Aphthae with special reference to the chronic recurrent variety of Mikulicz

Theron, Jacobus Arnoldus

APHTHAE WITH SPECIAL REFERENCE TO THE CHRONIC RECURRENT VARIETY OF MIKULICZ

J. A. THERON

ERRATA

p. 64 l. 43 ulcerine, read urine

p. 88 l. 36 without symptoms, read without nervous symptoms.

p. 104 l. 16 nature (Andermatt 1950; read nature. From the literature (Andermatt (1950;

p. 110 Under "Introduction" line 2 to 5 should read as follows: In a study of the toxic properties of Actinaria, Richet and his colleagues found that during repeated injection of an extract of the tentacles of this sea anemone into dogs, definite symptoms appeared. In some instances the symptoms were so severe that death ensued.

p. 145 l. 16 page and, read page 140 and

p. 157 l. 16 (see page)., read (see page 154).

p. 167 l. 21 (see page)., read (see page 121).

RIJKSUNIVERSITEIT TE GRONINGEN

APHTHAE WITH SPECIAL REFERENCE TO THE CHRONIC RECURRENT VARIETY OF MIKULICZ

A CLINICAL, ETIOLOGICAL AND HISTOLOGICAL STUDY

PROEFSCHRIFT TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE RIJKSUNIVERSITEIT TE GRONINGEN OP GEZAG VAN DE RECTOR MAGNIFICUS Dr. P. J. BOUMAN, HOOGLERAAR IN DE FACULTEIT DER RECHTSGELEERDHEID, IN HET OPENBAAR TE VERDEDIGEN OP WOENSDAG 2 DECEMBER 1959 DES NAMIDDAGS TE 3 UUR PRECIES

DOOR

JACOBUS ARNOLDUS THERON

GEBOREN TE

FRANKFORT, ORANJE-VRIJSTAAT, ZUID-AFRIKA

DRUK: V.R.B., KLEINE DER A 4 - GRONINGEN

PROMOTOR :

PROF. M. HUT

STELLINGEN

1. Chronische recidiverende aphthae worden niet veroorzaakt door het herpes simplex virus.

2. Bij langdurig gebruik van gefluorideerd drinkwater, dient men met de mogelijkheid van strumavorming rekening te houden.

3. Het verdient ernstige overweging de gebruikelijke behandeling van favus capitis door middel van een eenmalige Röntgenepilatiedosis, als routinemethode te vervangen door het orale antimycoticum griseofulvine.

4. Er bestaat geen bewijs voor de opvatting dat onyalai wordt veroorzaakt door het innemen van middelen verschaft door medicijnmannen ("toordokters").

5. Bij gereguleerde diabetici bestaat er geen contra-indicatie tegen het gebruik van locale anaesthetica waaraan adrenaline is toegevoegd.

6. Bij de bereiding van antigenen waarbij gebruik gemaakt wordt van Tyndallisatie, is het belangrijk om de temperatuur die daarbij wordt gebruikt te vermelden.

7. Het Röntgenologische beeld van nephroblastoma van de mandibula lijkt zeer veel op dat van neuroblastoma van de mandibula.

   A. Nesbitt. Brit. dent. J. 106:251, 1959.

8. Allergie komt bij de Bantoes minder frequent voor dan bij blanken.

9. Bij de opleiding van huisartsen wordt te weinig aandacht geschonken aan de ziekten van de mondholte.

10. Massale bloeding van de tractus gastro-intestinalis is een zeldzame complicatie van appendectomie.

Ter nagedagtenis aan my Vader
Aan my Moeder
Aan my Skoonouers
Aan Killa

As a result of a lack of time, due to circumstances beyond the control of the author and the printer, the necessary corrections of the proofs of the case histories had to be omitted.

VOORWOORD

Graag wil ek almal wat meegehelp het om hierdie proefskrif die lig te laat sien van harte bedank.

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CONTENTS

INTRODUCTION.

Our attention was first focussed on the disease which forms the subject of this study, when patients suffering from recurrent attacks of oral lesions attended for treatment.

In textbooks this condition was referred to under a variety of names, e. g. chronic recurrent aphthae, recurrent aphthous stomatitis, recurrent herpetic stomatitis, dyspeptic ulcers, canker sores, etc. From these references one was not always sure whether the authors had the same condition in mind. None of the treatments advocated – caustic pencils, X-ray treatment, hormonal preparations, vitamins, antibiotics, etc. – seemed to have any effect on the disorder. This led the author (Theron, 1955) to review the literature at his disposal. The conclusions arrived at were that the nomenclature of the disease was in utmost confusion, that very few descriptions deal with the histological picture of the disorder, that conflicting views exist as far as the etiology is concerned and that more research was necessary in this respect.

It was therefore decided to give a more extensive review of the literature and to conduct investigations into the clinical, etiological and histological aspects of the disorder. In order to do so the following scheme was decided upon:

1. A historical description of aphthae.
2. A classification of the various conditions characterized by the formation of aphthae or to which the name aphthae was applied.
3. A description of these conditions.
4. A special clinical, etiological and histological investigation of the chronic recurrent variety referred to above.

This variety of aphthae first described by Mikulicz and Michelson (1892) was subsequently included by Touraine (1941) under the heading "aphthosis". The latter includes manifestations of a serious nature. For this reason we decided to consider the chronic recurrent aphthae of Mikulicz, and aphthosis separately. The finding of a virus (Sezer, 1953; Evans et al. 1957) in cases of aphthosis made us decide on a comparative virological and histological study of the two conditions.

In our subsequent description the word "aphtha" will be used to denote a single lesion of the various aphthous diseases, while the plural "aphthae" will be used in the description of multiple lesions. The name "chronic recurrent aphthae" will be applied in the description of a specific disorder.

CHAPTER I

HISTORICAL NOTES ON APHTHAE

Ever since the concept "aphthae" first appeared in medical literature it has been used in descriptions of various disease entities to denote similar but not identical lesions. It is therefore impossible to give an exact definition of the term. Generally, however, the name aphthae denotes well defined, round or oval efflorescences of the mucosa, varying between the sizes of a pinhead and that of a bean, and which are superficially covered by an adherent fibrinous deposit (grayish-white or yellowish-white) surrounded by a red inflamed border of varying width. The lesions may appear single or multiple and develop from shortlived vesicles.

Billard (1828), Bohn (1866; 1880), Adlersberg (1939) and Chevallier (1940), among others, gave historical accounts of aphthae.

In this chapter we will deal with the origin of the term aphthae and the development of the concepts "chronic recurrent aphthae," "acute aphthous stomatitis" and "aphthosis".

Hippocrates of Cos (460-370 B.C.) first employed the word aphthae in his writings. The exact meaning he attached to the word is still unresolved. From the translations of his work we must infer that Hippocrates must have used the word to describe various pathological conditions.

The meaning attached to the word by the ancient Greeks is still unclear. There seems to be agreement amongst the students of Greek that the word aphthae is probably derived from the verb $\alpha\pi\tau\omega$ (Liddell, Scott and Jones 1940; Frisk 1954), meaning "kindle" or "touch". According to these authors various terms have been derived from $\alpha\pi\tau\omega$. Thus we find $\alpha\pi\tau o\mu\alpha\iota$ (to be set on fire) in Homer's Odyssee, while Herodotus used it in his description of a burning temple. Others to use words derived from $\alpha\pi\tau\omega$ were Plato, Aristotle and Galen. In the Greek text of the works of Hippocrates used by Heurnius (1609) we find the word $\alpha\varphi\theta\alpha\iota$ (in his Aphorisms: Book 3, twenty fourth aphorism) which, according to Liddell and co-workers (1940), presents the plural of $\alpha\varphi\theta\alpha$, meaning an infantile disease: thrush. In his seventh Book of Epidemics, Hippocrates used the word $\alpha\psi\iota s$ which means "touching". In medical literature dealing with aphthae, various explanations of the origin of the word are found, e. g. $\alpha\pi\tau o\mu\alpha\iota$ = burning (Fuchs 1931), $\alpha\varphi\theta\alpha\iota$ = oral ulcers, $\alpha\pi\tau\epsilon\iota\nu$ = to set on fire (Adlersberg 1939; Chevallier 1940; Sircus and co-workers 1957), $\alpha\varphi\theta\alpha\iota$ = oral ulcers and $\alpha\pi\tau o\mu\alpha\iota$ = I am inflamed (Kumer 1942). According to Carol (1948) the word aphthai (from aphthein = to be inflamed) meant the same as the word enanthem (e. g. denoting oral ulcers) to the Greeks; it was probably derived from the sensation of burning caused by the lesions. We have to agree with Carol where

he states that the use of the word is probably more traditional than is justified etymologically. The statement by Kranz (1949) that Hippocrates used the word to describe a disease of newborn infants may lead to a false impression. Evidence that Hippocrates also applied it to adults can be found in Coan Prognosis (section XXXI), where he described the occurrence of aphthae in conjunction with pregnancy (Chadwick and Mann 1950, p. 265; Grimm and Lilienhain 1837, p. 402).

While some authors (Ras 1665; Grimm and Lilienhain 1837; Adlersberg 1939 and Kumer 1942) are of the opinion that the concept aphthae as used by Hippocrates was restricted to oral diseases, we find that Billard (1828) and Martineau (1865) held the opinion that Hippocrates used it to describe all superficial ulcerations of the body. According to Martineau (1865) the honour goes to Galen (129 - 199 A.D.) for being the first to limit the use of the term to buccal conditions only.

