ship, 1963a); few systemic manifestations; in cases of extensive ulcerations there may be low-grade fever, cervical lymphadenopathy and malaise (Shafer et al., 1963); constitutional involvement is absent (McCarthy and Shklar, 1964); there is little if any oedema or systemic reaction (Ship, 1965a); little constitutional disturbance (Kramer, 1965); unassociated with any general disturbance (Scott, 1965); variable levels of oedema develop in the adjacent tissues (Brightman and Ship, 1966); usually no fever, but slight fever may occur in periadenitis type; a
generalized oedema of the oral cavity characterized by swelling of the tongue and oral mucosa was commonly seen. This sign has not previously been described (Graykowski et al., 1966); not preceded by or associated with an elevated temperature, regional node involvement, or secondary infection (Francis, 1970);

Systemic manifestations and widespread erythema are usually associated with ulcers of viral origin, but may be seen in severe cases of aphthous ulceration or, presumably, as the result of secondary inflammation. Most contributors mentioning this aspect of the lesions refer to a lack of systemic or widespread tissue involvement in normal aphthous ulcers. Graykowski and co-workers, who described a generalised oedema, were considering the major form of the disease.


extremely tender (Whitwell, 1934); severity varied from one which produced only mild annoyance to one which kept the patient from eating or sleeping for several days (Dodd and Ruchman, 1950); highly sensitive and painful (Kutscher et al., 1953); pain is a prominent symptom and may be so severe that nutrition is impaired (Stark et al., 1954); considerable disability (Sircus et al., 1957); the ulcer is usually painful, sensitive to movements of the tissues and to irritants (Farmer, 1958); these lesions are extremely painful, and eating, talking and other facial movements can become difficult manoeuvres. The pain appears to be out of proportion to the clinical appearance of the actual lesions (Driscoll et al., 1959); highly sensitive, especially to acid food such as the fruit juices; and the pain seems to radiate over the entire mouth and face
(Schaffer, 1960): painful ulcerations (Ship et al., 1960b); highly sensitive, especially to acid food, and there is pain which often extends over the entire face (Thoma and Goldman, 1960); painful and disturbing (ship et al., 1961b); very painful, consequently eating, speaking and other manoeuvres necessitating facial movements can be difficult (Ship et al., 1961c); the ulcer is exquisitely painful, but after two to three days there is an abrupt transition from the pain to discomfort only; on occasion, an ulcer will assume large proportions, and the associated pain may interfere with speech and the proper intake of food (Cooke, 1961); the local discomfort may prevent the patient eating a normal diet (Stones, 1962); it appears that susceptible persons voluntarily modify their diets to avoid foods containing ascorbic acid either because of fear of initiating new lesions or due to the pain and oral debility incumbent on their contact with existing lesions (Ship, 1963b); can be so painful that in the severest cases the patient cannot or is reluctant to eat (Ryan, 1963); the local lesions may be so painful as to seriously restrict eating for several days (Shafer et al., 1963); probably the most painful and irritating of all ulcerative lesions involving the oral mucosa. The discomfort may vary in degree, becoming more intense in the evening when fatigue sets in (McCarthy and Shklar, 1964); painful (Bhaskar, 1965); extremely painful; eating, speaking and other facial movements may be difficult. Indeed the pain often appears to be disproportional to the appearance of the lesions (Ship, 1965a); most painful of all ulcerations of the oral cavity (Huebsch, 1965); painful ulcers (Levin, 1965); the initial lesions are generally
reported to be mildly sensitive, whereas acute pain and discomfort usually follow within twenty-four hours. Eating, speaking and other facial movements may be painful, and the patient often avoids food, social contacts, and may even absent himself from work. The pain, however, frequently seems to be inconsistent with the degree of tissue damage. During the first twenty-four hours, the lesion grows in size, and acid and spicy foods aggravate the symptoms, causing the patient to seek relief (Brightman and Ship, 1966); intense oral pain, localized hyperaesthesia (Graykowski et al., 1966); often begins as a raw, burning pain (Samitz and Dana, 1967); varies from a trifling affair to one of incapacitation interfering with nutrition (Gold, 1967); painful oral syndrome usually mild, but when severe gives extreme pain (Ship et al., 1967); acute pain and discomfort usually are felt within twenty-four hours. Eating, speaking and other facial movements may be painful. Frequently, the intense pain seems to be inconsistent with the slight degree of tissue damage (Review Article, 1968); severe pain often leads to dysphagia and anorexia, while secondary depression aggravated by sleepless nights adds to the patient's misery (Leading Article, 1969); an early aphthous ulcer is usually felt as a burning sensation; later when the ulcer is established, pain may become intense (Pindborg, 1968); some patients have deep, persistent, and painful lesions at all times (Brody and Silverman, 1969); severity of pain is variable from one patient to another, but is usually of moderate intensity (Weathers and Griffin, 1970);
all patients complained of distress approximately two to three days following formation of the ulcer (Chellemi et al., 1970); an inordinate amount of pain and discomfort is a striking clinical feature (Francis, 1970)

All attest to the painfulness of these lesions; some regard them as the most painful of all oral ulcerations and others remark that the degree of pain appears to be out of all proportion to the amount of tissue damage. The pain in the case of major ulceration can be crippling.

Because of the constant pain associated with the disease in some patients, several have been reported as having been reduced to the contemplation of suicide (Kingsley, 1964; Schaffer, 1960) whereas others have become emaciated (Birt and Mather, 1968).

10. **Healing time.**

duration anything from one to eight weeks, the commonest time being about ten days (Whitwell, 1934); last up to two weeks (Rosenstein and Ziskin, 1942); heal in six to eight days (Strauss, 1947); in most instances heal in ten to fourteen days (Kutscher et al., 1953); usually heal in ten to fourteen days (Zegarelli et al., 1953); one to six weeks (Stark et al., 1954) heal in ten days (Jawetz, 1955); heal in about a week (Truelove and Morris-Owen, 1958); usually the healing starts after about six days and is complete within ten to fourteen days (Farmer, 1958); persist from seven to nineteen days (Driscoll et al., 1959); may take weeks to heal (Rushton and Cooke, 1959); most ulcers last
from eight to twelve days (Cooke and Armitage, 1960); persist for one to three weeks (Ship et al., 1960a); one to three weeks (Ship et al., 1960b); whereas a simple traumatic ulcer heals in three to four days, these ulcers take three or more times longer to heal. Yet, if an ulcer is excised, the site of excision heals normally. What it is that prevents these ulcers from healing is just as difficult to explain as why they form at all; may take ten to fourteen days or longer to heal (Cooke, 1961); ten to fourteen days (Dalmau et al., 1961); ten to fourteen days (Colby et al., 1961); persist from two to fifteen days (Ship et al., 1961b); ulcer persists seven to twelve days (Ship et al., 1961c); healing starts after about six days and is complete within ten to fourteen days (Stones, 1962); ulcers generally persist for seven to fourteen days and then heal gradually (Shafer et al., 1963); usually completely healed without scarring in ten to fourteen days (McCarthy and Shklar, 1964) ten to fourteen days (Huebsch, 1965); persist for one to three weeks, depending upon size, location and the patient's individual characteristics (Levin, 1965); self-limiting, lesions healing spontaneously in one to two weeks (Bhaskar, 1965); last seven to fourteen days (Kramer, 1965); four to fourteen days (Lehner and Sagebiel, 1966); heals within two weeks (Getz and Bader, 1967); lesion persists for a variable time, usually one to three weeks (Samitz and Dana, 1967); four to fourteen days (Lehner, 1967c); seven to ten days (Collins, 1968); ordinarily the ulcers persist for four to twenty days, depending on their location.
(Review article, 1968); ten to fourteen days (McFall, 1968); most heal in one to three weeks (Pindborg, 1968); most lasted one to two weeks (Lehner, 1968); heal spontaneously in ten to fourteen days (Brody and Silverman, 1969); heal mostly within ten days (Weathers and Griffin, 1970); healing occurs within ten to fourteen days (Francis, 1970).

It appears that individual lesions usually heal within two weeks. Those taking longer are probably the major variety, which may greatly exceed the usual healing time. In either case the lesion requires more time to heal than the amount of tissue damage would indicate. As Cooke remarks, the healing time is three or more times longer than that of a simple ulcer, and, as noted by Cooke (1961) and Ship et al. (1962) lesions that were biopsied early healed in a shorter time. Interestingly, Durocher (1966) found that trauma from a blade used to obtain cytologic scrapings also shortened the healing time.

Cooke (1961) states that ulcers may initially be small and infrequent, but after a varying time they become more frequent, larger, and take longer to heal. This period of latency seems to apply especially to females (Cooke, 1961).

11. Healing characteristics

It can be inferred that, apart from the unusual healing time, resolution proceeds normally. Most authors would no doubt agree with Gardner (1970) that healing is uneventful and complete epithelialization takes place. However, Brightman and Ship (1966) provide some clinical comments worth repeating:
"Ulcers on the tongue are often several millimetres in depth, and pink granulation tissue containing the buds of regenerating filiform papillae often presents an unusual appearance as healing proceeds. Aphthous ulcers on the uvula and fauces are the slowest to heal and frequently satellite ulcers coalesce to form large areas of continuous shallow ulceration. In these regions, islands of regenerating mucosal tissue interspersed with petechial haemorrhages, ulcerated tissue and erythema frequently present a bizarre clinical picture, quite different from that of the solitary, rapidly healing ulcer, and suggestive of more serious disease entities. Local lymphadenopathy is usually part of this picture."

Ship (1963) stated that the ulcers heal from the margins towards the centre. This is self-evident.

Cooke (1961) says that ulcers which occur over fibrous and muscle bands, such as frenæ, often last longest and are most painful. Often, he continues, large ulcers form on the scar tissue of previous ones.

12. **Scarring**

the more severe ulcers leave depressed atrophic scars (Whitwell, 1934); generally heals without a scar (Cahn and Bartels, 1942); heals with or without scar formation (Stark et al., 1954); the minor form heals without scarring (Truelove and Morris-Owen, 1958); deep ulcers that heal with a scar were designated periadenitis mucosa necrotica recurrens. In other ulcers scar formation was uncommon and usually appeared in those sites that could be easily damaged by teeth; (Farmer, 1958);
Other ulcers appearing in the same patients usually healed without scar formation (Farmer, 1958); heals without leaving a scar (Driscoll et al., 1959); only long-standing ulcers heal with a scar (Cooke, 1961); only long-standing ulcers heal with a scar (Cooke and Armitage, 1961); heal uneventfully without scarring (Ship et al., 1961b); no scar (Ship et al., 1961c); no scarring (Colby et al., 1961); obvious scar tissue formation resulting from the healing lesion is uncommon, except in those sites that are readily damaged by the teeth; even severe scarring usually disappears after about twelve months (Stones, 1962); no evidence of scarring (Shafer et al., 1963); heals without scarring (McCarthy and Shklar, 1964); usually leave no scars, but in an occasional case lesions are large and deep and produce considerable scarring after long duration (Ship, 1965a); heals without scarring (Huebsch, 1965); scarring rarely occurs (Brightman and Ship, 1966); no scar formation except for periadenitis type (Graykowski et al., 1966); heals without scar formation (Collins, 1968); no scar (McFall, 1968); heals without scarring (Francis, 1970).

As in other sections, most authors have not distinguished among the various types of lesions. One who has, however, is Lehner (1968), whose findings are therefore worth repeating in more detail. Scar formation resulted as follows:
<table>
<thead>
<tr>
<th></th>
<th>Total No.</th>
<th>Total %</th>
<th>Males No.</th>
<th>Males %</th>
<th>Females No.</th>
<th>Females %</th>
</tr>
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<tbody>
<tr>
<td>Minor aphthous lesions</td>
<td>11/133</td>
<td>8</td>
<td>6/58</td>
<td>10</td>
<td>5/75</td>
<td>7</td>
</tr>
<tr>
<td>Major aphthous lesions</td>
<td>16/25</td>
<td>64</td>
<td>9/14</td>
<td>64</td>
<td>7/11</td>
<td>64</td>
</tr>
<tr>
<td>Herpetiform ulcers</td>
<td>7/19</td>
<td>32</td>
<td>3/5</td>
<td>60</td>
<td>4/14</td>
<td>28</td>
</tr>
<tr>
<td>Behcet's syndrome</td>
<td>6/25</td>
<td>24</td>
<td>2/10</td>
<td>20</td>
<td>4/15</td>
<td>33</td>
</tr>
</tbody>
</table>

Comments on Lehner's findings:

1. Inasmuch as scar formation occurs in all varieties, it cannot be said to be diagnostic; however, in conjunction with other clinical signs, it is a helpful criterion of the major variety. Unfortunately Lehner does not stipulate his diagnostic criteria of major aphthous ulceration; the differentiation is obviously somewhat arbitrary.

2. As Lehner himself remarks, healing with scar formation probably depends on the extent of the lesion and the degree of secondary infection.

3. The presence of scarring in minor aphthous and herpetiform lesions seems surprising, especially in view of Lehner's relating the presence of scars to the degree of tissue destruction. He does not state how long scars persist.

4. Sexual differences with respect to scarring may be due to the small numbers of cases, although scarring in 60% of herpetiform ulcerations in males as against 28% of females seems to warrant further investigation.
Lehner states that most of the scars were initially stellar, but in a few patients with major aphthous ulceration they were more extensive and tethered down so as to cause a puckering of the mucosa. Microstomia has been reported to result from severe and prolonged involvement of the oral mucosa with aphthous ulceration.

Generally speaking, the minor variety of aphthous ulceration heals without scarring. The presence of scarring can be used as one criterion of the presence of the major form of the disease.

13. **Summary:**

The following composite account of the clinical appearance of the minor form of the disease is presented:

The lesion is heralded by a prodromal localized burning sensation for up to twenty-four hours. Then a macule appears, consisting of a small thickened and reddened area, which becomes ischaemic and ulcerates. There is no clinical sign of a vesicle. The central necrotic area is a light yellow or light grey in colour, covered by a fibrinous exudate, and surrounded by a narrow discrete zone of hyperaemia. Beyond that, the surrounding tissues are normal. The ulcer is rounded, except when its situation causes it to assume a more elongated shape, and its margins are usually regular and are not undermined. Systemic effects are absent, but localized pain can be exquisite. Complete healing takes place within two weeks, without scarring.

Details of size, number of ulcers in each attack, population incidence, frequency, etc., are presented in the following chapter.
CHAPTER 4 - STATISTICAL DETAILS

1. Size of individual lesions:

varies from a pin’s head to an inch in diameter (Whitwell, 1934); rarely more than 2 by 3 mm. (Thoma, 1946, 1950, 1956); commonly 1 to 12 mm. in size, but occasionally 2 or 3 cm. (Kutscher et al., 1953); commonly 1 to 12 mm. in size, but occasionally 2 or 3 cm. (Zegarelli et al., 1953); gradually increases in size for 3-6 days; ranging in size from a pin head to up to 2 cm. (Farmer, 1958); 2-20 mm. in diameter (Ship et al., 1960a); often 0.5 to 1 cm. in diameter (Cooke and Armitage, 1960); rarely more than 2 by 3 mm. (Thoma and Goldman, 1960); rarely more than 2 or 3 mm. (Schaffer, 1960); an occasional ulcer may be 2 cm. in diameter (Cooke, 1961); usually from 1 to 12 mm. but occasionally 2 to 3 cm. (Dalmau et al., 1961); 5 to 10 mm. (Ship et al., 1961b); about 1 cm (Ship et al., 1961c); size ranges from that of a pinhead up to 2 cm. or more in diameter (Stones, 1962); 2-3 mm. usually, but up to 30-40 mm. (Ship et al., 1962); occasionally lesions form which achieve the size of 2 to 3 cm. in diameter and several millimetres deep (Ship, 1963a); may be tiny or large, many millimetres in diameter (Engelman, 1963); 2-3 mm. in diameter (Ryan, 1963); 2 to 40 mm. (Shafer et al., 1963); varies from 2 to 5 mm. in diameter (McCarthy and Shklar, 1964); 2-20 mm. in diameter (Bhaskar, 1965); varying size (Huebsch, 1965); 2 to 5 mm. (Scott, 1965); in an occasional case the lesions are as large as 2 or 3 cms. in diameter and 3 to 4 mm. in depth (Ship, 1965a);
in occasional instances lesions as large as 2 to 3 cm. in diameter and 3 to 4 mm. in depth (Brightman and Ship, 1966); 2 to 10 mm. (Bishop et al., 1967); 2 mm. to 1 cm. (Ship et al., 1967); 1 mm. to 1 cm. (Collins, 1968); 1 to 2 mm. up to 55 mm. (Pindborg, 1968); pinpoint to 0.5 cm. (Brody and Silverman, 1969); 1 to 4 mm. in diameter (Chellemi et al., 1970); rarely smaller than 3 mm. (Weathers and Griffin, 1970);

As in the previous chapter, most authors did not specify the type of lesion they were describing. As the diagnosis of major aphthous ulceration appears to be quite arbitrary, it is suggested that a diameter of 1 cm. be adopted as one of the clinical criteria for the diagnosis of the major form of the disease. (This appears to have been a criterion adopted by Lehner, 1968).

Greykowski et al. (1966) reported the size distribution of a series of 62 cases as follows: "The diameter of the lesions was 10 mm. or greater in 6 patients (9%), 7 to 10 mm. in 19 patients (30%), 4 to 6 mm. in 23 patients (37%), and 2 to 3 mm. in 14 patients (22%). The largest lesion seen was 55 mm."

Inasmuch as he is the only one to divide non-herpetic oral ulcers into their various types, Lehner (1968) is worth citing more closely. Lehner found that the herpetiform group had the largest proportion of ulcers less than 3 mm. (42%) and the proportion would have been much greater if the lesions had been graded before individual ulcers had begun to coalesce.
Of ulcers greater than 10 mm, the highest frequency was, naturally, among the major aphthous lesions (80%). Most of the minor variety (83%) and Behcet's syndrome lesions (64%) were 3 to 10 mm in size. No marked variation in the size of the ulcers was shown with age and sex. An important difference in the mode of enlargement was revealed. Both major and minor aphthous lesions gradually increased in size, whereas herpetiform lesions coalesced to form a larger ulcer.

2. **Duration of the disease:**

from several months to up to six years (Rosenstein and Ziskin, 1942); 65 - 70% of patients had the disease from 1 to 14 years, while 30% had it for 15-40 years; there were no significant sex differences (Sircus et al., 1957); ulcers are multiple, and the patient may seldom, if ever, be free from them over a course of years (Truelove and Morris-Owen, 1958); 65% had the disease for 1 to 14 years, 30% for 15 to 40 years; no sex differences (Theron, 1959); 50% of both sexes gave a history of ulceration from 1-5 years; 33% of the males and 20% of the females 6 to 15 years; and 17% of the males and 30% of the females 16 to 40 years (Cooke, 1961); after 20 or 30 years, the attacks subside. Probably, as with some psychosomatic conditions such as asthma, duodenal ulcer and migraine, the condition "burns itself out" (Lancet, 1964\(^{303}\)); the onset is usually between the ages of 10 and 20; the lesions rarely occur for the first time after the age of 50 (Brody and Silverman, 1969); the lesions characteristically begin in childhood or early adulthood and usually remain status quo throughout the course of the disease (or the lifetime of the patient); in rare instances there may be a spontaneous remission after several years (Francis, 1970)
This aspect of the statistical details has not received much attention in the literature; figures relating to it are probably unreliable, as it is not possible to check out individual histories. Again, Lehner (1968) is unique in specifying the various clinical types. He found that the highest incidence of ulceration lasting over 15 years was in male patients with major aphthous ulceration (64%). The highest incidence lasting up to 5 years was in males with herpetiform lesions (60%). Generally speaking, the duration of the disease was longer in patients with major aphthous ulceration and Behcet's syndrome and shorter in minor aphthous ulceration and herpetiform ulceration.

3. **Site of occurrence:**

   anterior part of buccal cavity, under the tongue, inside the lower lip and inside the cheeks are the favourite places (Whitwell, 1934); various locasions on the mucous membranes, rarely on the gingivae (Rosenstein and Ziskin, 1942); occur on the mucosa of the lip, in the reflection of the mucous membrane, in the fold on the floor of the mouth, or on the alveolar gingiva (Thoma, 1944, 1950, 1954); anywhere on the oral mucosa, on the gums, the inside of the lips, on the cheeks, tongue, floor of the mouth, on the uvula and the fauces as far back as the pillars of the fauces (Strauss, 1947); occurred on inner surfaces of lips, the buccal mucous membrane, or more rarely at the gingivo-dental margin or on the palate. Lesions on the tongue occurred around the edges or on the tip (Dodd and Ruchman, 1950); anywhere in the oral cavity (Kutscher et al., 1953); anywhere
on the oral mucosa (Zegarelli et al., 1953); buccal mucosa, buccal sulcus, lateral margin of the tongue, mucosal surface of lips, floor of mouth, soft palate and gingivae (in order of decreasing frequency). Lesions of marginal gingivae are rarely seen (Stark et al., 1954); the sites of election were the inside of the cheeks opposite the molar teeth in the upper jaw, and inside the upper and lower lips, the upper and lower sulci were also commonly involved (Sircus et al., 1957); mostly occur on inside of cheeks opposite the molar teeth, inside the lips, and occasionally on the tongue, although any part of the mouth or pharynx may be affected (Truelove and Morris-Owen, 1958); anywhere on the oral mucosa and on the tongue (Farmer, 1958); the labial and buccal mucous membranes are the most common sites, particularly in the mucosal folds. The tongue, floor of the mouth, palate and gingivae are also affected, but less frequently (Driscoll et al., 1959); cheek, lip or tongue; the sites of ulceration are to a large extent determined by trauma (Rushton and Cooke, 1959); occur on the mucosa of the lip, in the reflection of the mucous membrane, in a fold in the floor of the mouth, or on the alveolar gingiva (Thoma and Goldman, 1960); mucosa of the lip, in the reflection of the mucous membrane, in the floor of the mouth, or on the areolar gingiva (Schaffer, 1960); labial, buccal, lingual and sublingual, gingival, and palatal mucosa (Ship et al., 1960a); labial mucosa, cheeks, tongue, gums, palate (in
decreasing order of frequency) (Ship et al., 1960c); non-keratinized mucosa; site determined largely by trauma and is commonly the lower lip, commissures, buccal sulci, or lateral margins of tongue (Cooke and Armitage, 1960); they may appear anywhere in the oral cavity (Dalmau et al., 1961); the minor form occurs on the non-keratinized mucosa only, whereas herpetiform ulceration occurs on any part of the mucosa. Trauma is often the localizing factor (Cooke, 1961); appears anywhere on the oral mucosa but rarely on the hard palate (Stones, 1962); mucosal surfaces of lips, cheeks, tongue, palate, gingivae and pharynx (Ship et al., 1962); inner aspect of the lips, the reflection of the mucous membrane, the floor of the mouth, and elsewhere (Ryan, 1963); mucous membranes of the lips, cheeks, tongue, palate, gingivae, floor of mouth, or pharynx (Shafer et al., 1963); the labial and buccal mucous membranes are the most common sites. It is unusual to find aphthous ulcers anterior to the wet line of the lips. The tongue, floor of mouth, palate and gingivae may also be affected, but less frequently (Ship, 1963); may occur in any area of the oral cavity. Common sites are the tongue, buccal mucosa, mucous membrane surface of the upper and lower lips, hard palate, and mucobuccal fold. The sites of involvement tend to vary with recurrent episodes (McCarthy and Shklar, 1964); may occur in any area of the oral mucosa (Huebsch, 1965); labial, buccal, lingual and sublingual gingivae
and palatal mucosa (Levin, 1965); inside of lip, cheek, tongue, floor of mouth, palate and gingiva (Bhaskar, 1965); the labial and buccal mucous membranes are the most common sites. It is unusual to find aphthous ulcers anterior to the wet line of the lips. The tongue, floor of the mouth, palate and gingivae are also affected but less frequently (Ship et al., 1965a); the oral mucosa lining the cheek opposite the upper molars, and within the upper and lower lips are the sites of election. The tongue, fauces and pharynx are often affected as well (Scott, 1965); the areas usually affected are those most susceptible to trauma, such as the lips and cheeks. Among 715 students, the labial sulci and the moist mucosa of the lips and cheeks presented over 60% of the lesions, while gingival, lingual, palatal and pharyngeal ulcers occurred less frequently (Brightman and Ship, 1966); the minor type affects the non-keratinized mucosa, the herpetiform type any part of the oral mucosa (Lehner and Sagebiel, 1966); buccal and labial mucosa, buccal and lingual sulci, tongue, soft palate, pharynx and gingiva (in decreasing order of frequency) (Graykowski et al., 1966); the lesions may occur anywhere on the oral mucosa from the mucocutaneous border back to the fauces (Getz and Bader, 1967); the labial, buccal and lingual areas are the most favoured sites, although the sublingual, gingival and palatal mucosa may also be affected (Samitz and Dana, 1967); rarely seen in areas of the mouth where there is good keratinization; Carruthers, 1967),
The hard palate is rarely involved, but the buccal mucosa where the surface layer is non-keratinized is a common site for aphthous ulceration (Carruthers, 1967); moist mucosa of the lips or cheeks (Ship et al., 1967); the minor type affects non-keratinized mucosa (Kramer, 1967); the minor type affects the non-keratinized mucosa, the ḏepetiform variety affects the keratinized as well as the non-keratinized (Lehner, 1967c); usually develop in areas of the mouth most susceptible to trauma, such as the lips, cheeks, tongue, palate and gingiva (Review Article, 1968 452); seen most frequently on labial and buccal mucosa (Pindborg, 1968); minor type confined to non-keratinized mucosa (Cooke, 1969); lesions are located on the movable mucous membranes - the lips, buccal mucosa, tongue, and particularly in the mucobuccal fold. Lesions of the hard palate and gingiva are rare (Weathers and Griffin, 1970); lesions predominate on the labial and buccal mucosa (Chellemi et al., 1970); occur most frequently on mucosal surfaces and less frequently on the heavily keratinized tissues (that is, attached gingiva ). They are commonly seen in the areas of the mouth associated with the most trauma (such as lips, buccal mucosa), but they can occur at any location from the attached gingiva, to the tip of the uvula, to the pharynx and larynx (Francis, 1970)
Despite the number of entries, there is a reasonable measure of agreement. The non-keratinized mucosa appears most commonly involved. Indeed, the authoritative British writers, Cooke, Kramer and Lehner, state that the minor variety of aphthous ulcers involves only the non-keratinized mucosa, whereas the herpetiform type involves the keratinized as well as the non-keratinized mucosa, and this may be a useful diagnostic sign. Unfortunately, most authors do not differentiate among the various types of ulcers. Lehner, who does, found that, except for the lips and cheeks, there are differences in the sites of ulceration among the various types. The involvement of the tongue, floor of mouth, palate, gum and pharynx rose progressively from minor to major aphthous ulceration, Behcet's syndrome and herpetiform lesions.

4. Population incidence:

there was an overall prevalence of 19.3% in a hospital outpatient population (Sircus et al., 1957); more than a million people in the British Isles are affected (Truelove and Morris-Owen, 1958); an incidence of 57.3% was found among 749 female students (mean age 19.1 years) and 52.4% among 1,039 male students (mean age 23.7 years) (Ship et al., 1960a); 20% in a sample population (Spouge and Diamond, 1963); estimated to occur in about 60% of the population (Bhaskar, 1965); estimates of incidence vary from 15% to more than 50% of the population (Brody and Silverman, 1969)

There are very few studies of population incidence of any consequence. The two largest are those of Sircus et al. (1957) and Ship et al. (1960a) with 1,738 and 1,788
subjects respectively. The former study comprised mainly patients attending hospital out-patients' clinics in an industrial area, with the addition of other patients from somewhat higher socio-economic groups. The study of Ship and his colleagues was of a professional school student population. The respective incidence figures, without regard to sex were 19.1% and 54.8%, a remarkable difference.

Cooke (1961) stated that the figures of Sircus et al. included all three types of ulceration, major, minor, and herpetiform, and presumably Ship's study did too.

Many authors quote the findings of Sircus and/or Ship: Driscoll et al. (1959), Stones (1962), Shafer et al. (1963), McCarthy and Shklar (1964), Getz and Bader (1967), Gold (1967), Samitz and Dana (1967), Pindborg (1968), and Francis (1970).

The figure of 54.8% given by Ship and his colleagues appears much higher than one would have expected, and may be inflated as a result of selection factors relating to the limited population. McCarthy and Shklar (1964) state that it is possible that a professional school student group would present a greater incidence than the general population. Their own experience, they state, tends to support this conclusion, which may be explainable by emotional factors.

However, in a further study of a student body, Ship et al. (1967) found an incidence of 66.2% in a population of 343. This compared with a 13.2% incidence among 242 hospitalized patients. Thus there was a ratio of 5:1 between the student sample and the hospital sample. The difference was said to depend upon socio-economic factors.
Whitwell (1934) stated that the condition is more common than would appear from hospital records, for many cases cease attendance after discovering that the physician cannot help them.

McFall (1968), quoting an American public health publication, gave the prevalence as from 20 to over 50% of the population. These figures, however, are too similar to those of the two large-scale studies cited to have been arrived at independently. Obviously a larger and more representative study is required, one with a completely randomized selection of subjects.

5. Sexual incidence:

the number of female clinic patients with recurrent aphthae was considerably greater than the number of males with this disorder. This frequency may be biased, however, since females with minor complaints are more apt to attend daytime clinics than are working males (Stark et al., 1954); one in four female subjects (1:4.3) and one in six male subjects (1:5.9) were affected. The sexual difference was most marked after age 50, due to postmenopausal factors. The overall difference is partly a reflection of the fact that women have more opportunity to attend day-time surgeries and clinics (Sircus et al., 1957); 80 females and 41 males comprised the study (Farmer, 1958); the condition is seen more commonly in females (Sutherland, 1959); 31 out of 46 patients were females (Theron, 1959); 52.4% of male students and 57.2% of female students had positive histories of the disease (Ship et al., 1960a); the incidence among females (32%) was higher than among males (13%).
52.

The explanation is not obvious, but females seemed to have better recall, whilst men were more inclined to produce an initial false negative, leaving positive symptoms to be elicited only by more detailed inquiry or resort to hospital records (Spouge and Diamond, 1963); there is general agreement that the young woman is the most likely candidate for this painful disease (Dent. Abstr. 670); slightly more common in females (Bhaskar, 1965); 71% of the patients were female (Graykowski et al., 1966); a slightly higher incidence among females, especially in the herpetiform group (Lehner, 1968); twice as frequent in female patients (Brody and Silverman, 1969).

Many authors have been impressed with the occurrence of aphthae in women, especially in connection with the menstrual cycle. This is discussed in the chapter on endocrine disturbance. Euler (1951) and Strauss (1947) considered the disease virtually confined to women, but this contention has been destroyed by later studies as shown above.

Ship and co-workers (1960b) state that the differences between male and female incidence figures are not understood, but mention the association between severe aphthous ulcerations and mental stress. They found that 18% of female students with severe forms of the disease associated aphthous lesions with the onset of the menstrual cycle, whereas only 3.8% of those with mild aphthous disease made this association. In a later publication (1961a), they failed to detect any meaningful correlation between aphthous disease and menstruation.
Increased activity of the lesions was seen during examination times and reduced activity during vacations. This tends to support the emotional factor, but the authors also mention the possibility of general fatigue.

Most recent contributions suggest a slightly higher incidence among females, although many of these are obviously quoting the findings of Sircus and his co-workers; they include Driscoll et al. (1959), Shafer et al., (1963), McCarthy and Shklar (1964) and Getz and Bader (1967).

6. Age incidence:
occurs mainly in adults (von Mikulicz and Michelson, 1892); the date of onset is often in childhood, but sometimes in adult life (Whitwell, 1934); rarely occurs in adults, but frequently met with in rachitic and weakly children, and is most common during the periods of dentition. In adults it occurs in those debilitated by illness, or may be associated with general inflammatory conditions. In women it occurs during menstruation, pregnancy, and during the puerperal period (Colyer and Sprawson, 1942); mostly appear in the age groups from early adolescence right through to late middle age. Occasionally they occur in children, but here the clinical picture is somewhat different (Strauss, 1947); the age range of 17 patients was 4 to 55 years (Bergman, 1954); in a series of 120 cases, the greatest number of initial lesions occurred in the second decade, and in more than 50% of the patients the onset of the disease occurred between the ages of 10 and 30. In females the recurrence rate was highest in the third decade.
and remained high through the eighth decade. In males the rate fell sharply after the fifth decade and no lesions were observed in the seventh. Thus persons of both sexes and almost all ages are susceptible. One of every ten women experienced the first episode of mouth ulcers as late as age 50. The difference between male and female incidence after middle age is almost entirely due to the occurrence of first attacks in the post-menopausal age group. The youngest patient was aged 11 months (Sircus et al., 1957); in a series of 121 patients the more common age of onset in the female was during the first two decades, the lesions becoming severe in the second and third decades, while in the male the ulcers started and also became more severe in the first and third decades. When the early age groups were split up into five-year groups it was found that while 61% of males start having ulcers before the age of 15, only 48% of females fell into this group. Again, while no males were recorded with onset between the ages of 15 and 20, this five-year period contained 25% of females. These findings may indicate that onset is not influenced by puberty. Unfortunately the number of males and females over age 45 was insufficient to draw any conclusions about the effect of the menopause. The probable lack of sex influence in the under forties is confirmed when the results of this study are combined with those of Sircus and his colleagues. The percentage of males and females in each group is almost exactly the same up to age 40. Thereafter, the numbers are probably too small to justify conclusions (Farmer, 1958); common in
children and young adults (Tuft and Girsh, 1958); in both sexes the onset of disease occurs most frequently in the second decade. In the female the incidence is highest in the third decade and remains high through the eighth decade of life, whereas in the male the peak diminishes rapidly after the fifth decade and disappears by the end of the seventh (Driscoll et al., 1959); occur both in children and adults (Thoma and Goldman, 1960); in a series of 90 patients, the highest incidence for both sexes was in the second decade, 50% of the females and 42% of the males. The peak incidence for females was between 10 and 14 years of age and for males 15 and 19 years of age. 73% of all patients were in the second and third decades (Cooke, 1961); the age of onset is commonly during the first or second decade of life but may be much later (Stones, 1962); more often affects adults (Burnett and Scherp, 1962); the majority of patients report onset of the disease between the ages of 10 and 30 years (Shafer et al., 1963); the greatest number of cases occur in the second decade of life (Dent. Abstr., 1963, 670); occur at all ages with greatest frequency in young adults (McCarthy and Shklar, 1964); usually starts in the late teens or early twenties. After 20 or 30 years the attacks subside, and this condition rarely is seen in patients over 60 years of age (Lancet, 1964 303); the first attack may occur in the first few months of life but most commonly the onset is between the ages of 10 and 20 years. Thereafter the incidence of first attacks declines steadily and
few individuals develop the disorder after age 50; almost all of those who have such a late onset are women (Kramer, 1965); usually occurs first between 10 and 30, although in about 10% of women the onset is delayed until after 50 (Scott, 1965); in a series of 62 cases, the range was 3 to 68 years, the mean 33 years (Grajewski et al., 1966); the lesions occur at all ages (Getz and Bader, 1967); the severity of the disease was directly associated with the age of the patient at onset in both student and hospital samples. In the student sample, 90% of those who had reported frequent recurrences had initial manifestations during the first decade, whereas those who reported occasional or rare attacks only, experienced onset during the first decade with decreasing frequency i.e., 75% and 60% respectively (Ship et al., 1967); although one tends to think of this condition in connection with adults, the onset may be early in childhood. As these lesions are characteristically recurrent, they constitute a considerable proportion of the total of mouth ulcers in children (Kramer, 1967); the ulcers usually first appear in the second decade of life (Review Article, 1968 452); first attack usually between ages of 10 and 20 (Pindborg, 1968); ulceration starts in the great majority of patients by 40 years of age; the usual age of onset for major and minor aphthous lesions was 10-19 years, and for herpetiform lesions 20-29 years; a significant increase of onset of ulceration during puberty was not found; clinical severity was not related to age of onset (Lehner, 1968); onset is
usually between the ages of 10 and 20 (Brody and Silverman, 1969); occur over a wide age range, they may begin in childhood and occur periodically (Weathers and Griffin, 1970); the lesions characteristically begin in childhood or early adulthood (Francis, 1970).