Since the beginning of the Christian era many references were made to aphthae and numerous descriptions given of it: Galen, Celsus, Mercuriales and Aretaios were some of the first authors in this connection. However none of their descriptions yields a solution to the problem of aphthae. It is possible that it might have had influence on their scholars and on those who followed immediately after them.

It was only from the beginning of the seventeenth century that clearer descriptions were given of aphthae, apparently very inaccurate. Most authors applied the concept indiscriminately to all possible mouth affections, some of which today are called noma, diphteria, moniliasis or the infection of Plaut-Vincent. Herman Boerhave (1668-1738), the famous Dutch physician, and Gerard van Swieten (1700-1772), one of his scholars who later founded the School of Vienna, defined aphthae as small, round ulcers of the oral mucosa which neccessitate a thorough examination in order to distinguish them from enlarged or eroded ducts of salivary glands.

When dermatology developed into a separate branch of medicine towards the end of the eighteenth century we observe great progress in the field of oral medicine. The pioneering work of Robert Willan (1757-1812) and Thomas Bateman (1778 -1821), who can be called the fathers of dermatology in England, Joseph Plenck (1738-1807) of Germany, and Cullen (1712-1790), Xavier Bichat (1771 -1802) and Sauvages (1706-1767) of France, is of note in this respect.

During this period it was first realised in France—among others by Lavoisier (1781)—that aphthae and thrush were different diseases. For many years these diseases were greatly confused, and a description of thrush under the heading "aphthae" was commonly found. If one scans the literature of those days dealing with aphthae, it becomes evident that the popular names for mouth diseases as used by the laiety in different countries

exerted great influence on the various authors. Ras (1665), in his Dutch translation of the Aphorisms of Hippocrates, translated the word aphthae with "sprou of sweringe in de mond" (sprue or ulcers in the mouth). The word "sprou" (also written "sprouw" or "spruw") was commonly used by laymen in the Netherlands to denote any eruption in the mouth, but especially what is called moniliasis or thrush today. A perfect example of this is the thesis by Ketelaer (1672) in which he gives a description of diphtheria under the title "Tractatibus de aphthis nostratibus s. Belgarum Sprouw".

In Germany the same happened. Here the lay term "Schwämmchen" was confused with the term aphthae. "Schwämmchen", like "sprouw" in the Netherlands, was the common name for thrush or monilia-like lesions. No wonder that Stark (1784) added comments pertaining to a study of thrush to his German translation of Ketelaer's thesis. Stark obviously had in mind the popular meaning of the word "sprouw". In their German translation of the works of Hippocrates, Grimm and Lilienhain (1837) also used the term "Schwämmchen" for aphthae. Like "sprouw" or "Schwämmchen" we find that the lay term "muguet" became the fashion in France. Similarly, in England, the word "thrush" was used as a synonym of aphthae. In his classification of skin diseases, Willan (1798), mentioned seven orders. He endeavoured to limit the use of the word aphthae and to give a more accurate description of it. He defined aphthae as small, round, vesicular lesions of the cheek mucosa (Willan's sixth order in Cazenave 1856). In his fourth order, however, Willan also used thrush as a synonym for aphthae occuring in infants (Friese 1799). Bateman (1817), who continued the work done by Willan, described the condition in infants with the name aphthae lactans or aphthae infantium and that in adults with the name aphthae adultorum.

The Dutch word "sprouw", interesting enough, even today is sometimes used by laymen in the Netherlands to denote monilia-like lesions. When Jan van Riebeeck established the Dutch settlement at the Cape of Good Hope in 1652, he probably introduced the term "spruw" into South Africa for we still find the word in use amongst the Afrikaans people as "spru" to denote thrush-like lesions in the mouth. In England the word "spruw" was changed to sprue, which today describes an entirely different disease than thrush, as will be shown later.

The concept aphthae for a long time implied stomatitis. After thrush was first differentiated from aphthae, more diseases followed. In 1826 Bretonneau gave the first description of diphtheria as a separate disease entity. Two years later Richter (1828) published his monograph on noma. This was followed by the first description (Taupin 1839) of stomatitis ulcerosa or, as it is generally called today, fusospirochetal infection of Plaut-Vincent.

In France, Billard (1828) gave an outstanding account of aphthae before 1850. In our opinion he must be credited for being the first to define aphthae as we accept it today. He not only gave us valuable facts with regard to the history of aphthae. but also a remarkable clinical description. He described the lesions as circumscribed superficial ulcers of the oral mucosa covered in the centre by a whitish substance and surrounded by a red halo. Billard found that they appeared on the inside of the lower lip, the edges of the tongue, the inside of the cheeks and on the gingivae. He clearly differentiated between aphthae and thrush. The latter was apt to occur more in children before the first dentition, while aphthae usually occurred after this period. According to Billard, aphthae was due to infection in the follicular glands of the mucosa and analogous to ulcerations in other parts of the digestive tract.

One of the first descriptions of aphthae in dental literature appeared in "Der Zahnarzt" of June 1848; the editor (Schmedicke) published an abstract of a discussion which took place at Stockholm on the thesis of Hoenenkopp entitled "de natura vegatibili aphtharum". From the description here, it is quite clear that this work dealt with thrush.

In the same year, Rogers, a dentist from Paris, gave a description in German of what he called the true aphthae as opposed to a disease of children bearing the name of "muguet". Erroneously enough, his description had been titled "Ueber die Schwämmchen". To Rogers the word aphthae in the dental pathology of 1848 meant a pustular eruption of the oral mucous membrane and its oesophageal extention. The disease originates in the mucous glands, but the etiology is not known. Old people, young people with a lymphatic constitution and especially women during the fifteenth year of life when the menses appear, are more often affected. The view held by Rogers and his contemporaries, namely that aphthae is a pustular eruption of the oral mucosa, must be regarded as an attempt to see it as an analogue of impetigo. This also was the reason why aphthae was often described in France under the name of "stomatite impétigineuse".

In the year 1864, Worms gave the first microscopic description of aphthae which he considered to be a conglomeration of fat globules. To him, the aphthous exudate was so constant and identical in all patients showing lesions, that he considered it to be pathognomonic of the disease bearing the name of aphthae.

Notwithstanding the fact that Billard (1828) and others have clearly shown that aphthae presents characteristic clinical lesions many authors continued to confuse it with other diseases of the mouth. This lead Bohn (1880), whom we might call the first stomatologist, to make the following statement: "Trotz aller dieser besondern und günstigen Verhältnisse haben die

Mundkrankheiten bis vor wenigen Jahrzehenten zu den verworrensten und unerquicklichsten Capiteln der Pathologie gezählt, und es dürfte vielleicht kein zweites Beispiel in der medicinischen Wissenschaft vorhanden sein, wo ein blosses Wort, ein Terminus Jahrhunderte lang die Forscher derart tyrannisirt und jeder bessern Erkenntniss so zum Hindernisse geworden ist, als bei den Mundkrankheiten der Name Aphthen". He considered aphthae an eruption which appears in a short space of time on the mucosa to form yellowish-white spots, surrounded by a narrow red border. The lesions according to him, may appear single or in groups and are formed beneath the epithelium. Sometimes they remain stationary, at other times they tend to coalesce, forming oval or irregular patterns. They may be just visible or can reach the size of a lentil. The spots soon rupture on the surface as the result of trauma or friction to expose a thick, yellow, dirty mass surrounded by a slightly raised epithelial edge. In an attempt to remove the plaque haemorrhage occurs. Bohn found that recurrences occur more often in adults. In women the lesions appear periodically in conjunction with the menses, in pregnancy and during labour. He felt that as far as the differential diagnosis of aphthae was concerned, herpes of the lip, cheek, gingiva and tongue were of special importance. In contrast with Rilliet and Barthez (1853), who considered the initial lesions of aphthae as fluid-filled vesicles to which they applied the name "stomatite vésico-ulcereuse", Bohn emphatically denied the existence of vesicles at any stage of the disease. We further find that Bohn used both the terms aphthae (German: Aphthen) and aphthous stomatitis (stomatitis aphthosa) in his description.

Henoch, cited by Fraenkel (1888), like Bohn could not accept the view that aphthae develop from vesicles. He believed them to be due to deposits of fibrin in the superficial layers of the mucosa, analogous to the pseudomembrane found in diphtheria. To him we owe the origin of the name "stomatitis fibrinosa".

While aphthous stomatitis in those days was still considered by most authors to be primarily a disease of childhood, we find that Bresgen (1884) drew special attention to the fact that it also frequently affects adults. He noticed the appearance of aphthae in conjunction with infectious diseases, occurring in adults especially after the ingestion of spicy foods.

The first attempt at a proper histological description of aphthae is that of Fraenkel (1888). To this account we will refer again in a description of acute aphthous stomatitis given later. His views corresponded to some extent with those of Hedoch, mentioned above, with the result that he adopted the name stomatitis fibrinosa from the latter to add the suffix disseminata or maculosa.

We have already shown that Bateman (1817) described aphthae in children and in adults, and that Bohn (1880) observed

recurrences in adults, but it is to Mikulicz and Michelson (1892) that we owe the first clear distinction between the recurrent form occurring mostly in adults and the more acute variety of childhood. The former they described under the name of chronic recurrent aphthae (German : chronische recidivierende Aphthen) and the latter as acute aphthous stomatitis. It is this chronic recurrent variety, as described by Mikulicz and Michelson, to which we will pay special attention in subsequent chapters.