Aphthous lesions were first differentiated from herpetic ones, partly on the basis of their occurrence in adults rather than in children (Mikulicz and Michelson, 1892). One wonders whether the comments of Whitwell (1934), Colyer and Sprawson (1942) and Strauss (1947) were not due to a confusion with herpetic lesions.

Certain general conclusions can be offered, based on what appears to be the weight of evidence.

1. These lesions can occur at any age.
2. Most commonly they affect young adults.
3. Support for the influence of the sex hormones is strongest in respect of the menopause, but doubtful in respect of puberty.
4. The lesions are rather uncommon after age 40, especially in the male.
5. Only Löhner separated herpetiform and aphthous lesions, and found the former to have a later age of onset (in the third decade usually, as against the second, in aphthous lesions), but with only 19 cases of herpetiform lesions, his results may be somewhat unreliable.

7. Number of lesions per attack:
sometimes the ulcers are single, but quite often 2 or 3 are present together (Whitwell, 1934); occur
singly or in batches (Strauss, 1947); single or multiple lesions (Kutscher et al., 1953); single or multiple (Zegarelli et al., 1953); usually solitary lesions; they may be multiple, however, in the sense that successive lesions may appear in new locations before the older lesions have healed (Stark et al., 1954); ulcers are multiple (Truelove and Morris-Owen, 1958); up to four ulcers in any one crop (Rushton and Cooke, 1959); it is unusual for more than 4 ulcers to be present at any one time (Cooke and Armitage, 1960; solitary or multiple lesions (Schaffer, 1960); solitary or multiple arrangement (Thoma and Goldman, 1960); minor aphthous ulcers occur in crops of 1 to 4 (Cooke, 1961); usually only one or two ulcers appear at irregular intervals, but not infrequently after about a year the attacks gradually become more severe with many ulcers appearing at one time, so that the patient may never be free from ulcers (Stones, 1962); lesions may occur singly or in crops, affecting several tissues within the mouth simultaneously or in sequence (Ship, 1963); may be single or multiple (Ryan, 1963); single or multiple (Shafer et al., 1963); a recurrent pattern of one or more ulcers (McCarthy and Shklar, 1964); may occur as single, isolated ulcers or as crops affecting several intraoral sites simultaneously. In excess of 30 ulcers have been observed to develop within 12-24 hours in several of our patients. In these circumstances adjacent ulcers may coalesce and form larger areas of mucosal damage (Brightman and Ship, 1966); single or multiple
(Graykowski et al., 1966); single or multiple (Bishop et al., 1967); the number varies from one to 5 to 10 (Pindborg, 1968); single or multiple ulcers (McFall, 1968); usually 1 to 3 in number in a rather localized area, but there may be multiple lesions in several areas of the mouth (Weathers and Griffin, 1970); from 1 or 2 lesions every other month to 30 or more small lesions present almost constantly in various stages of development (Francis, 1970).

The number of lesions present can be a useful diagnostic sign, but unfortunately most authors do not differentiate among the various types of lesions. This is most apparent in the comments of Brightman and Ship (1966), which read like a classical description of herpetiform ulceration.

Once again, Lehner provides the necessary details. His descriptions can be tabulated thus:

<table>
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<tr>
<th>Major aphthae</th>
<th>Minor aphthae</th>
<th>Herpetiform Ulcers</th>
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<tr>
<td>Lehner and Sagebiel (1966)</td>
<td>1-5</td>
<td>10-100</td>
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<tr>
<td>Lehner (1967c)</td>
<td>1-4</td>
<td>10-40</td>
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<tr>
<td>Lehner (1968)</td>
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Lehner (1968) reported a gradual increase in the number of ulcers from the minor aphthous variety up to herpetiform ulcers. More than 4 ulcers were present in 18% of minor aphthae, 40% of major aphthae, 64% of Behcet's syndrome, and 100% of herpetiform ulcers.
The only sex difference was seen in Behcet's syndrome, with 60% of males and only 20% of females showing 1-4 ulcers. Most patients with minor aphthae have 1-4 ulcers, major aphthae 2-10, and herpetiform ulcers 10-100.

Another distribution was provided by Graykowski et al. (1966) who did not consider the different types separately: 1-3 lesions per attack were seen in 42 patients (70%), 4-6 lesions in 14 (22%), 7-10 in 2 (3%) and more than 10 in 4 (6%). The largest number of discrete lesions in any one patient exceeded 100. Driscoll et al. (1959) mention several hundred separate ulcers present at the same time.

8. Frequency of recurrences.

Many recur every few days although some patients are free for long periods (Whitwell, 1934); recurrences may occur as frequently as 3 weeks to 3 months, at the same or different sites (Stark et al., 1954); of a population of 120 (80 females), nearly 40% of the females suffered crops of ulcers at intervals of less than 8 weeks, and usually with intervals of less than 1 month; 45% of males experienced new crops at intervals of 3-4 months or, alternatively, were never without lesions. A much higher proportion of male (17.5%) than female (3%) patients showed no periodicity, with wholly irregular intervals between attacks. Females tended to show greater frequency of lesions than males (Sircus et al., 1957) several attacks a year (Truelove and Morris-Owen, 1958); in a series of 121 patients (80 females) 20% of the males had regular occurrences of ulcers, 60% irregular, and 20% continuous; of the females
28% were subject to regular attacks, 37% irregular and 35% continuous. Thus males appear more likely to have the ulcers at irregular intervals while the number of females was fairly evenly divided between the three classified groups. 43% of the males and 40% of the females classified as having regular or irregular ulcers were getting recurrences within one month. About twice the proportion of males to females had ulcers at irregular intervals of over 3 months (Farmer, 1958); periodicity may be continuous or irregular, recurrences varying from 1 or 2 lesions per year to several hundred present in the mouth at one time (Driscoll et al., 1959); new ulcers may appear every few days followed by a lapse of some months (Sutherland, 1959); periods of freedom from ulceration may be enjoyed for months at a time (Rushton and Cooke, 1959); in a questionnaire study of 1788 students, 14% with a history of aphthous ulcers reported recurrences at intervals of one month or less, 50% had recurrences at intervals of from 2-11 months, and 36% had annual or less frequent attacks (Ship et al., 1960a); in an oral examination of 300 students from the previous population who reported recurrences of aphthae at intervals not exceeding one year, lesions were observed in 46%; 91% of those who reported daily or weekly recurrences had lesions; 73% of those who reported monthly recurrences, and 36% of those who reported 2-11 recurrences each year had active lesions at the time of examination (Ship et al., 1960c);
recur periodically; disappearance is soon followed by new crops with variable remission periods (Dalmau et al., 1961) in a study of 90 patients (57 females), 45% of the males suffered continuous ulceration, but only 18% of the females were so affected; 60% of the females experienced either a fortnight's or a month's remission between crops of ulcers. Apart from those patients who suffer continuous ulceration, there is a rhythmic periodicity in the attacks. Seven patients, after a history of severe ulceration for 2, 4, 4, 5, 6, 7, and 12 years respectively, experienced at least a year's complete freedom from ulceration before the ulceration returned at its former severity (Cooke, 1961); recurrences may be continual, with as many as several dozen ulcers at any given time, or irregular, with only one lesion every few years (Ship et al., 1961c); usually only 1 or 2 ulcers appear at irregular intervals, but not infrequently after about a year the attacks gradually become more severe with many ulcers appearing at one time, so that the patient may never be free from ulcers (Stones, 1962); analysis of the incidence of severity of the disease in a professional school student population indicated that 8 males and 1 female had weekly episodes. This represented only 2.2% of the group of 975 students with a positive history of the disease, and only 1.2% of the entire population. Thus the majority of patients experienced only occasional episodes of single ulcer formation (Ship et al., 1962); the pattern of recurrences generally follows a rhythmic periodicity ranging between 2 and 8 crops of lesions per year. Recurrences may be extremely frequent, measured in terms of days, although some
patients manifest only an occasional lesion every few years (Shafer et al., 1963); the lesions may recur as frequently as one month apart, and there are cases where for periods of years the individual is never without aphthous lesions, new ones forming as the previous ones heal. In other words, attacks may occur 2 or 3 times during a year (McCarthy and Shklar, 1964); recurrences may come fairly regularly every 2 to 4 months, although in some patients attacks are as rare as every few years (Lancet, 1964 303); recurrences are common and occur more frequently than those of herpes labialis (Bhaskar, 1965); 10% of patients are never free of the disease (Brightman and Ship, 1966); new ulcers may form before older lesions are healed, thereby presenting constant lesions in various stages of development (Getz and Bader, 1967); periodic or continuous (Bishop et al., 1967); attacks are variable. Most patients appear to have fewer than 6 per year; each attack consists of 1 or 2 superficial lesions (Brody and Silverman, 1969); irregular intervals year after year (Gardner, 1970).

Certain findings are best presented in tabulated form:

<table>
<thead>
<tr>
<th></th>
<th>Student Sample</th>
<th>Hospital Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>80 (35.2%)</td>
<td>11 (34.4%)</td>
</tr>
<tr>
<td>Occasional</td>
<td>106 (46.7%)</td>
<td>10 (31.2%)</td>
</tr>
<tr>
<td>Frequent</td>
<td>41 (18.1%)</td>
<td>11 (34.4%)</td>
</tr>
</tbody>
</table>

Ship and co-workers use the frequency of recurrence as an estimate of severity of the disease; they do not define "rare", "occasional" and "frequent".
64.

Cooke (1961):

<table>
<thead>
<tr>
<th>Periodicity</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Continuous</td>
<td>13</td>
<td>45</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>1-14 days</td>
<td>4</td>
<td>14</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>2-4 weeks</td>
<td>6</td>
<td>21</td>
<td>19</td>
<td>35</td>
</tr>
<tr>
<td>4-8 weeks</td>
<td>4</td>
<td>14</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>8-12 weeks</td>
<td>2</td>
<td>7</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

Lehner (1968) found little difference between the sexes in the frequency of monthly recurrences: 26% among male and 32% among female patients with the minor form of the disease. All female patients with major aphthous ulceration and males with herpetiform ulcers showed recurrences of up to one month's duration. In summary, Lehner found that recurrences of the minor form usually occurred within 1-4 months; recurrences of the major variety occurred more frequently than monthly and herpetiform ulcers also usually recurred more frequently than monthly.

As Brightman and Ship (1966) point out, aphthous ulceration, being a disease of exacerbations and remissions, can only be positively diagnosed during the presence of lesions. It is not possible at present to diagnose the condition in the subclinical state although the immunological investigations of workers like Lehner may render this ultimately possible. Consequently, the only means of investigating incidence and recurrence rates, is by case history analyses and longitudinal population studies. Both approaches appear to be valid, and Ship and his various co-workers have utilized them rather extensively.
By an analysis of the case histories of 1788 students of professional schools, Ship and his colleagues (1960a, 1960b, 1960c, 1961a) found that males and females experienced a similar frequency of recurrences. 14% of susceptible students reported episodes of one or more ulcers per month, while about 66% reported at least one attack per year. Oral examinations of 300 of those with positive histories confirmed the questionnaire findings.

A notable point of difference between Ship's findings and those of the British writers Sircus, Farmer and Cooke, is that Ship found no sex differences in the recurrence rate, whereas the others reported a greater tendency for the ulcers to occur continuously in males, and with more of a tendency for a rhythmical periodicity in females.

9. **Time lag between onset of the ulcers and their becoming severe:**

Both Farmer (1958) and Cooke (1961) reported and commented upon this phenomenon.

Farmer: "Twenty-six males (61%) and sixty-seven females (84%) stated that at first the ulcers were small and occasional and became severe and more frequent after a period of time varying from a few months to several years. A case was judged to be severe when the ulcers were either deep and large and/or multiple. Both sexes had a similar history and about 50% of both males and females who developed severe lesions did so within one year of the onset of the ulcers."
Cooke: "In many patients there is a definite latent period between the initial onset of the ulcers and their becoming severe. Initially the ulcers may be small and infrequent, but after a varying period of time they become frequent, larger, and take longer to heal. This latent period pertains to the females rather than to the males."

10. Geographical and racial incidence:

Very little information is available on this point. Theron (1959), however, states that cases have been reported from most civilized countries; the tropics (Simons, 1950) and Antarctica (Knoedler and Stanmeyer, 1958) have also been the source of instances.

Theron (1959) found no reference in the literature to racial incidence. His 46 patients in The Netherlands, were all of Caucasian stock, and he observed that, from personal experience in South Africa and Tanganyika, the disease was seldom encountered among the Bantu. Graykowski et al. (1966), likewise stated that over a four-year period in which more than 200 patients with aphthous lesions were examined, only one Negro was observed. In their 1966 study of 62 patients, 96% were white; the race of the remainder was not stated.

A professional school student population of 1,039 males and 749 females showed no significant differences in racial background (Ship et al., 1960a) but different racial origins were not discussed.

11. Seasonal incidence:

Loblowitz (1910) observed no relationship to seasonal or climatic conditions. Jordan (1933), however thought that the disease was subject to seasonal variations, and
Webshar (1939) felt that the incidence was greatest when tomatoes were seasonal. Graykowski et al. (1966) found no association between exacerbations and seasons of the year.

Ship et al. (1961a), by an inspection of monthly diaries from 230 students (120 male and 110 female) for periods of 3 to 12 months, found large seasonal variations, with increased activity in male and female subjects with both severe and mild disease during the winter and spring months, relative quiescence during the summer, and intermediate levels of activity during autumn.

Bhaskar (1965) stated that there was a greater prevalence during the winter and spring months, but may have simply been citing Ship and co-workers' findings. On the other hand, McCarthy and Shklar (1964) could formulate no clear-cut seasonal variations.

Theron (1959) considered seasonal variation to have little or no influence on the course of the disease. Francis (1970) stated that there is no association with seasonal allergy.

In the lack of any firm agreement on this point, and in the absence of comment by the great majority of writers, a seasonal variation does not appear very significant.

12. Religious differences:

It is difficult to see how religious differences might be of significance in the development of aphthous lesions, except perhaps per medium of socioeconomic, emotional or dietary factors. However Ship and colleagues have included this classification in their statistical analyses of aphthous ulcer patients.
In 1960, Ship and co-workers (1960a) found significant but different religious group differences for aphthous and herpetic conditions. For aphthous lesions, the religious groups, in order of frequency, were Protestant, Catholic and Jewish. For herpes labialis, the order was Catholic, Protestant, Jewish. The authors commented that the reasons for the differences were obscure.

The same results were obtained by Ship et al. in 1967 in both student and hospital samples. The prevalence of aphthae was highest among protestants, intermediate among Catholics and lowest among Jews; the prevalence of recurrent herpes was consistently different; highest in Catholics, intermediate in Protestants and lowest among Jews.

13. **Socioeconomic status**:

Ship (1962), aware of the difference between his figure and those of Sircus et al. (1957) relating to incidence of the disease, measured the socio-economic backgrounds of 1384 professional school students and concluded that "the differences observed between populations are probably unrelated to socio-economic status".

However, in 1966, Ship reported a linear relationship between socioeconomic status and aphthous ulceration. No significant relationship was found between socioeconomic class and the severity of the disease.

Brightman and Ship (1966) state that aphthous ulceration appears to be definitely related to socioeconomic factors: "population samples characterized by predominantly high socio-economic levels have higher frequencies of ulcers, whereas those from low socio-economic levels are virtually free from disease."
In 1967, Ship and colleagues found that the prevalence of aphthous ulcers was higher in a student sample than in a hospital sample by a ratio of 5:1, and attributed the difference to the socioeconomic status of the two samples, (Socioeconomic scores from the U.S. Bureau of Census Standards of 1960 were determined for the student sample based on parental occupations).

It appears that the disease may be more prevalent amongst the upper socioeconomic levels, as are ulcerations elsewhere in the gastro-intestinal tract. The explanation may lie in a greater exposure to emotional stress.

Whilst aphthous ulcers are said to be more common in the higher socioeconomic levels, herpetic lesions are more common in the lower. This situation is somewhat confused by the finding by Ship et al. (1967) that those with one of these diseases are more likely to incur the other.

Summary:

Of the comments presented, not all, of course, are of equal merit. Some result from large, carefully controlled studies, while others are mere clinical impressions. Some are derivative, others frankly contradictory.

Because he alone separated the various types of oral lesions, and commented separately upon them, Lehner's findings (1968) have been singled out, usually, for special mention. Lehner has presented a succinct yet comprehensive summary of the differences among these lesions and this is presented below:
<table>
<thead>
<tr>
<th></th>
<th>Minor Aphthae</th>
<th>Major Aphthae</th>
<th>Herpetiform Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio F:M</td>
<td>1.3:1</td>
<td>0.8:1</td>
<td>2.6:1</td>
</tr>
<tr>
<td>Age of onset (peak incidence)</td>
<td>10-19</td>
<td>10-19</td>
<td>20-29</td>
</tr>
<tr>
<td>Number of ulcers</td>
<td>1-5</td>
<td>1-10</td>
<td>10-100</td>
</tr>
<tr>
<td>Size</td>
<td>below 10 mm.</td>
<td>above 10 mm.</td>
<td>1-2 mm.</td>
</tr>
<tr>
<td>Duration</td>
<td>4-14 days</td>
<td>10-30 days</td>
<td>7-14 days</td>
</tr>
<tr>
<td>Healing by scar</td>
<td>8%</td>
<td>64%</td>
<td>less than monthly</td>
</tr>
<tr>
<td>Recurrence</td>
<td>1-4 months</td>
<td>less than monthly</td>
<td>less than monthly</td>
</tr>
<tr>
<td>Sites</td>
<td>lips, cheeks, tongue</td>
<td>lips, cheeks, tongue, pharynx, palate</td>
<td>lips, cheeks, tongue, pharynx, palate, floor, gum</td>
</tr>
<tr>
<td>Total duration</td>
<td>less than 5 years</td>
<td>more than 15 years</td>
<td>less than 5 years</td>
</tr>
<tr>
<td>Associated oral lesions</td>
<td>-</td>
<td>erythema</td>
<td>migranes</td>
</tr>
<tr>
<td>Treatment</td>
<td>corticosteroids</td>
<td>corticosteroids</td>
<td>tetracycline</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>raised IgG, IgA</td>
<td>raised IgG, IgA</td>
<td>raised IgA</td>
</tr>
<tr>
<td>Humoral antibodies</td>
<td>raised</td>
<td>raised</td>
<td>-</td>
</tr>
<tr>
<td>Cell bound antibodies</td>
<td>present</td>
<td>present</td>
<td>+</td>
</tr>
<tr>
<td>Intraepithelial vesicles and inclusion bodies</td>
<td>-</td>
<td>-</td>
<td>present</td>
</tr>
</tbody>
</table>

Detailed statistical analysis, by commentators such as Ship, in his many publications, has so far failed to provide clinicians with any great help in the anticipation of lesions. Francis (1970) measured parameters such as the occurrence of lesions, their duration, duration of remissions
between attacks, association with mental stress or physical trauma, etc., in an attempt to predict from past information any future event, such as when the next lesion would occur, how many would appear, etc. After analysis of the data and the construction of correlation coefficients between the various parameters, no significant results were obtained, indicating the apparent random occurrence of the lesions.
PART 11: FURTHER CONSIDERATIONS

CHAPTER 5  Histopathology.

CHAPTER 6  Major aphthous ulcers.

CHAPTER 7  Herpetiform ulcers.

CHAPTER 8  Traumatic ulcers: their relationship to aphthae.

CHAPTER 9  Herpetic infections.

CHAPTER 10 Aphthae in association with other lesions.

CHAPTER 11 Behcet's syndrome.

CHAPTER 12 Smoking and aphthous ulceration.

CHAPTER 13 Immunological theory.
CHAPTER 5 - HISTOPATHOLOGY:

Little reliance can be placed on histological descriptions published prior to 1930 because of the prevailing tendency then not to distinguish between aphthous and herpetic lesions. Theron (1959) states that some cases of aphthae were probably included in early reports by Worms (1864), Fraenkel (1888), Ziegler (1898), Siegmund and Weber (1926), and Aschoff (1936), but that the majority of their examples were probably herpetic ulcers.

An outstanding exception, of course, is the description by Sutton in 1911 of major aphthous ulceration, which he referred to as periadenitis mucosa necrotica recurrens, being impressed with the intense inflammatory reaction in the periglandular tissues. For reasons mentioned in another chapter, this condition is now not considered qualitatively different from minor aphthous ulceration, although Sutton quite rightly separated it from herpetic ulceration.

Another interesting description associated with a diagnostic error was that of Cahn (1936) who considered that herpetic and aphthous lesions differed only in their stage of development. From the general context of his article it appears that Cahn is describing aphthae when he says that they begin as microscopic intra-epithelial vesicles which contain degenerating epithelial cells. Ulceration follows and the ulcer is surrounded by normal epithelium and covered by a pseudomembrane consisting of cellular debris. Significant, in the light of later reports, was the marked perivascular infiltration in the
corium. The later description by Cahn and Bartels (1942) seems to be of herpetic lesions.

Kochs (1940) was unable to demonstrate an early vesicular stage, his examples showing a rapidly developing necrosis in the epithelium which was then involved with a fibrinous and inflammatory exudate containing lymphocytes and granulocytes. The margins of the ulcers were oedematous. Kochs was impressed by the similarity to early gastric mucosal defects.

A comprehensive study was undertaken by Frech (1945) whose initial finding was a cellular infiltration (polymorphs, lymphocytes and some plasma cells) and the formation of a fine fibrin network in the connective tissue beneath the epithelial defect. (Unfortunately these specimens were not taken early enough, as the ulceration had apparently already occurred). The epithelium showed marked intercellular oedema and the papillary layer could not be made out. Round cell infiltration occurred into the oedematous spaces and there was necrobiosis of the prickle cells. The inflammatory cells showed extensive karyorrhexis. Significantly, the vessels in the papillary and reticular layers were strongly dilated and surrounded by a round cell infiltrate. The change in the vessels consisted of endothelial thickening which began in the intima and was considered to be due to the stasis in the blood columns. The surrounding connective tissue showed a rapid oedematous change extending to the periglandular tissues. The fibres of the connective tissue lost their wavy and fibrillous appearance, but did not show any fibrinoid changes.
Frech considered that an aphthous lesion is a localised necrotic inflammatory reaction of the complete mucosa accompanied by cellular fibrinous exudation. There was no evidence of specific infection. Significant features, it seemed to him, were the rapid formation of an extensive round cell infiltration, vessel disturbances, massive red cell extravasation, and oedema.

Theron (1959) also undertook an important study of the histological features of aphthous lesions. In day-old lesions the epithelium was intact but showed slight parakeratosis. The prickle cell layer revealed spongiosis, but the intercellular bridges remained intact. There was no acantholysis as in pemphigus. In some areas there was evidence of intraepithelial vesicle formation. Beneath the basal layer could be seen a round cell accumulation invading the epithelium and extending into the connective tissue. In the corium were numerous dilated blood vessels with a perivascular infiltrate of lymphocytes and occasional polymorphonuclear leukocytes. No fibrin could be detected and the collagen fibres appeared normal. The endothelium of the dilated vessels revealed oedematous swelling. A fair number of mast cells could be demonstrated.

Two-day lesions showed an epithelial defect covered with fibrin. Under the defect was a cellular infiltration consisting of lymphocytes together with some neutrophil leukocytes and occasional eosinophils and plasma cells. Between the cellular elements fibrin could be detected. In some instances the picture was dominated by an infiltration of polymorphonuclear cells. Plasma cells and eosinophils were not much in evidence or completely absent, but mast cells were prominent in all specimens.
In early aphthous lesions Theron thought that the primary change was in the epithelium. No ballooning degeneration or intranuclear inclusion bodies were seen in any section. No involvement of the underlying glands was apparent. Significant numbers of mast cells were found in all specimens examined.

As mentioned previously, the early contributors failed to distinguish between aphthous and herpetic lesions. Similarly the notable contributions made later by Frech (1945), Theron (1959) and Graykowski et al. (1966) did not differentiate among major, minor and Cooke's herpetiform types.

Many authors have stressed the non-specific nature of the ulceration, and amongst these may be mentioned Stark et al. (1954), Jawetz (1955), Farmer (1956,1958); Rushton and Cooke (1959), Cooke (1961), Stones (1962), Ship et al. (1962), Shafer et al (1963), Kramer (1965), Samitz and Dana (1967), Getz and Bader (1967), Brody and Silverman (1969), Weathers and Griffin (1970).

If the ulcerations are non-specific, perhaps the most revealing examinations would be expected to be those carried out prior to frank ulceration (although one must then make the assumption that the lesions concerned would have gone on to form typical aphthae). This resolves itself into a consideration of the epithelium itself and of the underlying corium, and these will be considered separately.
Changes in the epithelium:

As mentioned above, Cahn stated that the lesions begin as microscopic intraepithelial vesicles, and Theron reported early spongiosis with preservation of the intercellular bridges. Farmer (1958) reported a thickening of the epithelium produced mainly by hypertrophy of the outer cells, with complete loss of the intercellular bridges.

Lehner and Sagebiel (1966) noted considerable intercellular oedema. In a later publication, Lehner (1969e) added that there was little epithelial hyperplasia and the basement membrane, except immediately adjacent to the ulcer, appeared intact. Unfortunately, Lehner’s investigations were not carried out on pre-ulcer specimens. Graykowski et al. (1966) examined pre-ulcer specimens but did not consider the epithelium per se and, in any case, appeared to be discussing major aphthous lesions, their attention being directed to the involvement of the minor salivary glands.

Brody and Silverman (1969) found hyperplasia and dysplasia of the prickle cell layer. Getz and Bader (1967) reported some spongiosis in the stratum spinosum and acantholysis (in contradiction of Theron) in the basal layer. Cooke (1961) noted liquefaction degeneration of the basal and lower prickle cell layers.

Although the details differ, there seems to be agreement that intraepithelial degeneration takes place prior to the loss of surface integrity. Although the procedure may introduce a diagnostic assumption, it is unfortunate that more investigations have not been carried out into the characteristics of the pre-ulcerative lesion.
Although Theron's opinion was that the primary changes in the development of these lesions occur in the epithelium, Cooke (1961) was convinced that the primary lesion appears to be in the corium in the form of a chronic inflammatory focus, and that the only changes seen in the epithelium are secondary, either from trauma to the surface or to the inflammatory reaction in the corium.

Changes in the corium:

Cahn (1936) mentioned the presence of a marked perivascular infiltration in the corium, as did Frech (1945) and Theron (1959). A diffuse lymphocyte and plasma cell infiltration in the corium was noted by Rushton and Cooke (1959) and by Cooke (1961). This diffuse chronic inflammatory reaction and the absence at this early stage of any change in the bordering epithelium suggested to Cooke and Armitage (1960) that the lesion may begin in the corium rather than in the epithelium.

Inflammatory cells were commonly reported in the corium by many other authors, but mostly their reports were on established ulcers and the implication is that the inflammatory process is extending into the corium rather than originating there. Stones (1962) observed that the inflammatory infiltrate in the corium increased with ulcer formation. Following ulceration, the microscopical picture appears to be dominated by polymorphonuclear cells, as attested to by the following contributors: Frech (1945), Rushton and Cooke (1959), Theron (1959), Ship et al. (1962), Graykowski et al. (1966), Lehner and Sagebiel (1966), Getz and Bader (1967), and Lehner (1969e). This is probably secondary to the ulceration - Lehner, 1969e.
Lehner and Sagebiel (1966) state that a perivascular lymphocyte, monocyte and mast cell infiltrate is a prominent early feature. In a later paper, Lehner (1969e) described the perivascular infiltration as a constant feature, and states that it consisted of lymphocytes, monocytes, some mast cells and occasionally plasma cells, in association with venules and arterioles.

Recent investigations have concentrated attention on the perivascular distribution of the chronic inflammatory exudate and made certain deductions concerning its significance.

One such deduction refers to an earlier suggestion of Touraine in 1941 who considered that there may be an arteriolitis of the deeper vessels in the underlying dermis followed by a secondary necrosis of the epithelium. Consistent with this, McCarthy and Shklar (1964) compared the development of the lesion with that of a localized minute infarct. A link between this concept and a hypersensitivity reaction was provided by Samitz and Dana (1967) who stated:

"Many characteristics of the disease suggest an allergic vasculitis, with an ensuing tiny infarct or necrosis of the oral mucosa. Clinically the lesion resembles a minute pyoderma gangrenosum; we have been impressed by the perivascular infiltrate and the profound necrotic nature of the underlying ulceration in biopsies of early aphthae."

The following authors have described the histopathology of aphthous ulcers as conforming to a delayed hypersensitivity reaction: Graykowski et al. (1964), Graykowski et al. (1966), Turk et al. (1966), Lehner and Sagebiel (1966),
Samitz and Dana (1967), Lehner (1967c), Brody and Silverman (1969), Lehner (1969d) and Lehner (1968e). The predominant cellular infiltrate is a mononuclear (lymphocytic) one in the early lesions (one to six hours old), being largely replaced over a period of eighteen hours by neutrophils. Lehner (1969e) reported a threefold increase in the number of mast cells, while nonspecific ulcers show a decrease in mast cells. Dolby et al. (1969) reported a decrease in mast cells in aphthous ulcers over forty-eight hours old.

The role of the lymphocyte has been investigated by Lehner in regard to his autoimmune hypothesis (q.v.). He reports that lymphocyte transformation into large 'blast' cells occurred in patients with aphthous ulceration following stimulation by foetal oral mucosa (Lehner, 1967b). In a later study of lymphocyte kinetics (1969b), he demonstrated a gradual increase in sensitized lymphocytes prior to ulceration, rising sharply two days before to two days after the appearance of the ulcer, with a falling to zero about three days later. Indeed, Lehner postulated the existence of four phases of the lymphocyte count (resting, initiating, destructive, and healing phases) and these appear to have clinical counterparts. The actual cytotoxic role of the lymphocyte is considered in the chapter on immunologic theory.

Lehner (1969e) undertook a detailed histopathological examination of this disease process using light, electron and fluorescent microscopy. He demonstrated mononuclear cells infiltrating the dermis through the basement-membrane, and invaginating between the basal and prickle cells being often seen in oedematous spaces. The presence of lymphocytes
and monocytes adjacent to damaged epithelial cells suggested to him that they may be responsible for epithelial destruction.

Lehner (1969e) cites the finding by Frech (1945), Theron (1959), Graykowski et al. (1966) and himself of the early intense lympho-monocytic infiltration, the often-mentioned appearance of polymorphs occurring subsequent to ulceration. Leskowitz and Waksman (1960) reported a similar cellular sequence in delayed hypersensitivity, mononuclear infiltration being followed by necrosis and then by neutrophils. Electron Microscopy revealed the presence of intracytoplasmic phagosome-like bodies which Lehner remarks resembled the early "invasive destructive" process by mono-nuclear cells of antigen-containing epithelial cells in delayed hypersensitivity reactions, as shown by Waksman (1962).

The perivascular cuffsing by lymphocytes and monocytes, especially around small venules (Lehner, 1969e) resembles the early histological changes in delayed hypersensitivity to intradermal antigen (Roitt and Doniach, 1967).

Immunofluorescent binding of predominantly IgG and IgM (See chapter on immunological theory) was found in autologous tissue in aphthous patients, but not in the case of other oral lesions or controls. Complement binding was also observed in some instances, but specific albumin staining was not seen (Lehner, 1969e). Lehner concludes that although non-immunological globulin binding cannot be excluded, the evidence favours specific immunological reaction of IgG and IgM with autologous cell cytoplasm of the prickle cell layer.
The main details of Lehner's study can be reiterated by contrast from his description of a non-specific ulcer: "The histology of non-specific ulcers differs ... in the less marked mononuclear and perivascular infiltration, a more pronounced neutrophil infiltration and fewer mast cells. Epithelial vesicles and intranuclear inclusion bodies are absent and the fluorescent antibody test is negative."

Finally, Lehner claims that his present findings conform to the histological criteria as laid down by Coe et al. (1966) for delayed hypersensitivity:

1. at least 3 perivascular or perineural clusters of mononuclear cells in a cross-section, or both;
2. dispersed mononuclear cells in the dermis without obvious pattern;
3. polymorphs constituting less than 5% of the infiltrating elements; and
4. absence of necrosis or smudging of walls of venules.

Brody and Silverman (1969) cite their findings of large numbers of lymphocytes and mast cells in early lesions, bound IgA at the site of the ulcer and the good response to corticosteroids as suggesting an immunologic aetiology.
CHAPTER 6 - MAJOR APHTHOUS ULCERS:

Truelove and Morris-Owen (1958) divided aphthous lesions into a common, or minor, form and a major form which is more severe. In the major form, they state, ulcers are multiple and the patient may seldom, if ever, be free from them over a period of years.