It is appropriate at this stage to draw attention to a variant of the term aphthae which was introduced into medicine in 1895 when Neumann first described aphthae that occurred simultaneously on the genitals and in the mouth of certain of his female patients. Some of them also exhibited skin lesions. To this condition the name aphthosis was subsequently applied in the literature.

The concept aphthosis like aphthae is difficult to define. Schoute (1954), in Pinkhof's descriptive dictionary of medical terms, defines it as a condition accompanied by the formation of aphthae.

Everyone is in agreement that aphthae is a prominent feature of aphthosis, but in a strict clinical sense not all conditions characterized by the formation of aphthae are designated as aphthosis. For our purpose we consider apthosis a systemic disease characterized by the occurrence of recurrent aphthae in the mouth or on the genitals, and sometimes accompanied by lesions of other organs of the body.

CHAPTER II

Classification of Clinical Entities characterized by the Formation of Aphthae or which at some time or other have been designated as such.

In Chapter I we devoted attention to the development of the concepts acute aphthous stomatitis, chronic recurrent aphthae and aphthosis as they form the basis of the subsequent description. Other diseases, however, have been designated as aphthae in the past, of which we already mentioned thrush, while many others not directly related to these concepts are actually characterized by the formation of aphthae. It is therefore necessary to arrive at a proper classification of all these disorders before a description of them can be given.

In literature various attempts at differentiation were made of which we can mention the following:

Hirsekorn (1935)
1. Aphthous stomatitis.
2. Chronic recurrent aphthae.
3. Solitary aphthae.

Kumer (1935)
1. Acute aphthous stomatitis (stomatitis maculofibrinosa).
2. Aphthoid of Pospischill.
3. Chronic recurrent aphthae.
4. Foot and Mouth disease.
5. Aphthosis of Neumann.
6. Bednar's aphthae.
7. Aphthous lesions of the mouth in cases of ulcus vulvae acutum.

Kumer (1942)
1. Acute aphthous stomatitis.
2. Aphthoid of Pospischill.
3. Solitary(metastatic) aphthae.
4. Acute aphthosis of Neumann.
5. Chronic recurrent aphthosis.
6. Behcet's syndrome.
7. Chronic recurrent aphthae (including periadenitis mucosa necrotica recurrens, ulcus neuroticum mucosae oris, stomatitis neurotica chronica, aphthae resistentiae and dyspeptic ulcers).
8. Bednar's aphthae.

Reul (1938)
1. Acute aphthous stomatitis.
2. Chronic recurrent aphthae.
3. Aphthoid of Pospischill.
4. Bednar's aphthae.
5. Aphthae tropicae.

6. Acute aphthous stomatitis with concurrent lesions on the genitals and other parts of the body. Including aphthosis of Neumann.
7. Chronic recurrent aphthae with simultaneous lesions on the genitals. In this group he considered the cases of Grütz (1926) and Behçet (1937).
8. Ulcus vulvae acutum (Lipschütz) with simultaneous lesions in the mouth and on the skin.

Prinz and Greenbaum (1939), cited by Strauss (1947)

Maculo-fibrinous stomatitis (aphthae).

A. Acute aphthae.
   a. Habitual or solitary type.
   b. Infectious type.

B. Chronic intermittent recurrent aphthae (Mikulicz's aphthae).
   Appendix: Trophoneurotic ulcers.

C. Pterygoid erosions or ulcerations (Bednar's aphthae).

Marti (1941)

1. Acute aphthous stomatitis.
   a. Acute aphthous stomatitis of children.
   b. Foot and Mouth disease.
   c. Aphthae preceding general systemic infections e.g. influenza.
2. Chronic recurrent aphthae.
   a. Aphthae with an irregular form and not accompanied by general symptoms as fever.
   b. Round aphthae giving rise to intense pain and accompanied by marked general disturbance and fever.
3. Solitary aphthae.
4. Toxic and traumatic aphthae (including Bednar's aphthae).
5. Aphthae accompanying serious general diseases of the body.
   a. Non-tropical sprue.
   b. Tropical sprue.
   c. Pernicious anaemia.
   d. Diabetes mellitus.

Frech (1945)

1. Infectious aphthous stomatitis.
2. Dermatitis fibrinosa faciei (Moro).
3. Aphthoid of Pospischill.
4. Foot and Mouth disease of man.
5. Solitary (non-recurrent = non-habitual and recurrent = habitual) aphthae.

Carol (1948)

1. Habitual oral aphthae.
2. Habitual genital aphthae (including cases of Neumann).
3. Chronic recurrent aphthous ulcers (including periadenitis mucosa necrotica recurrens, stomatitis neurotica chronica, ulcus neuroticum mucosae oris).
4. Behcet's syndrome.
5. Ulcus vulvae acutum (Lipschütz).
6. Aphthoid of Pospischill.
7. Aphthous stomatitis.
8. Foot and Mouth disease.
9. Bednar's aphthae.
10. Aphthae tropicae.
11. Aphthae of Mikulicz.
12. Malignant aphthae.

Thoma (1954)

1. Habitual aphthosis (including canker sores, Mikulicz's aphthae, dyspeptic ulcers).

2a Ulcerative stomatitis.
b Localized solitary ulcers.
c Trophic ulcers.
d Neurotrophic ulcers.

3. Herpetic stomatitis.

Truelove and Morris-Owen (1958).

1. Minor aphthous ulceration.
2. Major aphthous ulceration.
3. Mixed group (aphthous ulceration only one feature of a disease in which several mucous membranes and the skin may be involved).

a. (i) Erythema multiforme major (Stevens-Johnson syndrome).
(ii) Behcet's syndrome.
b. Ulceration symptom of underlying disease e.g. tropical sprue, idiopathic steatorrhoea and ulcerative colitis.

In order to arrive at a suitable classification it will be necessary to consider each of these entities separately.

The simplicity of Hirsekorn's classification (1935) is indeed an advantage as was pointed out by Marti (1941), but it is evident that not all aphthous diseases are covered by it. The concept aphthous stomatitis as used by Hirsekorn (1935) corresponds with the acute aphthous stomatitis, which was de-

scribed by Mikulicz and Michelson in 1892. Although these authors were unaware of the etiologic nature of the disease, they realised that it was a separate entity frequently occurring in children. Today it is universally recognized as a separate disease, caused by the herpes simplex virus, and has, i. a., been taken up in the classifications of Kumer (1935;1942), Reul (1938), Marti (1941), Frech (1945), Carol (1948); while it has also been given the names acute infectious aphthae (Prinz and Greenbaum, 1939) and herpetic stomatitis (Thoma, 1944). Mention of this malady has not been made by Truelove and Morris-Owen (1958) in their description.

The concept chronic recurrent aphthae is considered a distinct entity by Hirsekorn (1935), Kumer (1935; 1942), Reul (1938), Marti (1941), Prinz and Greenbaum (1939) and Carol (1948). Thoma (1954) described cases of this nature under the title habitual aphthosis, while Frech (1945) discussed it under the name of solitary aphthae. The name habitual aphthosis as proposed by Thoma (1944) may lead to confusion with the concept chronic recurrent aphthosis as used by Kumer (1942) in his classification, and which describe an entirely different clinical concept. It is also not in accordance with the definition given in Chapter one.

It should be noted that Kumer (1942) and Carol (1948) considered stomatitis neurotica chronica (Jacobi, 1894), ulcus neuroticum mucosae oris (Löblowitz, 1910), periadenitis mucosa necrotica recurrens (Sutton, 1911) and aphthae resistentiae (Jadassohn, 1930) as identical with chronic recurrent aphthae. This view is not shared by many Anglo-Saxon authors (Fergusson, 1939; Sutton Jr., 1941; Sobel and Eller, 1954; Weichselbaum and Derbes, 1957) who consider periadenitis mucosa necrotica recurrens an independent disease. We agree with Kumer (1942) and Carol (1948) that these cases should be regarded as chronic recurrent aphthae, but can find no explanation for the fact that Carol (1948) distinguished between chronic recurrent aphthous ulcers and the aphthae of Mikulicz. To us they are part of the same disease as we hope to show in our subsequent description.

The name solitary aphthae finds an entirely different application in the classification of Frech (1945) than in that of Hirsekorn (1935). Frech (1945) used it to describe a non-recurrent, non-habitual variety as well as a recurrent habitual type. From his description it is obvious that chronic recurrent aphthae had been included under this term. On the other hand, Hirsekorn (1935), supported by Marti (1941), made a clear distinction between chronic recurrent aphthae and solitary aphthae. In the former, Hirsekorn observed multiple lesions which tend to coalesce, while the patient develops a high temperature: more than 40° C. Debilitated persons and women during puberty, menstruation and pregnancy seem to be more predisposed. In the case of

solitary aphthae, Hirsekorn found that lesions appeared singly and that a hereditary factor seemed to play an important part. He also considered the use of alcohol and tobacco as predisposing factors.

Thoma (1944) considered localized solitary ulcers to be due to trauma of the oral mucosa followed by secondary infection.

We believe that the cases described by Hirsekorn (1935) under the name of solitary aphthae should be considered under the heading of chronic recurrent aphthae.

Kumer (1942) applied the name solitary (metastatic) aphthae to the oral lesions of the so-called ulcus vulvae acutum (Lipschütz). He considered these lesions to be metastatic manifestations of infection with B. crassus. He also suggested that the lesions of foot and mouth disease should be regarded as solitary (metastatic) aphthae due to the virus of this disease. Not only is the diagnosis ulcus vulvae acutum outdated and the application of the term solitary aphthae for such lesions therefore superfluous as we hope to show later, but Kumer (1942) himself declared: "Der alte Name - solitäre Aphthen ist nicht mehr zeitgemäsz, die Bezeichnung metastatische Aphthen vielleicht vorgreifend".