The major form was described by Sutton in 1911 under the title periadenitis mucosa necrotica recurrens, by which description it is still widely known. Other synonyms include: Sutton's disease, chronic scarring aphthae, Mikulicz's aphthae, ulcer neuroticum mucosae oris, recurrent scarring painful aphthae, aphthae resistantiae, periadenitis aphthae, stomatitis neurotica chronica, recurrent scarifying ulcerative stomatitis, recurrent canker sores, stomatitis aphtosa recurrens cicatricicans.

At the time Sutton wrote, the distinction between aphthous and herpetic lesions was blurred. Sutton was correct in regarding this condition as a completely separate entity from herpetic ulceration, but it is now considered to be only quantitatively different from the minor form of aphthous ulceration. Whether or not so-called periadenitis mucosa necrotica recurrens and the more usual forms of aphthous ulcer were separate conditions was disputed for many years 209, 286 but now appears to have been resolved, largely by the work of Lehner (1967c, 1968, 1969e).

Although Sutton appears to have been the first to describe its histopathology, earlier clinical examples have been presented, but not as a separate entity. There seems to be no doubt that one of Sibley's cases of 1899 was an example of this condition.
Sibley, who thought these ulcers of neurotic origin, mentioned Jacobi (1894) as reporting three cases. Other cases prior to Sutton were reported by Court in 1899 and Loblowitz in 1910. Prinz and Greenbaum credit Mikulicz with the first description of the disease in 1888, while Theron gives the honour to Mikulicz and Michelson in 1892. It is interesting that Shafer et al. (1963) use the term Mikulicz's aphthae to refer to major aphthous ulcers, whereas Cooke (1961) used it to refer to the minor variety, and was followed in his usage by Kramer, Lehner, Dolby, and by Brody and Silverman.

Sutton's patient was a sixteen year-old male who complained of red nodules developing on his oral mucosa almost fortnightly. After about four days the nodule would break down into an ulcer by the sloughing from its surface of a cone-shaped mass or plug of mummified tissue, following which the ulcer would become crusted with fibrinous exudate.

Sutton's histological description pointed out the presence of cellular infiltration in the neighbourhood of glandular acini, but the mucous cells were normal as to size and contour, and their staining reactions were the same as those in unaffected parts. Although the deeper glandular structures appeared to be only slightly if at all affected, Sutton emphasised the importance of glandular elements in this disease by the use of the term periadenitis. Cooke (1969) frankly described the condition as misnamed, Lehner (1969e) as cumbersome and misleading.
Bhaskar (1965) remarks on the exclusive appearance of these lesions on minor salivary gland-bearing mucosa, but this involves virtually all the mouth with the exception of the anterior part of the hard palate, where aphthous ulcers of whatever sort are rare.

Although many authors have described or implied the presence of vesicle stages in the minor form of aphthous ulceration, no reference to such a stage can be detected in respect of the major form. The first clinical sign of the lesion is, as described by Sutton, the formation of a nodule, or perhaps a plaque. This has been described by Loblowitz (1910), Sutton Jr. (1941), Alling (1956), Hurt (1960), Colby et al. (1961), Graykowski et al. (1964), Kramer (1965), Bhaskar (1965), Kramer (1967), Pindborg (1968) and Cooke (1969). The description appears to be uncontrover-sial.

The presence of the major form of the disease is implied in the upper limits of size and duration in various reported studies. Thus Zegarelli et al. (1953) spoke of occasional ulcers 2-3 cm. in diameter; Farmer (1958) reported individual lesions lasting as long as six weeks; and Clàus et al. (1961) mentioned aphthous lesions "about the size of a quarter" which take 2-6 (in one case 18) months to heal.

Most authors, however, give specific mention to the condition (usually as periadenitis mucosa necrotica recurrens, or periadenitis apthae) and emphasize its healing with scar formation.
Among these authors may be mentioned Sutton Jr., (1941), Alling (1956), Weichselbaum and Derbes (1957), Farmer (1958), Hurt (1960), Thoma and Goldman (1960), Colby et al. (1961), Ship et al. (1962), Shafer et al. (1963), McCarthy and Shklar (1963), Kramer (1965), Bhaskar (1965), Ryan (1966), Brightman and Ship (1966), Rovin (1966), Pindborg (1968) and Cooke (1969).

That scar formation is not an absolute diagnostic criterion of major aphthae is strongly implied by Lehner (1968) who states that 64% of major aphthae heal with scar formation, compared with 8% of the minor variety and 32% of herpetiform ulcers. Farmer (1958) had earlier said that scarring was uncommon in aphthous disease, and usually occurred in sites that could easily be damaged by the teeth.

The distinction between the major and minor types of aphthous ulceration is arbitrary. Lehner (1968) states that the major difference is the degree of severity, the major variety lasting longer, being more severe, larger in size and number, and recurring more frequently. However, the presence of scarring would appear to be a helpful diagnostic sign. There is also a tendency, as remarked by Lehner (1968) towards palatal and pharyngeal involvement. Kramer (1965) states that whereas these lesions occur mainly on the lips and tongue, their presence on the soft palate and fauces may be an ominous sign of a forthcoming Behcet's syndrome (q.v.).

The extent of the ulceration, and an echo of Kramer's warning are seen in the description of a patient of Birt and Mather (1968) who, although having no genital ulcers or uveitis, was regarded as having an incomplete form of Behcet's syndrome. "He presented with hoarseness and
and dysphagia which had been present for months. In addition to scarring and active ulceration of the buccal mucosa, palate and tongue there was an indurated ulcer extending from the tonsil to the pyriform fossa on the left pharyngeal wall. The right pharyngeal wall was scarred. The right arytenoid was swollen, with the right vocal cord fixed, while another ulcer was seen on the left false cord. There was extensive ulceration and scarring in the postcricoid region." The authors considered that should the condition worsen, laryngectomy may be indicated.

Reading (1966) spoke of the destruction of the whole epiglottis or the pillars of the fauces, and recalled one case in which the entire posterior pharyngeal wall was slowly eroded by ulceration, the patient finally perishing of a massive secondary haemorrhage from the throat. Graykowski et al. 1966) mention an ulcer 5 cm. in diameter.

Evidence that "periadenitis" lesions are not a separate entity:

Epstein presented a case to the American Dermatological Association in 1929. 158 One of those present, Professor Jadassohn, considered the lesion to be an example of "aphthae resistentae" and added, "Of course we know it has nothing to do with aphthous stomatitis." Whether Jadassohn was referring to the normal type of aphthous ulceration or herpetic disease is not clear. In any case, "periadenitis aphthae" were often regarded as a distinct entity, largely on the basis of their more severe clinical nature, and the presence, in histological sections, of a periglandular inflammatory infiltrate.
Graykowski et al. (1966) regarded these lesions as an exaggerated form of typical aphthae, with the same predisposing and precipitating factors, the same prodromal feeling of paraesthesia, and the same locations. These authors also stressed the fact that the disease usually began in the form of typical aphthae which developed in severity during the course of the affliction. This last point is moot. Lehner (1968) states that either form may change into the other, whereas Francis (1970) states that the disease usually remains status quo, i.e. the mild form usually does not develop into the severe form at a later time.

Graykowski and co-workers presented a detailed histological examination of lesions in various stages of development, showing the involvement of the deeper mucosal tissues with a cellular infiltration of the periglandular mucosa (periadenitis). The difference from typical aphthae was purely one of degree. This was also the finding of Ship et al. (1962). Cooke (1969) said that the persistence of necrosis and the lack of inflammatory reaction to the necrosis suggests important vascular damage. Williamson (1966) also mentioned a fairly deep vascular lesion in connection with these ulcers.

Graykowski and his colleagues gave an intradermal injection of a streptococcal vaccine to 30 patients with aphthous ulcers. All gave positive delayed hypersensitivity reactions, with the severity of the skin lesions tending to parallel the severity of the oral lesions in the patients concerned. Significantly, in four patients whose oral lesions developed scars, the skin reactions developed necrosis followed by scar formation. This appears to be further evidence of a merely quantitative difference.
The histological picture presented by Graykowski et al. can be summarized as: intact epithelium (in early state); corium, submucosa and minor salivary glands affected; no intranuclear inclusions; lymphoid cells predominate early (neutrophils later); destruction of epithelial layer; deep necrotic plug; scar formation.

In a detailed histological and electron microscopical examination of major and minor aphthous lesions carried out by Lehner (1968), no significant differences could be detected. Both conditions fulfilled the histological criteria for delayed hypersensitivity as laid down by Coe et al. (1966), and the incidence of focal sialadenitis was similar.

Lehner (1968) found humoral and cell-bound antibodies in both conditions. Both showed a raised incidence of haemagglutinating, complement-fixing and precipitating antibodies, and immunoglobulin binding was found in autologous tissue. Oral mucosa was found to stimulate lymphocyte transformation in both conditions, but skin had this effect only in the major form of the disease (Lehner, 1967b). Both lesions revealed raised IgG and IgA levels on serum immunoglobulin estimation, but only in the major form did the increase reach statistical significance. Salivary IgG and IgA remained normal in both cases.

In a later paper, Lehner (1969e) wrote: "MiAU (minor aphthous ulceration) and MjAU (major aphthous ulceration) do not differ pathologically, except in the degree of severity and extent of the microscopical changes; this is consistent with their clinical and immunological features."
They show an early and intense mononuclear cell infiltration and IgG and IgM binding by the spinosal cells. Focal sialadenitis of the minor salivary glands has not been a common finding in either type of aphthous ulcers. It is for these reasons that the cumbersome and misleading term 'periadenitis mucosa necrotica recurrens' (Sutton, 1911) has been changed to MjAU, which indicates the same disease process as occurs in MiAU, except for an increased severity."

Treatment has been administered as for ordinary aphthae (q.v.), but because of the severity of the condition, systemic hydrocortisone therapy has more often been utilised -- Alling (1956), Reading (1966), Ryan (1966). Ryan administered oxyphenbutazone 200 mg. daily for 3 to 4 days with 10 to 20 mg. of prednisolone. Cooke (1969) comments that because of the possible changes involving the deeper capillaries and the effect of this drug on the endothelium, it would appear a logical treatment needing further investigation. Weichselbaum and Derbes (1957) suggested that the complete suppression obtained with prednisone confirms this as a separate disease to Behcet's disease and simple aphthae (sic).

A satisfactory summary is provided by Francis (1970): "The severe form ... is similar to the mild form in many respects, except that it is greatly exaggerated. The prodromal symptoms of burning and pain associated with swelling and inflammation are more intense. The initial lesion begins as a 1 to 5 mm. white plaque or swelling that expands and ulcerates quite rapidly reaching a diameter of 10 to 30 mm. or more. These recurrences are associated
with considerable discomfort, induration, and tissue destruction, and frequently the patient will complain of generalized fatigue. These large lesions may remain for weeks or months, and they commonly heal with scarring. Over a period of years, considerable destruction with scarring of the intraoral tissues may occur."
CHAPTER 7 - HERPETIFORM ULCERS:

In 1960 Cooke described a condition which he called "Recurrent Herpetiform Eruption", characterized by "recurrent crops of multiple shallow erosions, often 20 or more in number, on any part of the mouth or oropharynx" which failed to show the histological and cytological characteristics of a herpes simplex infection. Apart from lacking the diagnostic signs of herpes, the disease behaved clinically like a recurrent herpetic infection, hence Cooke's usage of the term herpetiform.

This condition may well have been anticipated by Farmer (1956) who indicated, after histological examination of early lesions from 18 subjects, that more than one type of aphthous lesion existed. He found in one case inclusion bodies resembling those of herpes simplex origin.

Strean et al. (1958) had previously suggested the use of the term herpetiform to include the lesions of herpetic gingivostomatitis as well as aphthous ulceration, both of which, they claimed have a vesicular stage. This all-embracing meaning is the one intended by a contributor to Queries and Minor Notes 426 and by Claus et al. (1961) and Colby et al. (1961), and criticised by Schaffer (1960) as "rather meaningless". Schaffer's objection is that the use of the term results in a purely descriptive word acquiring the status of a specific disease. Ironically, that is precisely what Cooke intended, although he used the term in a narrower sense.

Although the term is a legitimate usage to describe a lesion which resembles an herpetic one, it is rather unfortunate in that it leaves us with two clinical entities,
herpetic lesions and herpetiform lesions, which are so alike in terminology, but mutually exclusive as pathological conditions. Weathers and Griffin (1970) have criticised the term, while Brody and Silverman (1969) appear to use it reluctantly.

The following clinical details were given in Cooke's original description of the condition in 1960:

1. Recurrent crops of 20 or more pin-point ulcers on any part of the oral mucosa.
2. Swelling of the affected tissues and enlargement of the cervical lymph nodes.
3. No macroscopical vesicles observed.
4. Neither epithelial smears nor histological details are characteristic of infection with the herpes simplex virus.
5. The ulcers are too numerous and too small as compared with minor aphthae, but since they are similar histologically they may be allied conditions.
6. Whereas normal aphthae are not affected by a 2% Aureomycin mouthwash, it is almost diagnostic that this mouthwash b.d.s. for two days will allow the herpetiform ulcers to clear temporarily.
7. They occur anywhere in the mouth, whereas Cooke (1961) considers normal aphthous ulcers to occur only on the nonkeratinized mucosa.

Cooke's clinical segregation of his herpetiform lesions from the normal type of aphthae received good support from the investigations of Lehner and Sagebiel (1966) into the fine structural detail of recurrent oral ulcers. With light
microscopy, the herpetiform type differed in that it revealed vesicles within the stratum spinosum containing predominantly lymphocytes and histiocytes. Electron microscopy confirmed this finding and, additionally, revealed intranuclear inclusion bodies and intra-cytoplasmic phagosome-like bodies. The intranuclear bodies, significantly, did not resemble the herpetic virus. According to the authors, the intranuclear bodies in herpetiform ulceration appear to have a virus-like structure, and the clinical features resemble a known viral lesion; nevertheless the proof as to a virus aetiology can come only from cultural studies.

In the following year, Lehner (1967c) stated that herpetiform ulceration favours a virus aetiology because:

(a) clinically it resembles a known virus lesion (herpetic stomatitis),
(b) it responds dramatically to tetracycline treatment which is known to be effective against large viruses,
(c) intra-epithelial vesicles are seen in sections of the ulcer
(d) intra-nuclear inclusion bodies are found on electron microscopy
(e) a significant incidence of antibodies against oral mucosa is not detected.

It appears unquestioned that these lesions are a distinct entity, different from both normal aphthous lesions and the lesions of herpes simplex. Lehner (1969e) stated that herpetiform ulcers differ from normal aphthous lesions by the presence of epithelial vesicles, intranuclear inclusion bodies, lack of immunofluorescent binding and a low incidence of antibodies to oral mucosa. These features, and the clinical resemblance to a viral disease (herpes simplex infection) suggest a viral aetiology. Herpetiform
lesions differ from herpes simplex infections, according to Lehner and Sagebiel (1966), in that the vesicular stage is rarely seen clinically, and multinucleated giant cells, typical intranuclear inclusion bodies, and a rising titre against herpes simplex virus have not been recorded.

The number of individual lesions may be very high. Lehner (1969e) states that up to 100 may be present, Cooke (1960) 20 or more, Lehner and Sagebiel (1966) 10 to 100, Kramer (1967) 40 or more, Lehner (1967c) 10 to 40, and Brody and Silverman (1969) 10 to 100.

It is very difficult to assess the incidence of the condition, as it has been so infrequently described, and may be mistaken for herpes simplex infection. However, Lehner and Sagebiel (1966) claimed 8 cases in a series of 100 patients with oral ulcers. Lehner (1967c) states that herpetiform lesions are relatively common in Behcet's syndrome.

Tetracycline therapy provides very effective palliation. Kramer (1967) remarked that the viral hypothesis of herpetiform ulceration accords with the good response to tetracycline therapy. Cooke (1961) stated that the lesions may be made worse by hydrocortisone and Kramer (1969) found no response to idoxuridine.

In 1968, Lehner presented a detailed comparison between herpetiform and major and minor aphthous ulcers, although with only 8 cases of the herpetiform variety, the statistical details pertaining to them may not be absolutely reliable.
Nevertheless his findings in respect of herpetiform ulcers are as follows:

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<table>
<thead>
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<tr>
<td>Sex ratio F:M</td>
<td>2.6:1</td>
</tr>
<tr>
<td>Age of onset (peak incidence)</td>
<td>20-29 years</td>
</tr>
<tr>
<td>Number of ulcers</td>
<td>10 to 100</td>
</tr>
<tr>
<td>Size</td>
<td>1-2 mm.</td>
</tr>
<tr>
<td>Duration</td>
<td>7-14 days</td>
</tr>
<tr>
<td>Healing by scar</td>
<td>32%</td>
</tr>
<tr>
<td>Recurrence</td>
<td>less frequently than monthly</td>
</tr>
<tr>
<td>Sites</td>
<td>lips, cheeks, tongue, pharynx, palate, floor of mouth, gum</td>
</tr>
<tr>
<td>Total duration</td>
<td>Less than 5 years</td>
</tr>
<tr>
<td>Associated oral lesions</td>
<td>none</td>
</tr>
<tr>
<td>Treatment</td>
<td>tetracycline</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>Raised IgA</td>
</tr>
<tr>
<td>Humoral antibodies</td>
<td>-</td>
</tr>
<tr>
<td>Cell-bound antibodies</td>
<td>+</td>
</tr>
<tr>
<td>Intra-epithelial vesicles and inclusion bodies</td>
<td>present</td>
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CHAPTER 8 - TRAUMATIC ULCERS: THEIR RELATIONSHIP TO APHTHAE.