We, however, believe that the name solitary aphthae could serve a useful purpose if reserved for instances where a single aphthous lesion usually makes its appearance in the mouth, and where relapses are unknown. Cases of this nature include those described by Thoma (1944) as localized solitary ulcers, trophic ulcers and neurotrophic ulcers. Frech (1945), as we already pointed out, considered cases of this nature, together with cases of recurrent aphthae, under the title solitary aphthae.

The concept aphthosis, as we have shown, was originally applied to cases described by Neumann (1895). Cases of a similar nature were subsequently designated as ulcus vulvae acutum by Lipschütz (1912). Kumer (1942), who firmly believed in the B. crassus nature of the latter, considered both ulcus vulvae acutum and aphthosis of Neumann in his classification, but questioned the validity of aphthosis as a separate entity. He was unable to find cases of such a nature and suggested that the cases of Neumann might have been caused by herpes virus. Interestingly enough, Reul (1938), to whom the etiology of acute aphthous stomatitis was still unsettled, also considered Neumann's cases as belonging to acute aphthous stomatitis.

Scherber, cited by Kumer (1942), considered ulcus vulvae acutum and the aphthosis of Neumann as identical, while Carol (1948) called cases of Neumann habitual genital aphthae.

Kumer (1942) described cases showing similar oral lesions as those of chronic recurrent aphthae, but where lesions on the

genitals and skin also appeared. As the lesions were of a recurrent nature, while no crassus bacilli were observed, he referred to them as chronic recurrent aphthosis.

In the meantime, Behcet (1937) observed the simultaneous occurrence of oral aphthae, aphthae on the genitals and eye lesions in patients, and considered them to constitute a distinct entity to which nowadays reference is often made as Behcet's syndrome (Norbis and Malbràn, 1955; Phillips and Scott, 1955; Dernoncourt, 1955; Zeavin and co-workers, 1956; Evans and co-workers, 1957). Kumer (1942) and Carol (1948) included it in their classifications as a separate disease.

In France, however, Touraine (1941) observed the striking similarity between cases described as aphthosis of Neumann, chronic recurrent aphthosis, ulcus vulvae acutum, Behcet's disease and chronic recurrent aphthae. He concluded that they all belonged to one and the same disease, which he called aphthosis. Touraine (1941) received support for this from various authors, i. a. Curth (1946a;1956), Cordonnier et al. (1953), Herbeuval et al. (1957), Laugier (1957), Vilanova and Pinol Aguadé (1958), Bataille (1958) and Schuermann (1958b).

As far as the concepts aphthosis of Neumann, chronic recurrent aphthosis, ulcus vulvae acutum and Behçet's syndrome are concerned, we believe that Touraine (1941;1955) is justified in considering them one disease, but we still have reservations as far as chronic recurrent aphthae is concerned. Curth (1946a) who holds the same view as Touraine, pointed out that "it would be going too far to consider as abortive forms of the syndrome cases with only one recurrent manifestation, such as repeated attacks of severe oral aphthae". We also prefer the name aphthosis to Behçet's disease, for the combination of symptoms considered by Behçet (1937) to constitute a new disease, had already been described by Adamantiades (1931) and Dascalopoulos (1932) before 1937, while the simultaneous occurrence of uveitis and aphthae were recognized by Weve as long ago as 1923. Reul (1938) considered the cases of Behçet (1937) under the heading chronic recurrent aphthae with simultaneous lesions on the genitals, while, as Haensch (1953) pointed out, Kumer (1938) unwittingly linked his cases of chronic recurrent aphthosis with those of Behçet. For instance, Kumer considered the cases of Whitwell (1934) and Weekers and Reginster (1938) as chronic recurrent aphthosis, while Behçet (1937, 1938, 1940) reserved them for his syndrome. Haensch (1953) also considered Behçet's syndrome as being the same as chronic recurrent aphthosis. Curth (1946a) pointed out that simultaneous recurrences of oral and genital aphthae are not essential for the diagnosis of aphthosis. A single coexistence of the two manifestations was reported by Neumann (1895), Planner and Reminovsky (1922), Pils (1925), Talalov (1934), Carol and Ruys (1929) and Kumer (1930).

In his classification, Marti (1941) distinguished between three diseases under the heading of acute aphthous stomatitis. There need not be any difference of opinion today as far as the distinction between acute aphthous stomatitis and foot and mouth disease is concerned. In our opinion, however, the aphthae preceding general systemic infections, as described by Marti, should be considered as cases of acute aphthous stomatitis (in itself an acute infectious disease) often accompanying other infectious diseases, as will be shown later.

The clinical distinction made by Marti (1941) of two types of lesions under the heading of chronic recurrent aphthae is not necessary in our opinion, for not only was Marti uncertain as to the value of this division, but both types of lesions are often encountered in the same patient at the same time, according to our own observations. Marti's description (1941) of aphthae accompanying serious general diseases of the body is more difficult. We, however, consider tropical and non-tropical sprue as distinct aphthous diseases since the almost constant association of aphthae with them can hardly be considered casual. The aphthae described by him in conjunction with pernicious anaemia and diabetes mellitus are difficult to evaluate, for they are not a constant feature of these diseases. They can therefore either be grouped with what we called solitary aphthae, or with cases of chronic recurrent aphthae, predisposed by these diseases.

The distinction made by Truelove and Morris-Owen (1958) between a major, a minor and a mixed group is in our opinion too vague; while the inclusion of erythema multiforme and Stevens-Johnson syndrome in their classification can only lead to more confusion, apart from the fact that these diseases have never generally been considered as aphthous diseases.

In our attempt at a suitable classification we will have to consider the aphthoid of Pospischill, dermatitis fibrinosa faciei, Bednar's aphthae and malignant aphthae mentioned in the differentiation of Kumer (1942), Reul (1938), Frech (1945) and Carol (1948). Some of these are characterized by the formation of aphthae, while others were at one time or another coupled with the name aphthae.

In this classification due regard has been paid to the views of the authors mentioned above, while other entities not mentioned by them are included.

With the etiology of many of the conditions still unsettled, and with great confusion of terminology, it is evident that any classification at this stage may stand open to serious criticism. This attempt should therefore be considered only as an aid to further description.

A. Diseases characterized by the formation of aphthae.
   I. Of known etiology.
      a. Due to a filtrable virus.
         1. Herpes simplex.

(i) where aphthae is a prominent feature:
acute aphthous stomatitis
aphthoid of Pospischill
dermatitis fibrinosa faciei (Moro),
(ii)where aphthae is occasionally observed:
herpes labialis
herpes corneae
herpes progenitalis
eczema herpeticum
herpes encephalitis
herpes sepsis
other manifestations of herpes infection.

2. Herpangina
3. Foot and mouth disease (aphthae epizoöticae)
4. Vesicular stomatitis
5. False foot and mouth disease
6. Due to trauma:
Bednar's aphthae of infants
Decubital ulcers
Traumatic lesions of the oral mucosa

II. Of doubtful etiology: Due to a filtrable virus?
Aphthosis (including the aphthosis of Neumann, ulcus vulvae acutum of Lipschütz, chronic recurrent aphthosis of Kumer and the Syndrome of Behcet).

III. Of unknown etiology.
a. Chronic recurrent aphthae (including stomatitis neurotica chronica of Jacobi, periadenitis mucosa necrotica recurrens of Sutton, ulcus neuroticum mucosae oris of Löblowitz and aphthae resistentiae of Jadassohn).
b. Tropical aphthae.
c. Non-tropical sprue.
d. Solitary aphthae (including localized solitary ulcers of Thoma, trophic ulcers and neurotrophic ulcers).

B. Diseases which have been named aphthae, but which are not characterized by the formation of typical aphthae.

I. Of known etiology.
a. Thrush or moniliasis (Stomatitis aphthophyta) due to monilia albicans.
b. Malignant aphthae (Orf) due to a filtrable virus.

II. Of unknown etiology.
Aphtha cachectia (sublingual fibroma of Riga-Fede).

CHAPTER III.

APHTHOUS DESEASES OF KNOWN ETIOLOGY

A. DUE TO HERPES SIMPLEX VIRUS.

1. Acute aphthous stomatitis.

(Synonyms: aphthous stomatitis, stomatitis fibrinosa, stomatitis fibrinosa maculosa, herpetic stomatitis, herpetic gingivostomatitis, acute herpetic gingivostomatitis, primary herpetic gingivostomatitis, stomatitis fibrinosa disseminata and acute infectious stomatitis).

Many authors have described the clinical picture of acute aphthous stomatitis. Amongst some of the descriptions we must mention those by Kumer (1942), Flusser (1930), Rebel (1948), Frech (1945), Kranz (1949), Cath (1955), Blank and Rake (1955), Schuermann (1958) and Nasemann (1958).

After a prodromal stage lasting from one to two days, characterized by a rise in temperature up to 40 °C, general malaise and a diffuse reddening of the oral mucosa, multiple (from twenty to as many as fifty) tiny, yellowish - white, fibrinous plaques or macules on the mucosa surrounded by an intense red halo. They appear anywhere in the mouth, on the throat, the tongue and the gingivae. The latter are swollen, coated with fibrin and bleed easily. The disease usually affects children between the second and fifth year and occasionally also young adults. The lesions cause pain with eating or drinking, and is accompanied by swelling of the regional lymph glands and foetor ex oris.