Solitary ulcers, whether of aphthous or traumatic origin, have received some special consideration in the literature and have caused some confusion.

Theron (1959) makes a distinction between chronic recurrent aphthae ("CRA") and solitary aphthae. Synonyms for the latter condition, he states, are localised solitary ulcers, trophic ulcers, neurotrophic ulcers, and non-recurrent non-habitual solitary aphthae. Solitary aphthae are carefully distinguished from traumatic ulcers.

A distinction between aphthous ulcers on the basis of their recurrence of apparent lack of it was also made by Hirsekorn (1935), Marti (1941), Kumer (1942), Frech (1945) and Schaffer (1951).

Thoma (1944, 1950, 1954) and Thoma and Goldman (1960) describe a variety of lesions under the general title of localised solitary ulcers, which they state are generally the result of injury to the oral mucosa, from which an infection spreads peripherally. The ulcers placed in this general classification are:

1. Simple ulcers, originating from the gingival margin or around broken-down infected teeth.

2. Bednar's aphthae, which occur in a symmetrical fashion on the palates of young children and are thought to be due to pressure from the nipple when nursing or from cleaning the mouth with rough gauze.
3. Decubital ulcers, which occur on the tongue from irritation from a decayed tooth, or are due to pressure from a denture.

4. Trophic ulcers, said to be the result of a disturbance in the nutrition of the tissues, such as following the injection of a local anaesthetic. Thoma says this is generally due to the addition of escharotics to the anaesthetic.

5. Neurotrophic ulcers, caused by impairment of nutrition because of a defective peripheral nerve. The nerve may have been injured by trauma or heat.

It is obvious that there is scope for a good deal of confusion. Aphthous and traumatic lesions can be clinically similar, and trauma may serve to provoke aphthous lesions and herpetic ones also.

Although Theron and Thoma agreed in separating solitary and recurrent lesions, they differed in regard to aetiology and terminology. Thoma considered the solitary ulcers to be of traumatic origin and referred to the recurrent type as "habitual aphthosis". Theron believed that the solitary type were not traumatic, but a special type of aphthous ulcer. Theron employed the term aphthosis in the sense adopted by Touraine (1941), namely, to apply to a condition in which oral aphthae appeared in conjunction with lesions on the genitals and perhaps the skin, and originally called aphthosis by Neumann in 1895.

Francis (1970) claims that trauma is the most frequent precipitating factor in aphthous ulcer formation, citing Ross et al. (1956) and Cooke (1969).

Many of the traumatic details mentioned by the above authors as provocative of aphthous lesions correspond to those listed by Thoma in his non-aphthous category. There is aetiological overlap and, as remarked by McCarthy and Shklar (1964), close clinical similarity.

Important differences exist between aphthous and traumatic ulcers, however, and will be discussed under the following headings.

**History:**

Brody and Silverman (1969) state simply that trauma may be ruled out by the history. This will be so in many cases, but the issue is not always so clear-cut. Trauma may provoke an aphthous lesion.
McCarthy and Shklar (1964) also stress the importance of the history. Those with traumatic lesions usually have no history of periodic lesions and the patient may be aware of the traumatic incident; in other instances the traumatic lesion may be related to a sharp tooth or faulty denture.

**Clinical appearance**

It is generally agreed that traumatic ulcers tend to lack the regular outline of aphthous ones.

Stark et al. (1954): Traumatic aphthae have irregular margins.

Driscoll et al. (1959): Traumatic lesions have irregular undermined margins and are accompanied by inflammation.

McCarthy and Shklar (1964): Traumatic ulcers are not so well circumscribed and localized, and the margins not so sharply defined.

Ship (1965a): Traumatic lacerations and contusions have irregularly undermined margins and are accompanied by acute inflammation.

Brightman and Ship (1966): The traumatic ulcer is usually irregular in shape and discrete, and its shape and location may give clear evidence of its cause. The margin of the ulcer may show considerable oedema with an erythematous response for several days after the injury, but old ulcers are more likely to be surrounded by indurated tissue with little erythema.

**Duration:**

It is a feature of aphthous ulcers that they require more time to heal than the amount of tissue damage would indicate. Cooke (1961) states that it takes anaphthous lesion three or more times longer than a simple ulcer to heal.
It has been pointed out that taking a biopsy accelerates the healing of aphthous lesions - Cooke (1961), Ship et al. (1962), Brody and Silverman (1969). Durocher (1966) reported a similar increase in the healing rate following the scraping of aphthous lesions for the taking of cytology specimens.

Whereas aphthous ulcers may require 10-14 days to heal, traumatic ulcers heal in 2-5 days (Driscoll et al., 1959), 2-3 days (Cooke, 1961), 2-4 days (Ship, 1965a).

**Histopathology**

The essential difference here is that a traumatic lesion manifests a simple inflammatory reaction whereas the aphthous ulcer, as pointed out in an earlier chapter, conforms to a delayed hypersensitivity reaction.

The differences are well summarized by Lehner (1969e): The non-specific ulcer differs from the aphthous type "in the less marked mononuclear and perivascular infiltration, a more pronounced neutrophil infiltration and fewer mast cells. Epithelial vesicles and intranuclear inclusion bodies are absent and the fluorescent antibody test is negative."

In history, clinical appearances, duration and histological details then there are distinct differences between aphthous and traumatic lesions. What can be said of the relationship between them?
Clearly, not all aphthous lesions result from trauma, although trauma has been said to be the most significant precipitating factor (Francis, 1970). In an analysis of the histories of 230 students, Ship et al. (1961a) found that 14% considered local injury to precipitate their aphthous lesions. Sircus et al. (1957) did not find a strong correlation in this regard. Of the 62 patients of Graykowski et al (1966), 74% considered trauma a precipitating factor. Farmer (1958) found that 19% of his 121 patients attributed the onset of lesions to factors such as toothbrush injury or cheek biting. In Brody and Silverman's study in 1969, trauma was not considered an apparent aetiological factor at all.

As several authors have remarked, there is a qualitative difference or predisposition existing in aphthous patients which distinguishes them from those who would respond to a traumatic episode, not by the formation of an aphthous ulcer, but by a more simple lesion. Among these may be mentioned Everett (1950), Sircus et al (1957), Ship et al. (1962), Shafer et al. (1963), Kramer (1967) and Davies-Thomas (1968). However, little experimental work appears to have been carried out on the different behaviour of aphthous-prone and non-aphthous-prone oral mucosa to traumatic insults.

One such study, however, is that by Ross et al. (1958). These authors subjected both sides of the lower mucobuccal fold (where no ulcers were present) to trauma in patients from aphthous and non-aphthous groups. No ulcers appeared in any of the controls. Only some of the patients with a history of recurrent aphthae developed lesions, and
these were smaller in size, less severe in intensity, and probably of shorter duration than those normally experienced. During the course of the experiment, several patients acquired typical aphthae at sites remote from the experimental trauma. This study must cast serious doubt upon the alleged primary role of trauma.

In reply to Moore (1968) who saw trauma as a prime cause of aphthous ulceration in healthy mouths, Carruthers (1968) cited the experience of women obtaining freedom from aphthous ulceration during pregnancy or while taking oestrogenic preparations, and the low incidence of the disease in the over-60 age group. Carruthers saw the reasons for these experiences as due to a change in resistance to trauma as a result of increased cornification from the effects of oestrogen on the one hand, and the aging process on the other.

This chapter is not intended as a review of traumatic ulcers, or as an investigation of the aetiology of aphthous ulcers, but is offered to show some of the problems that have arisen in the literature in the association between these two lesions.

In summary, although some aetiological and clinical overlap may exist, traumatic ulcers can usually be distinguished from aphthous ones on the basis of their history, clinical appearance, duration and histopathology.
CHAPTER 9 - HERPETIC INFECTIONS:

In 1920, Gruter inoculated material from herpetic corneal lesions into rabbits and a human subject, reproducing clinically identical lesions. In the following year Luger and Launda proved that the infecting agent was a filtrable virus, and Lipschutz (1921) described intracellular inclusion bodies in the epithelial cells of a lesion of herpes labialis.

In 1924 Gans, noting the similarity between aphthous lesions and herpes labialis ("tendency to recur, short-lived immunity, general disturbance, temperature"), investigated the possibility of an herpetic cause of aphthous lesions in six patients. Employing the methods described by Gruter, Gans achieved a positive result in one case only. He concluded (fallaciously, in the light of later knowledge) that the five negative cases resulted from their mild nature. Gans' experimental findings were repeated by Feyrter (1927).

Templeton (1926), in an article entitled "Is aphthous stomatitis due to the virus of herpes simplex?" reported his failure to produce corneal lesions in rabbits after inoculation with material from oral ulcers. Like Gans before him, Templeton was almost certainly dealing with recurrent aphthae and not herpetic lesions.

In 1930, Flusser demonstrated the infectious nature of herpetic stomatitis and pointed to its occurrence in more than one member of the family.

Zamorani in 1930 appears to have been the first to demonstrate positively the herpetic nature of what was then known as "acute aphthous stomatitis".
Using material from six patients with the disease, he produced, in carefully controlled animal experiments, positive results from corneal inoculation. Kumer (1932) reproduced these results with material from eight patients.

Despite the work of Zamorani and Kumer, the later literature bears repeated instances of failure to heed their findings. Thus Blanke's article in 1934 makes no reference to their work, Hirsekorn (1935) thought it impossible to tell whether acute and chronic aphthae (sic) had the same aetiology, and Black (1938) was impressed by the state of the gingival tissues in the acute condition which he considered identical with Vincent's infection.

However, Dodd and his co-workers in 1938 reaffirmed the herpetic cause of "acute aphthous stomatitis" in twelve cases, and Burnet and Williams in the following year reported the finding of neutralizing antibodies to the herpes simplex virus in the sera of patients convalescing from the disease. These findings were confirmed by Scott et al. (1941) who described the typical clinical features of acute herpetic gingivostomatitis. They showed a history of contact in 33 cases and stated that the incubation period was 3–9 days.

Burnet and Williams divided herpetic lesions into primary and recurrent infections. They postulated that, following the initial attack, the virus remained in an intracellular location and caused recurrent episodes when the resistance of the host was lowered by local or systemic factors. This is an attractive hypothesis which explains the association between recurrent herpetic attacks and factors such as sunlight, fever, anxiety and menstruation (Ship et al. 1967) although, according to Driscoll et al. (1959),
no conclusive evidence exists for the persistence of the virus in the tissues during remissions. This question of the latency of the virus in the tissues will be considered subsequently.

In 1938 Black reported on 69 cases of acute herpetic stomatitis, 80% of which occurred before the age of four. He speculated that the cause was a virus, and that fusospirochaetal invasion occurred secondarily.

Black, in 1942, demonstrated the relationship of herpes simplex virus to recurrent herpetic lesions by inoculating the gingiva of a child with material from a typical "cold sore". He observed the ensuing illness which was recognized as primary acute herpetic gingivostomatitis. Isolation of the virus and demonstration of a rising antibody titre with convalescence were reported.

Davies and Longson (1970) state that early descriptions of acute herpetic gingivostomatitis were given by Gubler (1858) and by Trousseau (1861). A severe form of the disease occurring in debilitated children was described by Pospischill in 1921 and called aphthoid of Pospischill.

Possibly because of authoritative reports by authors like Dodd et al. (1938) and Burnet and Williams (1939), the occurrence of oral herpetic lesions has been associated with children, and only more recently has acute herpetic gingivostomatitis in adults been established as a clinical entity. Various authors have suggested that the primary attack of herpes simplex virus may be delayed from infancy to adulthood because of improved living standards —
Yoshino et al. (1962), Smith et al. (1967), Southam et al. (1968) and Davies and Longson (1970).

Burnet and Williams believed that the non-herpetic possessed a resistance which, because of the absence of antibodies against the virus, they regarded as non-immunological. Rustigian et al. (1966), using in vitro cultures of oral mucosa from non-herpetic individuals, found a variability in susceptibility to small doses of inoculations of herpes virus.

Buddingh and co-workers (1953) recovered the virus from the mouth and stools for 23 days following infection, and demonstrated maximal antibody titres during the second and third weeks, following which the titre fell and, apart from fluctuations, remained at a low level. These workers could not confirm the "all or none" response described by Burnet (1945). There is considerable controversy over the stability of antibody titres, and the situation is documented in the chapter on the alleged viral aetiology of aphthous lesions.

In 1949, Tzanck and Avon-Brunetiere demonstrated epithelial giant cells in smears taken from the vesicles of herpes simplex, herpes zoster and varicella. The authors regarded these cellular aberrations as pathognomonic of viral infection. The technique was evaluated by Blank et al. (1951) who concluded that it is a simple, rapid and dependable method of diagnosis of viral disease. Further confirmation was provided by Cooke (1958, 1960, 1963).
Griffith (1963) described a fluorescent antibody technique for the definitive diagnosis of herpes simplex virus. In this technique, only cells infected with the herpes simplex virus will stain. This paper established beyond doubt the presence of recurrent intraoral herpetic infections the occurrence of which was previously a disputed point. Unfortunately, the evidence was misinterpreted by some as suggesting that the herpes simplex virus was the cause of aphthous ulcers. 

Evidence that the herpes simplex virus is the cause of herpes labialis:

Various techniques have been employed to establish an aetiological relationship between the herpes simplex virus and herpes labialis. Some of the relevant studies are cited below.

1. Tissue inoculation:
   Blank et al. (1950), Dodd and Ruchman (1950), Dascomb et al. (1955), Griffin (1963).

2. Tissue culture:
   Ship et al. (1961)

3. Serological methods:
   Burnet and Williams (1939), Stark et al. (1954), Dascomb (1955), Sircus et al. (1957), Driscoll et al. (1959).

4. Fluorescent antibody techniques:
   Biegeleisen et al. (1959), Lebrun (1956), Griffin (1963).

5. Biopsy:
   Blank et al. (1951), Driscoll et al. (1959), Cooke (1960).
6. Cytology:
   Blank et al. (1951), Cooke (1960), Griffin (1963)

7. Autoinoculation:
   Black (1942)

The latency of the virus in the tissues.

Burnet and Williams (1939) postulated the persistence of the virus in an intracellular location following the initial infection. Andrews (1967) and others have stated that the virus remains latent in epithelial cells or in local nerves or nerve ganglia.

Among those who have favoured a dermotropic role are Burnet and Williams (1939) and Carton and Kilbourne (1952). A neurotropic role has been suggested by others, including Nicolau and Poincloux (1924), Goodpasture (1929) and Paine (1964).

According to Smith (1963), the herpes simplex virus demonstrates a preference for ectoderm, principally the skin, mucous membranes and eyes, and the central nervous system. Paine (1964) states that experimental studies in animals and activation of latent infections in man after operation for trigeminal neuralgia indicate a distinct neurotropism.

Paine (1964) offers an elaborate neurotropic hypothesis for the rationale of latency of HSV in man: (i) Primary infection probably involves sensory nerve endings in addition to epithelial cells. (ii) The virus travels centripetally in sensory nerves through contiguous endoneural supporting cells, particularly the Schwann cells. (iii) Ganglionic nerve cell nuclei are invaded when the
centrally moving infection of the neuroglial cells reaches the level of the ganglia. (iv) The noninfective core of the herpesvirus may remain in its latent state in the sensory ganglia, usually the Gasserian ganglia, (v) On activation of the herpesvirus, new infective virus particles may be synthesized in the nerve cell nucleus and released into the cytoplasm of the nerve. (vi) By means of an axonal flow due to nerve fibre peristalsis, the infective virus particles move in a centrifugal direction down the axon of the peripheral nerve until epithelial cells are reached, where the characteristic vesicles are produced.

However, Rustigian et al. (1966) state that the virus cannot be recovered during its quiescent state in the tissues. Similarly Findlay and MacCallum (1940) were unable to recover the virus from recurrently affected skin sites in the intervals between attacks by inoculation of scrapings into the corneae of rabbits.

Recent papers have suggested that the virus may be present in secretions rather than within ectodermal cells. Kaufman et al. (1967) state that true latency has never been proved, and suggest that the virus remains actively multiplying in the salivary and lacrimal glands, and is frequently present in secretions from these glands. Platt (1969) has suggested that localized trauma may act to reduce cellular resistance to the virus actively present in secretions, rather than to disturb a symbiotic relationship thought to exist between the virus in its latent state and the epithelial cell.
Recurrent herpetic infection of the oral mucosa

The existence of a true recurrent herpes simplex infection of the oral mucosa has been questioned (Cooke, 1960), and even denied (McCarthy and Shklar, 1964). In 1960 Cooke described an "herpetiform" lesion, not due to the herpes simplex virus, which nevertheless appears to be of viral origin (Lehner, 1967c).

Certain authors affirmed that herpetic gingivostomatitis gave rise to recurrences. Among them are Scott et al. (1941), Ziskin and Holden (1943), Cahn (1950), Kilbourne and Horsfall (1951), Kerr (1952a, 1952b), Farmer (1956) and Strean (1957). Others, however, denied the possibility of recurrence - Dodd et al. (1939), Ruiter (1950), Blank and Rake (1955), Vest (1957) and Dekking (1958).