Individual lesions begin as fluid-filled intra epithelial vesicles which soon rupture to leave the characteristic fibrinous yellowish-white patches surrounded by a red halo, as described above.

In infants a resulting dehydration and acidosis may lead to grave prostration and even to death.

The lesions must be differentiated from those of foot and mouth disease, the infection of Plaut-Vincent, chronic recurrent aphthae, chicken-pox, vesicular stomatitis and syphilis.

In chapter 1 we have shown that aphthous stomatitis was described by Billard (1828), Bohn (1880) and others, but that it was Mikulicz and Michelson (1892) who first gave a separate description of acute aphthous stomatitis and chronic recurrent aphthae. Afterwards many accounts appeared under the name of aphthous stomatitis in which the two varieties were considered to be the same disease, showing different characteristics in children and in adults. Although many suspected an infectious agent, especially of the acute variety in children, the etiology remained obscure. It was noticed that infectious diseases like pneumonia, diphtheria, whooping cough and catarrhal inflammations of the mouth, nose and throat often accompanied the disease in children (Bohn, 1880; Bresgen, 1884; Baume, 1890; Ziegler, 1898 and Scheff, 1903).

Bohn (1880) considered the lesions to be analogous to that of impetigo. This view was supported by Jadassohn (1896), who found staphylococci in the lesions. Stooss (1895), cited by Kümmel (1922), reported finding diplococci, while Prochazka (1924) held streptococci, responsible in the case described by him. To Kümmel (1922) however the cause of the disease was still unkown.

In the meantime Grüter (1920) described the etiological agent of herpes. He could reproduce herpes corneae in rabbits and in man. After inoculating material from the eye lesions of patients on the corneae of rabbits and on those of a blind person, he obtained the typical lesions of herpes corneae. A year later Luger and Lauda (1921) proved that the infective agent was a filtrable virus. About the same time Lipschütz (1921) reported the finding of intranuclear inclusion bodies in the affected epithelial cells of a patient suffering from herpes labialis.

These discoveries led Gans (1924), on the grounds of similarity between aphthous stomatitis and herpes labialis (in his own words: tendency to recur, short-lived immunity, general disturbance, temperature) to investigate the possibility of a herpetic etiology in six of his patients suffering from aphthous lesions. After using the methods employed by Grüter in his experiments, Gans obtained positive results in only one patient. He considered the failure to obtain positive results in the other cases as being possibly due to their mild nature. In our own opinion it is very likely that these five patients suffered from recurrent aphthae. Gans himself, without drawing definite conclusions, urged for more research in the matter. Peiser (1924) was of the opinion that the results of Gans were inconclusive evidence for a herpetic etiology. Two years later Peiser (1926), however, reported an epidemic outbreak of aphthous stomatitis in 45 adults.

In an article "Is aphthous stomatitis due to the Virus of Herpes Simplex?" Templeton (1926) reported negative results after corneae inoculations on rabbits. In reading this article, however, one finds that all his patients probably belonged to the category of chronic recurrent aphthae. In the same year Mayer (1926) succeeded in producing typical herpes lesions after inoculation on the corneae of rabbits. He obtained his material for inoculation from a patient suffering from typical herpes labialis together with aphthous lesions in the mouth.

More reports appeared of aphthous stomatitis occurring in conjunction with other diseases. Zulkis and Spitzer (1928) described aphthous stomatitis in a woman, twenty years of age, and suffering from influenza. Schindler and Schindler (1929) reported a case of mumps (a girl of fourteen years) who also had aphthae in the mouth together with herpes on the lips. The similarity of this to fusospirochetal infection made them decide that the Treponema vincenti played an important part.

In an outstanding clinical description of chronic recurrent aphthae and acute aphthous stomatitis, Flusser (1930) clearly pointed out the contagious nature of the latter and its occurrence in more than one member of the same family. In cases of acute aphthous stomatitis he also observed skin lesions which were identical to those first described by Moro (1911) under the name of "Dermatitis fibrinosa faciei". To the acute contagious variety of aphthae Flusser applied the name "infectious aphthae" and to the chronic recurrent variety the name "habitual aphthae". The etiology of these diseases was still unsettled, according to him.

Zamorani (1930) was the first to prove the herpetic nature of acute aphthous stomatitis. In carefully conducted animal experiments he obtained positive results after corneal inoculation with material from six patients suffering from the disease. This evidence was further substantiated by the results of Kumer (1932), who produced herpes corneae in rabbits after inoculation with material obtained from eight patients. Kumer suggested the name "Stomatitis herpetica atypica" for the disease.

The findings of Zamorani (1930) and Kumer (1932) were not immediately recognized. Zinsser (1930) still believed in a possible relationship between acute aphthous stomatitis and foot and mouth disease. Blancke (1934), in an otherwise excellent report on aphthae, was obviously ignorant of the findings of these authors, while, according to Hirsekorn (1935), it was impossible to tell whether acute and chronic aphthae had the same etiology. One of the two adult patients of Hirsekorn was a typical case of acute aphthous stomatitis, while the description given by him of the other patient makes it difficult for us to draw any definite conclusions. According to Hirsekorn this patient was acutely ill with a high temperature, suffering from recurrences. He therefore considered this patient to be a case of chronic aphthous stomatitis.

Black (1938), after a detailed study of 69 patients suffering from what he called acute infectious gingivostomatitis, arrived at the conclusion that the terminology of this disease was in the utmost confusion. According to him it was variously known as Vincent's stomatitis, Vincent's angina, ulcerative or ulceromembranous stomatitis, necrotic stomatitis, fusospirochetal stomatitis, aphthous or aphtho-ulcerative stomatitis, trench mouth etc. He believed that all these terms denoted the same acute infectious disease which primarily affects the gingivae and therefore proposed the name acute infectious gingivostomatitis. According to him, the name aphthous stomatitis was a term usually applied to soreness of the mouth in which gingivitis is minimal or absent and the characteristic lesions are "aphthous ulcers". The word "aphthous" was, according to Black, originally applied to thrush and more recently to su-

perficial small ulcers of the oral mucosa and he regards it as one of those pretentious medical terms without etiologic significance and of poor descriptive value which richly deserved to be discarded from standard usage.

In reading Black's article one is immediately struck by three facts. Firstly that he stressed the importance of the gingival condition in the disease, which obviously led him to believe that the disease was identical to Vincent's infection. Secondly, that he also found aphthous ulcers in the condition (64% of his cases). This caused him to remark: "It is not improbable that aphthous stomatitis and acute infectious gingivostomatitis have the same, as yet unidentified primary cause". Thirdly, one gathers that Black was obviously ignorant of the clinical description of Flusser (1930) and of the experimental findings of Zamorani (1930) and Kumer (1932), for he only considered the possibility of a virus in the etiology of the disease after having read the work of Dodd and co-workers (1938) in which these authors confirmed the herpetic nature of acute aphthous stomatitis.

Final proof for the herpetic origin of the disease was given by Burnet and Williams (1939), when they demonstrated the production of neutralizing antibodies in the reconvalescent sera of patients suffering from it. They considered acute aphthous stomatitis to be a primary or first infection with the herpes virus, while persons with antibodies against the virus in their blood usually suffer from recurrent labial herpes or herpes corneae. After the primary infection the virus remains latent in the cells of the patient, who then harbours it as long as he or she lives, only to produce fresh outbreaks after certain stimuli or under such conditions as heat, cold, fever, menstruation, trauma etc.

Dodd et al. (1938), Burnet and Williams (1939), Kilbourne and Horsefall (1951) and Cath (1955) found that the primary infection with the herpes virus usually occurs in childhood. According to Andrewes and Carmichael (1930), Burnet and Lush (1939) and Hayward (1949) the majority of adults (65% to 90%) possess antibodies in their sera.

Kilbourne and Horsfall (1951), Youmans (1932), Ziskin and Holden (1943), Rogers and co-workers (1949), Ruiter (1950) and Blechman and Pascher (1959) reported a primary infection with the herpes virus in adults.

In the literature we find opposing views as far as recurrences are concerned. Dodd et al. (1939), Ruiter (1950), Blank and Rake (1955), Vest (1957) and Dekking (1958) are of the opinion that acute aphthous stomatitis never gives rise to any recurrences, while Scott et al. (1941), Ziskin and Holden (1943), Cahn (1950), Kerr (1952a;1952b), Kilbourne and Horsfall (1951), Farmer (1956) and Strean (1957a) do not share this view. These contradictory views have an important bearing

on our subsequent investigations, and will therefore be considered fully in the chapters dealing with chronic recurrent aphthae.

In the course of our description we have already mentioned three other clinical manifestations of herpes virus infection, namely herpes labialis, herpes corneae, and dermatitis fibrinosa faciei. Others mentioned in literature are herpes progenitalis, eczema herpeticum, herpes encephalitis, herpes sepsis and the so-called aphthoid of Pospischill. As all of them have been descrbed in conjunction with aphthous lesions in the mouth, we feel that it is necessary to give a short account of each.

2. Aphthoid of Pospischill.

This clinical manifestation of herpes infection — sometimes also referred to as the aphthoid of Pospischill-Feyrter — was first described by Pospischill (1921), when he observed it in children suffering from whooping cough.