Griffin (1963, 1965) presented four cases of intraoral recurrent herpes simplex virus infections, the diagnosis being verified in each instance by cytologic and fluorescent techniques. There can be no doubt that recurrent intraoral herpes exists as a clinical entity. A case was presented by Muller (1968), the diagnosis being confirmed by cytology and virus isolation. Southam (1969) described a case, diagnosed by cytological smears, in which there was no apparent history of herpes labialis. Others who attest to the presence of this condition are Brightman and Ship (1966), Greenberg et al. (1969) and Weathers and Griffin (1970).

The occasional isolation of evidence of viral infection from aphthous-like lesions must have served to prolong the belief of some that aphthous lesions were caused by the virus of herpes simplex. Kilbourne and Horsfall (1951) recovered herpes simplex virus from a
lesion clinically resembling an aphthous ulcer on three separate occasions. Collings and Dukes (1952) found intranuclear inclusion bodies, typical of the herpes simplex virus, in a lesion clinically resembling an aphthous ulcer. Farmer (1956) reported 10 cases of primary herpetic stomatitis with histories of recurrent oral lesions but without systemic effects. A biopsy of a vesicle demonstrated the presence of intra-nuclear inclusion bodies.

It has also become established in recent years that the primary attack of herpes simplex infection may not occur until adulthood, as Davies and Longson (1970) affirm. Various authors had found that the condition usually occurs in children - Dodd et al. (1938), Burnet and Williams (1939), Kilbourne and Horsfall (1951), and Cath (1955). However, the literature bears many instances of primary cases being reported in adults. Among them may be cited cases of Youmans (1932), Ziskin and Holden (1943), Rogers et al. (1949), Ruiter (1950), Kilbourne and Horsfall (1951) and Blechman and Pascher (1959). As mentioned earlier, a later age incidence has been attributed to a rise in living standards. As Reade (1961) points out, secondary bacterial infection, usually streptococcal, may complicate herpetic infections. The condition sometimes referred to as streptococcal stomatitis or streptococcal gingivitis is actually an herpetic condition secondarily invaded by streptococci.

The incidence of herpes virus antibody in the population: Buddingh et al. (1953) have been extensively quoted as showing that 90% of the population over 15 years of age have neutralizing antibodies to the herpes simplex virus.
Another report, using the less sensitive complement-fixation technique gives a figure of 86% in the same age groups - Holzel et al. (1953). It has become apparent that the incidence is influenced by socioeconomic factors - Anderson and Hamilton (1949), Smith et al. (1967).

Smith et al. (1967) found an incidence of only 40% among Edinburgh medical students, 48% among nurses, and 36% among Oxford medical students. On the other hand, a high incidence of neutralizing antibody (75-100%) was found among children under 6 months. The incidence then declines to 19% at 6-11 months, then rises slowly until 15-25 years when it reaches 65-69%. Thereafter it increases to an ultimate 97% in the over 60 age groups.

Comparison of the Edinburgh survey (710 samples of sera) with the figures of Buddingh et al. (1953) from white children in New Orleans reveals that in the under 6-month group, the incidence of antibody was very similar. In subsequent age groupings, however, there was a sharper decrease in the Edinburgh figures, although the graph lines tended to approximate above age 30. Figures released by Yoshino et al. (1962) for Japan show a similar trend except for an increased incidence in the 10-19 year group.

Widespread activity of the herpes simplex virus:

A wide range of pathological activity has been accredited in later years to the herpes virus. It has been well-known for many years that the organism has a predilection for muco-cutaneous junctions (Reade, 1961), and intra-orally, herpetic lesions tend to occur on the epithelium attached to the periosteum (palate, alveolus and gingiva) while aphthous lesions occur on the mobile mucosa (Weathers and Griffin, 1970.)
Even in the earlier literature there was evidence of a more widespread activity. Thus Bruusgaard (1930) reported extensive herpes simplex lesions with a retrobulbar neuritis; Keining (1933) recurrent herpes of the third and fourth fingers of the left hand, with swelling of the back of the hand and forearm resembling erysipelas; Kicevaci (1934) labial and nasal herpes, accompanied by a scarletiform rash on the skin; and Esteves and Pinto (1952) isolated the herpes virus from a case of urethritis.

Examples of later reports of even more far-reaching activity can be listed as follows:

Infections of the female genital tract: Kleger et al. (1968)
Infections of male and female genitalia: Parker and Banatvala (1967), and Reade (1961).
Infections of skin: Boake et al (1951), Brightman and Guggenheimer (1970)
Autoinoculation of hand or arm: Cooke (1960), Reade (1961), Davies and Longson (1970)
Disseminated neonatal herpes from inoculation by a genital infection in the mother: Nahmias et al. (1967).
Infections of the central nervous system, including meningitis and encephalitis: Read (1961), Smith (1963), Shafer et al. (1963), Shearer and Finch (1964)
Hepatitis: Smith (1963)
Conjunctivitis: Shafer et al. (1963)
Infections arising from traumatic implantation of the virus: Findlay and MacCallum (1940), Lazar (1956), Stern et al. (1959), Rizzo and Ashe (1964).
Serious and even fatal infections have been reported by Hayes et al. (1968), Smith (1963) and others. The virus has also been associated with neoplastic disease, more specifically leukaemia and lymphoma (Rauscher, 1968) and carcinoma of the cervix (Rawls et al., 1968).

There is a greater recognition of herpetic skin infections resulting from contact with infected saliva or vesicular fluid. Snyder et al. (1969) state that many of these have gone unrecognized or perhaps treated as staphylococcal infections. These have been typically reported for:

**Wrestlers:** Selling and Kibrick (1964), Wheeler and Cabaniss (1965), Porter and Baughman (1965), Dyke et al. (1965).

**Nurses:** Stern et al. (1959), Kanaav (1966), Knyvett (1966).

**Dentists:** Pascher and Blechman (1959), Bart and Fisher (1965), Snyder et al (1969).

**Life Cycle of the virus:**

The most complete sequence of events making up the life cycle of a virus has been worked out for vaccinia. This is presented by Levin (1965) as follows:

1. The host is invaded by an elementary body of the virus, an elementary body being a single infective unit of virus.

2. The host stops metabolic process of benefit to itself and commences to manufacture virus particles. During this stage, a few hours after invasion of the cell by the elementary body, an inclusion body in the cell is formed. This is called the plaque stage, or the early form of the inclusion body.
3. When a sufficient number of virus particles have been produced, the host cell lyses, and releases many new elementary bodies, which are now free to invade new host cells, and the cycle is repeated. In this stage, after formation of the inclusion body, the cell nucleus is pushed to the periphery and the inclusion body occupies most of the cell. Then lines or trabeculae form inside the inclusion body. The inclusion bodies split into thousands and millions of elementary bodies, and when lysis of the cell occurs the cell wall ruptures, releasing all of the elementary bodies. These elementary bodies are composed of protein and a nucleic acid. When attached to the cell, they split into two parts. The protein dissolves the cell wall but stays on the outside of the cell. Only the nucleic acid fraction of the elementary body enters the cell and induces it to make more virus. The noteworthy thing in this sequence of events is the fact that the host cell, instead of fighting the invasion of the parasite, is actually assisting in the formation of a virus material, thus committing suicide.

Release of the virus may occur in two ways: (1) The cell may burst, as in molluscum contagiosum, or (2) there may be defects in the cell walls through which the elementary bodies escape, as in herpes simplex.

Clinical and histological features of herpes virus infection:
This account is taken from Levin (1965):
"In the adult the first clinical symptoms of herpes simplex may be soreness or pain in the mouth and throat; bleeding, swollen, and painful gingivae; discomfort on swallowing;"
enlarged and tender submaxillary glands; and malaise. Several days later small, rounded vesicles appear anywhere on the oral mucosa, tongue, or lips. The vesicles soon rupture, liberating a clear yellow fluid, and leave raw painful ulcers with erythematous margins. The ulcers may be discrete or confluent."

"Histologic study shows oedema and congestion of the corium, with vesicle formation and infiltration of many neutrophils in the corium as well as into the epidermis around the vesicles. The epidermal cells show hyperplasia and necrosis. There are large eosinophilic nuclear inclusions and many infected multinucleated viral giant cells, which often fill but do not extend the nuclei. There is condensation and margination of the nuclear chromatin, so that the nuclei are represented by an irregular black margin surrounding the inclusions but often separated by a clear zone. The electron microscope shows spherical and doughnut-shaped elementary bodies. The inclusions are definitely granular when suitably stained, and the relatively large size of the virus (175 my) would suggest that elementary bodies might be visible."
CHAPTER 10 - APHTHAE IN ASSOCIATION WITH OTHER LESIONS:

In 1895 the Viennese physician Neumann described a condition referred to as aphthosis, in which oral aphthae appeared together with similar lesions on the genitals and occasionally also with skin lesions. The skin lesions resembled erythema nodosum or erythema multiforme together with papules or pustules with a red areola. Mild pyrexia was usually present. The condition seemed to involve females and young subjects in poor circumstances, and of the fourteen cases originally described all had genital lesions, 11 oral and 4 skin lesions (two with an erythema nodosum and two with an erythema multiforme-like condition). Whitwell (1934) believed that the association of oral aphthae with erythema nodosum placed the former as almost certainly infective in origin.

In 1912 Lipschutz described an acute ulcer of the vulva ("ulcus vulvae acutum") which he considered a separate pathological entity. From these lesions he isolated numerous thick Gram-positive bacteria which he called Bacillus crassus and which he considered to be the aetiological agent.

Whitwell (1934) stated that aphthous vulvitis clinically resembles oral aphthae. He evidently saw the two conditions as being distinctly related, stating that in some women the preponderance of ulcers is seen on the vulva, in others both sites are involved, and in a third group the mouth only. Whitwell described the vulval ulcers as occurring on the inner surfaces of the labia majora and minora, but sometimes on the inside of the thighs and round the anus.
The diagnosis of ulcus vulvae acutum is, according to Theron (1959), out of date, although it is noted that this diagnosis was suggested of a case presented in the American Medical Association Journal in 1950. Whitwell says that against the pathogenicity of B. crassus must be set the failure of autoinoculation, and the fact that the organism is an acidogenic one found in the healthy vagina.

Many workers subsequent to Lipschutz reported combinations of genital lesions and oral aphthae, or genital lesions, oral aphthae and skin lesions. Nearly all those who described cases of ulcus vulvae acutum, according to Theron, were able to isolate B. crassus from the lesions, and some isolated this organism from oral lesions. Indeed, B. crassus had a popular reign as the causative agent of oral aphthae, especially on the Continent between 1923 and 1932 (Sircus et al., 1957; Ship et al., 1962).

The difference between the aphthosis of Neumann and ulcus vulvae acutum seemed to rest on the isolation of B. crassus. Kumer (1930) saw the two conditions as similar but distinct in that B. crassus could not be demonstrated in aphthosis. However, because of their failure to identify the organism consistently in their cases, Wien and Perlstein (1932) concluded that the two conditions were one and the same disease.

Various ophthalmologists reported cases in which eye lesions were accompanied by oral and genital lesions. Among these may be mentioned Weve (1923), Adamantiades (1931) and Dascalopoulos (1932).
Although he was not the first to describe it, the combination of eye, oral and genital lesions has been associated with the name of Behcet ("The Triple Symptom-Complex of Behcet") since his first publication in 1937. Phillips and Scott (1955) state that ulcus vulvae acutum of Lipschutz, periadenitis mucosa necrotica recurrens of Sutton and aphthosis of Neumann are identical with the genital and oral lesions of Behcet's syndrome. In the absence of eye involvement, they say, it seems to be a purely academic problem which name to use. Fraser-Moodie (1953) agrees that the lesions of Lipschutz and Sutton may be examples of Behcet's syndrome in partial form.

Theron states that Behcet's contribution was a very significant, though not an original, one because:

1. He realised that the concurrent appearance of oral aphthae, genital ulcers and eye lesions constituted a distinct disease entity, of which the cases reported previously by dermatologists and ophthalmologists formed a part.

2. He seemed to scotch the idea that B. crassus could be found in all cases of ulcus vulvae acutum.

3. He stimulated much interest in this aspect of pathology.

Because of the close relationship between Behcet's syndrome and oral aphthae, the syndrome will be discussed more fully in the next chapter.

Among those stimulated by Behcet's papers was Touraine (1941), who reviewed the literature in respect of
cases presenting similar features to Behcet's syndrome, and concluded that aphthosis of Neumann, ulcus vulvae acutum, Behcet's syndrome and recurrent aphthous ulceration were all one and the same disease, which he referred to as aphthosis. Theron agreed with this concept except for reservations with regard to purely oral lesions, and endorsed the use of the term aphthosis as the most suitable one for the total syndrome. In a personal communication to Touraine (1955), Behcet expressed the desire for his syndrome to be regarded as a part of aphthosis. Immunological support for Touraine's view was later provided by Lehner (1968).

In 1925 Baader had reported two patients with a combination of oral and pharyngeal lesions who later developed skin lesions, especially around the genitals. Diphtheria, foot-and-mouth disease and erythema multiforme were excluded in the diagnosis, and Baader considered this a new pathological entity which he called dermatostomatitis.

The rather cumbersome term ectodermosis erosiva pluriorificialis was applied by Rendu (1916) to a syndrome marked by inflammation of the oral, nasal and genital mucosae with conjunctivitis and a varicelliform skin eruption. The duration of this disease, also reported by others, was from three to six weeks, during which time the patient experienced fever and marked prostration. The papulo-vesicular skin lesions tend to become confluent and are associated with haemorrhage.

Stevens and Johnson in 1922 described an eruptive fever in conjunction with ophthalmia and stomatitis. The disease is characterized by a maculo-papular skin eruption,
purulent conjunctivitis, corneal ulceration, ulceromembranous stomatitis and pyrexia. The condition is known as Stevens-Johnson syndrome. Burket, in 1946, considered it a severe form of herpetic stomatitis, but in 1957 classified it with erythema multiforme. Many other authors, amongst whom may be mentioned Shafer et al. (1963) and Bhaskar (1965), also regard Stevens-Johnson syndrome, as well as ectodermosis erosiva pluriorificialis and even Behcet's syndrome as variations of erythema multiforme. Shafer et al. (1963), additionally, includes Reiter's syndrome in this category (at least tentatively), as did Robinson and McCrumb (1950), Burket (1957) and others.

Phillips and Scott (1955) regard Stevens-Johnson syndrome as possibly identical with ectodermosis erosiva pluriorificialis, but certainly different from Behcet's syndrome. They point to Stevens-Johnson syndrome as a self-limiting process occurring as a single attack and having no recurrent, cyclical nature like Behcet's syndrome. Not only is the clinical behaviour of the disease different, however, but the clinical appearance of the lesions is dissimilar.

Reiter described his syndrome in 1916 after observations of a patient suffering from urethritis of a non-specific nature, conjunctivitis followed later by an iritis, arthrosis, rheumatic pains and intermittent fever. Reiter was able to isolate a spirochaete from the blood of this patient and named it spirochaeta forans, but other workers have failed to repeat this. According to Theron (1959), only one case has been reported of oral aphthae accompanying Reiter's syndrome.
In the consideration of the mucocutaneous and mucocutaneous-ocular syndromes it is possible both to over-simplify and to over-specify. A common attitude is expressed by Shafer et al. (1963):

"In the light of the present evidence, it is most likely that these diseases (Stevens-Johnson syndrome, Behcet's disease, Reiter's syndrome and ectodermosis erosiva pluriorificialis) all represent variants of erythema multiforme, with the possible exception of Reiter's syndrome. There is no justification for the separation of symptom groups into distinct entities, particularly when such overlap exists among the syndromes."

Although this attitude has much to commend it, one must object to the inclusion of Behcet's syndrome at least. The reasons for this will become obvious in the next chapter.
CHAPTER 11 - BEHCET’S SYNDROME:

Hippocrates was probably describing Behcet's syndrome in his third book of endemic diseases when he wrote: "There were other fevers about which I am going to write. Many had aphthous ulcers in the mouth. Discharges and sores about the genitalia were common with tumours both externally and internally. Watery inflammations of the eyes also occurred which were long-lasting and painful, and also tumours of the eyelids both externally and internally and in many cases sight was lost." 167

According to Phillips and Scott (1955), the "triple symptom complex" of recurrent genital and oral ulceration associated with lesions of the anterior chamber of the eye was described by Planner and Remenovsky (1922). Other reports were published by Weve (1923), Adamantides (1931) and Dascalopoulos (1932). Nally (1968) credits Bluthe (1908) with drawing attention to the simultaneous appearance of oral and genital ulcerations in some cases of hypopyon. Theodore (1952) mentions this date also in connection with the early history of Behcet's syndrome.

Notwithstanding earlier reports of the association of oral, eye and genital lesions, this syndrome is universally linked with the name of Behcet who published a series of papers on this topic during the years from 1937 to 1940. His first paper suggested that the condition was caused by a virus, but in 1938 he advanced focal infection as the cause, rejecting it in 1940 in favour once again of the viral hypothesis.
Some authors regard the presence of two of the three lesions as adequate for a diagnosis of Behcet's syndrome, among them being Curth (1946), Theodore (1952), Phillips and Scott (1955), Truelove and Morris-Owen (1958), Forbes and Robson (1960), Oshima et al. (1963) and Kramer (1965). Birt and Mather (1968) describe a case of extensive laryngeal ulceration which, despite the absence of genital ulcers or uveitis, was considered to be an incomplete form of Behcet's syndrome.