In a short space of time (overnight) the skin around the mouth is covered by thick-walled vesicles ranging in size from that of a lentil to that of a finger nail. The lesions tend to coalesce, thereby covering a considerable area — extending as far as the nose, the cheeks and even the ears. Towards the edge of the lesions a red erythematous zone is visible. After a couple of days the central portion becomes umbilicated together with crust formation, while the raised erythematous edge shows peripheral extensions. The regional lymph glands are enlarged and tender.

The disease usually appears in children suffering from whooping cough, measles, diphtheria, scarlet fever or acute bronchitis.

The temperature may be elevated and the general condition of the patient so severe that death ensues (Kumer 1942; Frech 1945; Mathis 1951; Schuermann 1958a).

Fessler and Feyrter (1926) and Feyrter (1927) provided the first experimental evidence that the lesions are due to infection with herpes virus. This finding was substantiated by Gottron (1931).

While Kumer (1942) beyond any doubt, considered the herpes virus to be the etiological agent of the condition, Schuermann (1958) felt that the etiology of the disease had been proved in all respects, except one, namely that after infection of the rabbit corneae with material from patients suffering from the aphthoid of Pospischill no definite lasting immunity to herpes virus could be demonstrated.

3. Dermatitis fibrinosa faciei.

This herpetic manifestation encountered in infants was first described by Moro (1911).

In conjunction with aphthous lesions in the mouth, lesions appear on the skin in the form of red, elevated papules which are soon subjected to necrotic changes in their centres. Around the periphery a red erythematous border is visible. The eruption is usually located around the mouth, but may sometimes effect other parts of the skin.

The lesions of dermatitis fibrinosa faciei were at one time considered to be of the same nature as those of impetigo contagiosa (Jadassohn, 1898).

Moro (1911) considered the lesions on the skin as due to contamination with infected saliva.

Further descriptions of the disease were given, among others, by Carol and Postma (1936), Flusser (1929), and Mayer (1934).

4. Herpes labialis. .

This form of herpes infection is so well-known that a description is hardly necessary. That Shakespeare was familiar with the disease (Blank and Rake, 1955; Cath, 1955) is evident from Mercutio's lines in Romeo and Juliet (Act I, Scene IV), where he gave the following description of Mab, the fairy queen:

> O'er ladies' lips, who straight on kisses dream,
> which oft the angry Mab with blisters plagues,
> Bacause their breaths with sweetmeats tainted are.

After a patient had suffered from a primary infection with herpes, the virus which remains latent in the tissues are activated by various local or general stimuli to produce the typical fluid-filled vesicles on the lips. These vesicles soon dry to form superficial crusts. The process usually heals in a few days without scarring. Amongst the commenest stimuli causing recurrences are sunlight (an example is the "Gletscher herpes" of the Alps), fever, cold, heat, menstruation and nervous tension (Cath 1955). Trauma and surgical procedures often play an important part (Schröpl, 1927; Hruszek, 1933; Pizer, 1954).

In some patients with repeated attacks no specific flaring factor can be demonstrated. Blank and Brody (1950) subjected a group of such patients to psychologic investigations. They found that the initial reaction of these patients to psychiatric treatment revealed an astonishing uniformity. All of them developed a rapid positive transference which, according to Blank and Brody, points to a high degree of infantile sexuality. These authors further concluded that the patients would be classified psycho-analytically as oral receptive people in whom the attacks of herpes simplex appeared as a vegetative responce.

5. Herpes corneae.

Herpes virus infection of the eye is encountered either as an initial infection or as a recurrent manifestation.

Gallardo (1943) reported a purulent kerato-conjuctivitis as the result of a primary infection with the virus.

Gundersen (1936), cited by Cath (1955), in a study of 221 patients suffering from herpes infection of the eye, frequently observed the presence of an iritis. Thirteen of Gundersen's patients also had a hypopyon. From four of the thirteen he was able to isolate the virus. 37.4% of his cases had an accompanying herpes infection of the skin of the face.

Cath (1955) in most cases considers herpes corneae to be a complication of an earlier herpes infection of the skin.

According to Blank and Rake (1955) the primary lesions of the eye is of a more severe nature than the recurrent variety.

6. Herpes progenitalis.

In men, herpes infection gives rise to small erosions on the glans or corona penis, while groups of vesicles are to be found on the remainder of this organ. In women erosions are found on the labia minora and majora, and in the lower part of the vagina (Cath, 1955).

Slavin and Gavett (1946) were the first to describe acute herpetic vulvovaginitis in adult women.

The transmission of genital herpes from one person to another through sexual intercourse have been described by Hruszek (1937) and Schmitz (1937).

7. Eczema herpeticum.

This condition — first described by Kaposi in 1887 as a "varicelliform eruption" and named by him "eczema herpetiforme"— was subsequently decribed under a variety of names. Juliusberg (1898) gave it the name of "pustulosis acuta varioliformis". Other names are "disseminated cutaneous herpes simplex" or "viral pyoderma" (Blank and Rake, 1955).

In the classical case, as described by Cath (1955), the patient (usually a child) gives a previous history of eczema. After a few days of general malaise and a high temperature, often accompanied by an extensive local oedema, a papular eruption appears on the oedematous area. Within 24 hours the eruption changes into vesicles, to be followed by pustules with an umbilicated centre. The pustules are surrounded by a red halo and are subject to rapid dessication with crust formation. In the course of the disease, recurrent outbreaks of fresh pustules may occur. Regional lymphadenopathy is a constant feature. In uncomplicated cases the temperature subsides after one or two weeks with disappearance of the lesions.

That herpes virus may be responsible for the condition was demonstrated by Seidenberg (1941), cited by Blank and

Rake (1955), Barton and Brunsting (1944), Ruiter (1949) and Ruiter and Nelemans (1949).

Various authors, however, found that the clinical picture of eczema herpeticum may also be due to infection with vaccinia virus. According to Blank and Rake (1955) "it is now clear that the lesions produced by herpes simplex or vaccinia in a patient may be clinically indistinguishable".

Grist (1953) isolated vaccinia virus in four out of nine patients presenting the clinical picture of eczema herpeticum, while herpes virus was demonstrated in two cases.

Brain and Lewis (1939) considered herpes simplex as the etiological agent in 50%, and vaccinia virus in 25% of their cases.

8. Herpes encephalitis.

Smith and co-workers (1941) were the first to show that herpes virus may be responsible for encephalitis. The fatal nature of the condition was described by Zarafonetis and co-workers (1944) and Warren (1949).

Goudsmit (1949), however, described an epidemic outbreak of acute aphthous stomatitis in which transient cerebral symptoms were a prominent feature, while Afzelius-Alm (1951) demonstrated that herpes encephalitis may be a non-fatal primary infection, during which specific antibodies appear.

According to Blank and Rake (1955), the condition, whether fatal or not, is indistinguishable clinically from other types of viral encephalitis or aseptic meningitis.

Clinically one finds fever, headache, dizziness, somnolence, stupor, convulsions, paresis of ocular and other muscles and sensory changes. The spinal fluid usually shows a lymphocytic pleocytosis and may be under increased pressure. Lesions of the skin and mucous membranes may appear during the attack.

9. Herpes sepsis.

Primary infection with the virus sometimes cause a generalised infection especially in premature infants. As a result of viraemia, multiple metastatic necrotic lesions are to be found in the liver, spleen, adrenals, kidney, brain, lung, skin, conjunctivae and gastrointestinal tract. Within a few days after delivery the infant either develops a temperature or hypothermia accompanied by jaundice, lethargy, respiratory distress, vomiting, dyspnoea, cyanosis, circulatory collapse and enlargement of the liver. Symptoms include an accumulation of mucus in the throat, while hypothrombinaemia causes a severe bleeding tendency (Quilligan and Wilson, 1951; Zuelzer and Stulberg, 1952).

The virus can be isolated from the affected organs, while it was also possible to demonstrate inclusion bodies in the diseased tissues. The condition usually ends fatally.

10. Other manifestations of herpes infection.

Apart from the clinical manifestations of herpes infection already discussed, a number of others have also been reported in literature.

Bruusgaard (1930) described a patient with extensive herpes simplex lesions together with a retrobulbar neuritis.

Keining (1933) reported a case suffering from recurrent herpes of the third and fourth finger of the left hand, accompanied by a swelling of the back of the hand and forearm. The swelling was of the nature of erysipelas.

Kicévac (1934) observed a case suffering from labial and nasal herpes, accompanied by a scarlatiniform rash on the skin.

Goncalves (1948), cited by Blank and Rake (1955), demonstrated the presence of herpes virus in the vagus nerves removed from patients suffering from recurrent gastroduodenal ulcers. The findings of Goncalves, however, could not be confirmed by Palmer and Reagen (1953).

Ruiter (1950) described a case of aphthous stomatitis who also suffered from a herpetic paronychia, while Fleck (1951) reported an unusual case of herpes simplex which healed with the subsequent formation of leucoderma.

From the urethra of a patient with urethritis, Esteves and Pinto (1952) isolated herpes virus.

THE HISTOLOGICAL PICTURE OF ACUTE APHTHOUS STOMATITIS

We have already mentioned that Worms (1864) gave the first microscopical description of aphthae, where he considered the aphthous exudate to be a conglomeration of fat globules, and that Fraenkel (1888) was the first to give a proper histological account of the lesions.

At the time of Fraenkel's publication, as we have seen, aphthae of the oral cavity was still considered to include acute aphthous stomatitis and chronic recurrent aphthae. Both these entities were regarded as different manifestations of the same disease with probably the same etiology, independent of whether it occurs in adults or in children, or whether it was of an acute or chronic nature.

Fraenkel (1888) obtained his biopsy material for histological examination from three patients. From the clinical description of these cases it is obvious that they suffered from acute aphthous stomatitis. All were acutely ill with fever and foetor ex oris. No mention was made of any recurrence. He found the aphthous lesions to be covered by a pseudomembrane resembling that of croupous inflammation and diphtheria in the throat. The epithelium showed necrosis and a superficial deposit of a fine fibrinous exudate. In the fibrinous mass Fraenkel observed leucocytic infiltrates and occasional epithelial cells. These epithelial cells showed degenerative changes in the

form of swelling. The process stretched as far as the mucosal papillae, which were compressed sideways, but otherwise revealed no changes. He was unable to demonstrate any vesicle formation.

In dealing with the histological picture of aphthous stomatitis, many authors (Ziegler, 1898; Siegmund and Weber, 1926; Aschoff, 1936) accepted the views of Fraenkel.

Cahn and Bartels (1942) considered the lesions to begin as intraepithelial vesicles which quickly break down into the characteristic small superficial ulcers. The vesicles, according to them, result from oedematous degeneration of the epithelial cells (the degenerative swelling described by Fraenkel, 1888?). The fully developed vesicle represents s cavity in the epithelium, the contents of which are a meshwork of fibrin in which balloon cells, other degenerated epithelial cells and occasional polymorphonuclear leucocytes are to be found. The base of the vesicle, according to these authors, is composed of oedematous epithelial cells of the basal and lower prickle cell layers. The roof is formed by the compressed upper layers of the stratum spinosum and the granular zone. The cells adjacent to the vesicle also show oedematous changes. Vesiculation is further aided by intercellular oedema.

Blank (1949) and Blank and Rake (1955) found that within a few hours after infection the chromatin granules and the nucleolus become indistinguishable in the nucleus, which contains a basophilic material. This basophilic or Feulgen-positive material (desoxyribonucleic acid) fills the nucleus, while the chromatin becomes marginated to form a thickened nuclear membrane. Condensations of chromatin may appear in the nucleus and divide to form small locules, each containing inclusion material. Between the inclusion material and the chromatin, clear zones are visible. In the non-loculated nucleus the clear zone increases in size, while the Feulgen-positive material diminishes until it disappears. According to these authors the remaining eosinophilic body in the centre of the nucleus is the same as the so-called "inclusion bodies" first described by Lipschütz. Blank and Rake (1955) further pointed out that these "inclusion bodies" are thought to be the end stage of the process after the virus has escaped from the cell, and are considered by them to be a non-specific change, for identical "inclusion bodies" are also found in non-viral diseases such as certain metallic poisonings. The loculated nuclei, however, continue to grow while the inclusion material increases in amount until each compartment becomes rounded and eventually assumes the size and shape of an individual cell nucleus. In this way, viral-type giant cells containing as many as fifteen or more nuclei are formed. These giant cells may sometimes measure more than 50μ in diameter.

While it is generally agreed that "inclusions" are some-

times aspecific it was found that in some viral diseases typical "inclusion bodies" appear with such regularity, that they may be considered specific and even of diagnostic importance (Verlinde, 1950).

An interesting fact is that, although the viruses of herpes simplex and varicella are unrelated, they produce identical cytological changes (Blank and Rake, 1955). On the other hand, an identical histological picture is observed with all the manifestations of herpes virus infection, whether of primary or recurrent nature.

B. HERPANGINA

(Synonym: Herpesangina).

In the United States, Zahorsky (1920) observed an epidemic disease in children, characterized by small aphthous lesions in the posterior part of the mouth and throat, which he called "herpetic sore throat". The cause of the disease was unknown, but the great resemblance to the lesions of herpes virus earned for it the name of herpangina (Zahorsky and Zahorsky, 1943).

Zahorsky (1920) originally described the disease as follows: "The disease begins suddenly with a high fever. The temperature often rises to 104 F. A convulsion may occur. Vomiting is often present. Anorexia and prostration are sometimes marked. The throat and posterior part of the mouth show minute vesicles, or if these have ruptured, small punched-out ulcers. They occur on the anterior pillar of the fauces, the tonsils, the pharynx and the edge of the soft palate. The number of lesions varies from two to twenty. Dysphagia is often marked. The disease may be confused with ulcerative stomatitis, which sometimes begins in the throat. The prognosis is favourable and the treatment is symptomatic ".

In 1948, Dalldorf and Sickles, during investigations on poliomyelitis isolated a virus from the stools of children in Coxsackie, New York. This virus was called Coxsackie virus. A year later, Curnen and co-workers (1949) found certain strains of the virus responsible for what is now called Bornholm disease or epidemic pleurodynia. Other strains of Coxsackie virus were established as the etiological agent of herpangina by Huebner and co-workers (1952). These authors concluded that Coxsackie A virus is the cause of herpangina, while Coxsackie B type is responsible for epidemic pleurodynia.

Mitchell and Dempster (1955) reported the finding of genital lesions in a patient (a girl seven years old) with herpangina.

Herpangina must be differentiated from acute aphthous stomatitis (Schlack, 1953; Parrot and co-workers, 1954).

No description of the histological picture of the lesions could be found in the literature.

C. APHTHAE EPIZOÖTICAE

(Synonyms: aphthous stomatitis, aphthous fever, fièvre aphteuse, Aphthenseuche, foot and mouth disease, hoof and mouth disease, stomatitis vesiculosa infectiosa).

This disease, which is principally one of cattle, pigs, sheep and goats, was probably first described by Hieronymus Fracastorius (1514) in his work titled "De contagione et contagiosis morbis et curatione" (Waldman and Nagel, 1939).

The striking resemblance of the oral lesions to those found in acute aphthous stomatitis of man explains why the term "aphthous" has also been used in conjunction with the disease (Kümmel, 1922). No wonder that for many years acute aphthous stomatitis of man, and foot and mouth disease were considered by some authors (Ebstein, 1896; Margulies, 1920; Fischl, 1924) to be the same.

Loeffler and Frosch (1897) were the first to demonstrate the viral nature of epizootic aphthae. Later it was shown that guinea pigs were also susceptible (Waldman and Pape, 1920; Alberca, 1927). The virus can be grown in tissues from susceptible animals (Hecke, 1930; Köbe and Fertig, 1936). Chickens, ferrets and horses seem to be resistant (Blank and Rake, 1955). Skinner (1954), however, was able to infect newly hatched chickens and chick embryos.

The disease has a low infectivity for man. Drooglever Fortuyn (1912) reported only a few doubtful cases in humans, whereas 70, 000 head of cattle at that time were infected in the Netherlands.

Cases in man have been reported, among others, by Weinberger (1933), Nixon (1937), Flaum (1939) and Rochaix and Delbos (1938). Infection takes place either through direct contact with diseased animals or after ingestion of infected dairy products.

Clinically the disease in humans is characterized by an incubation period varying from two to eighteen days (Blank and Rake, 1955). After a prodromal stage lasting from one to two days in which headache, malaise and fever dominate the picture, the oral mucosa feels dry and hot, and vesicles appear, especially on the lips and tongue. The palate, throat, hands and feet are affected to a lesser extent. The vesicles soon rupture to leave eroded spaces with a yellowish-grey surface and surrounded by a red halo. According to Burket (1946) salivation and lymphadenopathy are prominent features. Healing takes place without scar formation after about ten days.

The histopathology of the lesions has been described by Gins (1922) and Siegmund and Weber (1926). Initially one finds hyperkeratosis followed by intracellular oedema and disintegration of cells in the rete Malpighi. This leads to vesicle formation. Around the lesions leucocytic infiltration and deposition of fibrin takes place. In the adjacent epithelial cells Gins (1922) observed acidophilic intranuclear inclusions.

D. VESICULAR STOMATITIS

(Synonyms: Stomatitis contagiosa, equine vesicular stomatitis, sore mouth of cattle, mycotic stomatitis, mal de yerba).

This disease of horses and cattle was first described in horses by Burton (1917), and presents similar lesions to those of foot and mouth disease.

Coltar (1927) was the first to discover a virus as the etiological agent of the disease. Olitsky and Long (1928) could readily infect guinea pigs with the virus.

Scott and co-workers (1941) were of the opinion that the type of stomatitis described in textbooks as vesicular stomatitis was in actual fact the same as chronic recurrent aphthae. Bieling (1951), however, rightly pointed out that vesicular stomatitis of horses and cattle should not be confused with aphthous stomatitis of man.

Human infection with the virus of vesicular stomatitis has been reported by Heiny (1945), Hanson and co-workers (1950). Bieling (1951) and Kowalczyk and Brandly (1954).

The disease in man although of less severe nature than foot and mouth disease, can only be differentiated from the latter by means of laboratory studies. Important is the fact that horses are readily infected with vesicular stomatitis virus, while they are resistant to infection with that of foot and mouth disease.

Complement fixation tests and electron microscopic studies (the virus of vesicular stomatitis is much larger than that of foot and mouth disease) are valuable aids in differentiating the two diseases (Blank and Rake, 1955).

The histological description given of the lesions by Olitsky and Long (1928) shows no appreciable difference to that of foot and mouth disease.

Fisher and Leider (1951) used the term vesiculo-erosive stomatitis to describe the common aphthous lesions of man. We are of the opinion, however, ,that this term should not be used for such cases as it can easily be confused with vesicular stomatitis.