There are many instances on record in which the development of the third or even the second symptom has not occurred for years: Curth (1946), Adamantiadis (1951), Theodore (1952), Oshima et al. (1963), Linenberg (1963), Namo and Baghdassarian (1964), Kramer (1965), Scott (1965) and Francis (1970).

Forbes and Robson (1960) apparently see the rare development of genital lesions and the even more rare development among these patients of eye lesions as an extension of the basic pathology underlying recurrent aphthous ulceration.

On clinical grounds, at least, Behcet's syndrome can be distinguished from the other mucocutaneous syndromes in that so many authors have described the oral lesions as aphthous ulcers: Strandberg (1918), Fordyce (1920), Ravell (1932), Hunt (1934), Whitwell (1934), Theodore (1952), Fraser-Moodie (1953), Queries and Minor Notes (1955 432), Phillips and Scott (1955), Sircus et al. (1957), Truelove and Morris-Owen (1958), Farmer (1958), Theron (1959), Forbes and Robson (1960), Ship et al. (1960b), Schulze (1960),

Others, however, have suggested a likeness to herpetic infections, for example Katzenellenbogen (1946) and Radden and McIntyre (1957); and Behcet had originally suggested a viral infection. The discrepancy here might be due to herpetiform ulcers being mistaken for herpetic ones, and this might also explain the controversy over the isolation of a virus (which will be mentioned shortly). A propos of this, Lehner (1967c) remarks: "Herpetiform ulcers resemble clinically herpes simplex; they usually respond dramatically to tetracycline therapy; and the epithelial vesicles seen microscopically and intranuclear inclusion bodies observed with the electron microscope are consistent with a viral aetiology. If a virus were to be grown from this lesion, then it would be tempting to suggest that both recurrent focal oral ulceration and Behcet's syndrome are divisible into two aetio logically distinguishable groups - namely, viral and non-viral. This might explain the serious discrepancies in the reported success and failure in growing viruses from patients with Behcet's syndrome." Lehner (1968) claimed that the incidence of herpetiform ulcers is raised in Behcet's syndrome; Kramer (1965) had earlier stated, however, that herpetiform ulceration is unlikely to be the forerunner of Behcet's syndrome.
It seems that the oral lesions in Behcet's syndrome may resemble either typical aphthous or herpetiform ulcers. Lehner (1968), who had previously (1967a) shown that the oral lesions of Behcet's syndrome and oral aphthae behave immunologically in the same way, stated: "Oral manifestations in Behcet's syndrome are indistinguishable from the focal oral ulcers, except for the raised incidence of herpetiform ulcers. Oral ulcers in Behcet's syndrome display all the variations of the three types of focal ulcers (i.e. major and minor aphthae and herpetiform ulcers). This analysis offers support for Touraine's concept (1941, 1955) that RAU (recurrent aphthous ulcers) are part of a wider condition named 'aphthosis'." In a later publication (1969e) Lehner reiterated that oral ulcers in Behcet's syndrome can be any of the three focal types.

Several authors have stated or shown by case reports that oral ulcers may be the first manifestation of the syndrome: McCoy (1955), Forbes and Robson (1960), Thorne (1963), Kramer (1965), Scott (1965), Mounsey (1965), Smith et al. (1967), Lehner (1967a), Nally (1968), Mowat and Mothersall (1969), and Francis (1970). Oshima et al. (1963) found that oral lesions occurred in 98% of their 85 cases, and appeared first in 52% and second in 32%. Lehner (1968) states that in Behcet's syndrome ulcers were found to involve the palate, pharynx and gum in that order of frequency. Kramer (1965) remarked that major aphthous ulceration involving the soft palate and fauces may be an ominous sign of an impending Behcet's syndrome.

It has become apparent, since Behcet, that other tissues besides the classic triad may be involved in this disease process, and Berlin (1960) significantly entitled
his paper "Multiple-symptom complex". The following is
a list of some of the many authors who have reported others
tissues or diseases as being involved in Behcet's syndrome:

Adamantiades (1931): periodic hydrops of the knee
Curth (1946): arthritis, rheumatic pains, skin lesions
Adamantiadis (1951): thrombophlebitis
Phillips and Scott (1955): joint lesions, central
nervous system symptoms, skin lesions
Pallis and Fudge (1956): central nervous system lesions
including multiple sclerosis-like conditions,
brain stem lesions, cranial nerve palsy,
meningomyelitis and meningoencephalitis; gangrene
Evañs et al. (1957): central nervous system involvement
Truelove and Morris-Owen (1958): vascular lesions
leading to neurological complications
Berlin (1960): lesions of blood vessels, skin, central
nervous system, joints, viscera
Schulze (1960): skin and central nervous system
Oshima et al. (1963): skin lesions, arthritis, gastro-
intestinal tract (diarrhoea), raised erythrocyte
sedimentation rate, dysproteinæmia, (These authors
consider Behcet's disease as a general systemic
disease affecting visceral organs on a wide scale).
Farnarier and Genevet (1964): vascular involvement
Pallis (1965): recurrent thrombophlebitis
Mounsey (1965): arthralgia, skin lesions, recurrent
venous thrombosis leading to aortic aneurysm.
Holzmann (1965): Vascular involvement
Schneider (1965): vascular involvement
Szel (1965): benign pericarditis and recurrent neurologic
involvement
Hartmann et al. (1966): vascular involvement
Smith et al. (1967): retinal vascular lesions.
Hills (1967): aortic aneurysms
Gold (1967): central nervous system involvement
Lehner (1967a): neurological features, deep-vein
thrombosis, arthritis.
Lehner (1967c): skin, joint, nervous system and venous thrombotic manifestations
Fowler et al. (1968): neurological manifestations
Cunliffe and Menon (1969): thrombosis
Mowat and Hoterhsall (1969): gangrene, arthralgia, skin lesions
Enoch (1969): gangrene
Lehner (1969e): vasculitis, joint and intestinal abnormalities
Francis (1970): cutaneous, neurological, gastrointestinal and vascular manifestations

Symptoms of eye disorders are obviously an important diagnostic consideration. It is not intended to discuss these at length, but merely to give a summary of this aspect of the syndrome as presented by Fraser-Moodie (1953). Fraser-Moodie states that there may be considerable variation, e.g. conjunctivitis, keratitis, episcleritis, neuro-retinitis haemorrhagica, corneal ulceration, retinitis, phlyctenulae, iritis, iridocyclitis, choroiditis, and iritis with hypopyon. The last is the gravest and may cause total blindness. Behcet’s early cases presented episcleritis and corneal ulceration and did not suffer from iritis with hypopyon. The eye lesions may dominate the clinical picture and may precede, coincide with or follow the oral and genital lesions.

**Aetiology:**

Behcet (1937) reported the finding of inclusion bodies in scrapings from the ulcers, and suggested a viral aetiology. According to Fraser-Moodie (1953) this finding has never been verified, but a virus has subsequently been isolated by Sezer (1953, 1956), Evans et al. (1957), Nakagama and Shingu (1958), and Mortada and Imam (1964). Sezer and Evans and co-workers reported the presence of complement-fixing and neutralizing antibodies respectively.
Numerous other workers have failed to incriminate a virus. These include Curth (1946), Katzenellenbogen (1946), France et al. (1951), Zeavin et al. (1956), Braley (1958), and Breslin (1962).

Behcet's focal infection theory (1938) has not been confirmed by later writers and was rejected by Behcet himself in favour of the virus theory (Behcet, 1940).

A viral cause has been a rather popular choice. Schulze (1960) stated that the virus aetiology had definitely been demonstrated, but gives no further details. Thorne (1963) stated that although the aetiology is unknown, the disease behaves in some ways like a virus infection, and Katzenellenbogen (1946) thought that the disease bore a great resemblance to herpes.

Linenberg (1963) said that the disease has been described as being caused by reactions to drugs, antisera, and a virus. Other causes have been suggested, including staphyloccoccal infection (Adamantidis, 1931); Feigenbaum and Kornblueth, 1946), focal infection (Behcet, 1938), allergy (McMenemy and Lawrence, 1957), and tuberculosis (Weekers and Reginster, 1939). No support for these theories has been convincing, with the exception possibly of the viral one.

The possibility of an autoimmune mechanism being responsible for the disease was suggested by Oshima et al. (1963) and subsequently by Shimizu et al. (1965). These workers stated that dysproteinaemia was a distinct abnormality found in their experiments and seemed to be important diagnostically. The dysproteinaemia consisted basically of
a rise in serum globulin (especially the gamma fraction) and a decrease in albumin. In certain cases they noted a rise in serum protein-bound hexoses which they considered characteristic of the syndrome, as no such change is observed in rheumatoid arthritis and other "collagen diseases".

"It is assumed that these abnormalities of the serum proteins reflect changes in various organs, suggesting a systemic disease" (Oshima et al., 1963). Francis (1970) states that the increase in serum mucoprotein and serum sialic acid demonstrated by Oshima et al. and Shimizu et al. have not been reported in patients with oral aphthae.

Studies by Oshima et al. (1963) using the tanned-cell haemagglutination technique introduced by Boyden in 1951 revealed the presence of antibody against human mucous membrane in 42% of 40 cases. The antibody titre altered in accordance with the clinical state of the lesions, but remained negative in healthy controls. The authors concluded that although the demonstration of circulating antibody against oral mucous membrane does not necessarily involve auto-immunization as a primary causative factor, it suggests the involvement of such a mechanism in the pathogenesis of the disease.

Shimizu et al. (1965) demonstrated a rise in serum globulin, the presence of haemagglutinating antibodies against oral mucosa and immunofluorescence of epithelial cell cytoplasm. They also demonstrated a positive delayed type of skin test reaction to heat-aggregated human gamma globulin in these patients.
In 1967 Lehner (1967a) showed the presence of haem-agglutinating, complement-fixing, and precipitating antibodies in patients with Behcet's syndrome (but not in normal controls) to foetal oral mucosa. His immunological tests failed to distinguish between "complete" and "incomplete" forms of the disease, except that the former tended to show higher haemagglutination titres. The oral lesions in these patients showed both aphthous and herpetiform lesions, the latter suggesting a viral aetiology, although the two lesions behaved the same immunologically. Lehner speculated that Behcet's syndrome may consist of two aetiologically distinguishable groups.

In another publication (1967c) Lehner states that his autoimmune hypothesis for aphthous ulcers (q.v.) is equally applicable to Behcet's syndrome. Lehner in fact has advanced this hypothesis to the point where it has by far the most impressive body of experimental evidence to support it: evidence which suggests that aphthous ulceration and Behcet's syndrome differ only in respect of the tissues involved.

A significant demonstration by Lehner (1969b) was that of antigenic cross-reactivity between human mucosa of the mouth and of the pharynx, larynx, oesophagus, conjunctiva, vagina, colon and the skin. This finding offers an explanation for the involvement of extra-oral tissues in Behcet's syndrome, but poses the question of why the condition is restricted so often to the mouth in the form of focal ulceration.

Francis (1970) raises a similar inquiry as to why, when similar immunologic mechanisms appear to underly both aphthous ulcers and Behcet's syndrome, certain patients have
very severe oral lesions with no other signs of Behcet's syndrome, while other patients with severe Behcet's disease have only minor oral ulcers. It is obvious that complete elucidation has not yet been achieved.

Other findings reported by Lehner were that the humoral antibodies present belong predominantly to the IgM and to a lesser extent the IgG class of antibodies, that the lymphocyte transformation test (an indication of cell-bound antibody) shows a clear relationship to the clinical state of the oral lesions, and that the antigen may be localised to the cytoplasm of the cells of the stratum spinosum, as revealed by immunofluorescence studies. Although non-immunoglobulin binding cannot be ruled out, the evidence favours specific immunoglobulin reaction of IgM and IgG with the prickle cell cytoplasm (Lehner, 1969d).

Histological and electron-microscopic examination of biopsy specimens by Lehner (1969e) revealed similar findings as in oral aphthae, i.e., an early intense lympho-monocytic infiltration consistent with a delayed hypersensitivity reaction. Herpetiform ulcers differed from the aphthous type in that they revealed epithelial vesicles and intranuclear inclusions suggesting a viral cause. As in oral aphthae, the mast cell count was significantly raised over that found in other lesions and controls. The literature offers considerable support for a vascular abnormality in Behcet's syndrome. Lehner did not detect vascular abnormalities in oral aphthae, but reported endothelial proliferation in Behcet's syndrome.
Francis (1970) provides a summary of the histological aspects of Behcet's syndrome which he too states is identical with that seen in oral aphthae: "The lesions are characterized by early intense lymphomononuclear infiltrate and later by chronic inflammation with tissue destruction. Positive cytoplasmic fluorescence has been observed in polymorphonuclear cells from peripheral circulation of Behcet's patients and smears from the oral lesions when obtained with fluorescence-labelled antiglobulins. Lehner has also demonstrated by fluorescence microscopy specific immunological reaction of IgG and IgM with autologous cell cytoplasm of the stratum spinosum in oral lesions from Behcet's disease."

According to Francis (1970) the most widely accepted aetiology is an autoimmune one. He cites the experimental evidence of Dolby (1969), Lehner (1967a, 1969b), Oshima et al. (1963) and Shimizu et al. (1965) to the effect that antibodies against oral mucosa have been detected in the serum of these patients and that the antibody levels fluctuate with the clinical severity of the disease. Nally (1968) commented that gastrointestinal ulceration in Behcet's syndrome seems to be similar to ulcerative colitis, which is considered to be an autoimmune disease.

**Basic pathology:**

The basic pathology in this syndrome has been said to be a vasculitis (Herbert and Zalusky, 1961; Hills, 1967; Cunliffe and Menon, 1969). Thomas (1947) reported that the pathology of the skin lesions was primarily a venous thrombosis and Berlin (1960) described thrombosed vessels in the genital lesions.
Decreased fibrinolytic activity of the blood has been reported in patients with vasculitis (Cunliffe, 1968; Cunliffe and Menon, 1969; Menon et al., 1969) and Pallis stated: "I think Behcet's syndrome should be kept in mind whenever a patient complains of venipuncture sites repeatedly going septic or thrombosing." According to Francis (1970) thrombophlebitis and erythema nodosum are frequent features of the disease which may have a vascular or allergic basis.

The full extent of possible systemic involvement was shown in a post-mortem study by Sulheim (1959) who found marked fibrosis of the lung and spleen, atrophic oesophagogastronenteritis, panophthalmitis, and disseminated cerebral atrophic-degenerative lesions. It seems reasonable that such widespread dissemination of the disease process should follow a vascular involvement.

Pallis suggested that thrombophlebitis is perhaps a more common third component of the syndrome than ocular signs and symptoms. Relevant to this statement, France et al. (1951) reported a 25% incidence of thrombophlebitis and Dowling (1961) 12%.

According to Schneider (1965) little attention has been paid to arterial involvement, but clinical complications of aortic aneurysm have been reported by Mishima et al. (1961), Mounsey, Shikano (1966), and Hills (1967). Femoral arterial aneurysms have been reported by Mishima et al. (1961) and aneurysms of other arteries by Oshima et al. (1963). Fatal aneurysms have been encountered by Shikano (1966) and Mounsey.
Complications of gangrene were met by Pallis and Fudge (1956), Mowat and Hothersall (1969) and Enoch (1969). In Enoch’s two cases arterial lesions were a prominent feature.

**Prognosis:**

Behcet’s syndrome is a benign disease (Linenberg, 1963; Theodore, 1952) when confined to the oral and genital regions. Eye lesions may give rise to blindness (Theodore, 1952; Smith et al., 1967). When central nervous system symptoms arise, the prognosis is regarded as grave (Queries and Minor Notes, 1955; Evans et al., 1957; Cronin, 1966).

According to Phillips and Scott (1955) symptoms of central nervous system involvement vary from headache and giddiness to major attacks with associated diplopia, blurring of vision, vomiting and nystagmus.

Francis (1970) presented a succinct summary of the prognosis of the inter-related conditions of aphthous ulcers and Behcet’s syndrome:

**Recurrent aphthous lesions:**
1. Chronic recurrence of lesions
2. Tissue destruction with scarring in the severe form of the disease
3. Possibility of developing symptoms of Behcet’s disease.

**Behcet’s disease:**
1. Chronic exacerbations of symptoms
2. With eye involvement, blindness usually results.
3. With central nervous system involvement, prognosis is poor.
It is not intended to review the complete ramifications of Behcet's syndrome, and nothing will be said of incidence except that it is probably not very frequent outside the Mediterranean area. However, there is no universal agreement on the subject of incidence and cases may go unrecognised.

The purpose of this chapter is to demonstrate that oral ulceration may be associated with very serious and widespread disease, of which the oral lesions may be the first manifestation.

In conclusion, a recitation of the salient points of the syndrome is presented (as per Francis, 1970):

**Triad:**
1. Recurrent oral ulcerations
2. Recurrent genital ulcerations
3. Ocular inflammation (uveitis, episcleritis, hypopyon)

**Other:**
1. Pyoderma
2. Erythema nodosum
3. Erythema multiforme
4. Arthralgia and arthropathy
5. Hyperreactive skin tests
6. Central nervous system involvement
7. Malaise and fever
8. Muscle pain
9. Gastrointestinal involvement
Francis suggested the following differential diagnosis:

Aphthous lesions from:
1. Viral lesions
2. Behcet's syndrome

Behcet's syndrome from:
1. Rheumatoid disease
2. Reiter's syndrome
3. Erythema multiforme
4. Systemic lupus erythematosus
5. Lymphogranuloma venereum