E. FALSE FOOT AND MOUTH DISEASE

Mention must be made of a virus disease resembling foot and mouth disease and vesicular stomatitis, described in France by Mollaret and co-workers (1953). It affects both cattle and man, and can be differentiated from the other two diseases on serological and clinical grounds (Blank and Rake, 1955). According to these authors, the disease runs a febrile course and gives rise to small red ulcerations on the buccal and pharyngeal mucosa, while herpes labialis in conjunction with meningitis were observed in the latter stages.

Blank and Rake (1955) described it under the title false foot and mouth disease.

F. TRAUMATIC LESIONS OF THE ORAL MUCOSA

In our classification we mentioned aphthae as the result of trauma. This included among others Bednar's aphthae and decubital ulcers. In literature only the lesions of Bednar's aphthae have been tied up with the name aphthae. The inclusion of decubital ulcers and other traumatic lesions in our classification should not be interpreted as an attempt to link the name aphthae to trauma of the oral mucosa in general. The reason for its inclusion is the fact that lesions of this nature, conforming with our definition of aphthae, are often encountered in dental practice. This especially applies to decubital ulcers.

The name decubital ulcers is often used in the description of lesions due to pressure caused by ill-fitting dentures. These prosthetic ulcers do not differ from other aphthous-like traumatic lesions of the mouth. A separate description is therefore unnecessary. Mention must be made of the fact that some authors (Thoma, 1946; Jeanneret, 1947) applied the name decubital ulcers not only to lesions caused by ill-fitting dentures, but also to injuries from other causes. The latter include cheek-biting, sharp edges of carious or fractured teeth, injury during mastication, tooth brush injuries, and accidental trauma of the mucosa during dental treatment.

The lesions appear as grayish-white ulcers of varying size, often of irregular outline, and surrounded by an area of inflammation. In the case of prosthetic ulcers the lesions are sometimes fairly deep. The lesions are painful when touched but they do not, however, give rise to spontaneous aching.In the case of the denture lesions, severe pain may be experienced when eating. After removal of the cause the lesions heal rapidly. With continuous irritation the lesions gradually lose their aphthous appearance. The edges become indurated and eventually hyperplasia and hypertrophy set in.

Orban and Wentz (1955) described the histological picture of tootbrush injuries and decubital ulcers. In cases where the mucosa was punctured by a toothbrush bristle, these authors found that the epithelium may show surface damage and invasion by numerous leucocytes. Proliferation of epithelial ridges occurred, and the underlying connective tissue revealed mild inflammation. On the other hand, when the injury was more extensive, the epithelium was completely destroyed and an ulcer developed. According to Orban and Wentz, the ulcerated surface was covered by necrotic tissue debris and fibrinous exudate. Similar changes were found by them in decubital ulcers. They concluded that the histological picture of decubital ulcers revealed similar changes to those caused by other physical injuries.

Bednar's aphthae.

(Synonym: Pterygoid ulcers).

In 1850 the Vienese pediatrician Aloisius Bednar (1816-1880) applied the name aphthae to a condition found only in infants. It is still today referred to as Bednar's aphthae.

The condition is characterized by the formation on the palate of groups of small, raised, irregular ulcers, the size of a pinhead, which tend to coalesce in the shape of a butterfly with stretched wings. The lesions are well demarcated, yellow to gray in colour and surrounded by a red inflamed border. They appear characteristically where the hamuli pterygoidea and the bony median suture protrude from the palate, and are caused by pressure on a teat or by too energetic nursing of the mouth. The thin mucosa over these areas contributes to the ease with which traumatic ulceration takes place (Kumer, 1942; Reul, 1938; Frech, 1945; Prinz and Greenbaum, 1939; Carol, 1948).

CHAPTER IV

APHTHOUS DISEASE OF DOUBTFUL ETIOLOGY

A. APHTHOSIS.

Introduction.

(Synonyms: Aphthosis of Neumann, ulcus vulvae acutum (Lipschütz), chronic recurrent aphthosis, Behcet's syndrome, Behçet's disease, Fragmentary Behcet's syndrome, Abortive syndrome of Behçet, L'aphtose, Grand aphthosis of Touraine etc).

The name aphthosis, as we have pointed out in Chapter I, was first applied to a condition described by Neumann of Vienna in 1895 under the title "Die Aphthen am weiblichen Genitale". The main characteristics were the occurrence of aphthae on the genitals, aphthae in the mouth and occasional skin lesions in the form of erythema nodosum or erythema multiforme-like efflorescences, together with papules or pustules surrounded by a red halo. His patients often had a temperature ranging from 39 to 39.6° C. In his experience, the disease only affected women and young persons living in bad hygienic conditions. Neumann considered the majority of the mucosal lesions to be analogous to those seen in the mouths of men suffering from aphthae. The age of the fourteen patients described by him ranged from 17 to 48 years. All of them had genital lesions but only 11 of the fourteen suffered from lesions in the mouth, while four exhibited skin lesions (two with erythema nodosum and two with erythema multiforme-like lesions). Five years later Neumann (1900) demonstrated a further case, that of a 32 year old unmarried woman who suffered from aphthous lesions on the genitals together with scattered nodules on the skin varying between the size of a millet seed and that of a pea. The skin lesions were surrounded by a red border, while they had a pustular appearance in the centre. No oral lesions were present. As the condition might have led to confusion with lues, Neumann emphasized its forensic importance.

According to Reul (1938), Christlieb (1895) described a similar case of oral and genital lesions together with skin manifestations.

In Sweden, Welander (1903) observed twenty-four cases with genital ulcers. None of his patients suffered from oral aphthae. He described the cases as suffering from "Insonte oberflächliche (Ano-) Genitalgeschwüre". Similar cases were described by Sachs (1905) as "pseudotuberculous ulcers."

Ulcus vulvae acutum.

Lipschütz (1912) regulary found numerous, thick Gram positive bacteria in the smears from vulval ulcers in his patients. He called the bacteria Bacillus crassus; and conside-

ring the ulcers to be a separate disease entity, caused by this bacillus, he named it "ulcus vulvae acutum".

Scherber (1918, 1919), whom we must credit for being the first to obtain a pure culture of B. crassus anaerobically, considered them as being identical to the vaginal bacillus described by Döderlein (1892). He therefore proposed the name "Scheidenbazillen-Geschwüre" instead of ulcus vulvae acutum.

The name "ulcus vulvae acutum", however, seemed to be more popular and gained universal recognition. It soon became evident that it was a very inappropriate name. First, Volk (1914) described ulcers on one of his patients' penis from which he obtained B. crassus, and later Brünauer (1920) reported a patient who had lesions at some distance from the vulva, and in which he was able to isolate the bacillus.

Lipschütz (1918), cited by Bingel (1921), expressed the wish that the name "ulcus vulvae acutum" should only be employed in cases where B. crassus had been isolated. Bingel (1921) himself, however, reported seven cases under that name without being able to demonstrate the bacillus. Lipschütz interpreted his constant failure in recovering the bacillus from the oral lesions as evidence that oral aphthae and genital ulcers were two different diseases, occurring at the same time. This view was not acceptable to Schugt (1925) who, on clinical and histological grounds, considered the genital and oral lesions in his patient as being due to the same etiological agent. Schugt was unable to find B. crassus in oral lesions while a pure culture was obtained from those on the genitals. He considered this positive finding in the genitalia to be of no etiological significance.

That a diagnosis of ulcus vulvae acutum was only feasible after demonstration of B. crassus caused many authors (Planner and Remenovsky, 1922; Chauffard et al., 1923; Pils, 1925; Grütz, 1926; Schnabl, 1927; Carol, 1935) to describe similar cases (where the bacillus was absent) under a variety of names.

Cases of ulcus vulvae acutum presenting genital lesions as the only manifestation were described by Bingel (1921), Roederer and Sloimovici (1927), Carol and Ruys (1929), Rosenthal (1930), and Assnin and Sutejew (1934). Genital lesions accompanied by oral aphthae were reported by Schugt (1925), Jaffé (1930), Kumer (1930), Ito (1931), Wien and Perlstein (1932) and Philadelphy (1933), while a combination of genital ulcers, oral aphthae and skin lesions were found in patients of Carol and Ruys (1929), Walter and Roman (1930), Kumer (1930), Matras (1932), Assnin and Sutejew (1934), Talalov (1934), Rosenthal (1934), Yamazaki (1937), Fuhs (1937), Popoff (1938) and Volavsek (1938).

Samek and Fischer (1929), Dreyer (1932), and Popoff (1938) reported cases with genital and skin manifestations,

while Nishimura (1935) observed a girl, 16 years of age, suffering from painful genital and oral lesions followed by an acute iritis.

With the exception of Bingel (1921), all the authors who described cases under the name ulcus vulvae acutum were able to demonstrate the presence of B. crassus in the genital lesions of their patients. Bingel found various bacteria, including staphylococcus aureus, Gram negative rods, spirochaetes (not pallida), Gram positive cocci, pneumococci, diphtheria and pseudodiphtheria b cilli, etc.

Popoff (1938) considered the genital lesions to be a secondary manifestation of the skin condition (erythema nodosum and polymorph erythema) while the B. crassus was considered of no etiological significance.

B. crassus was demonstrated in the oral lesions by Ito (1931), Matras (1932), Philadelphy (1933), Rosenthal (1934), Talalov (1934), Nishimura (1935) and Fuhs (1937), while Carol and Ruys (1929), Kumer (1930), Walter and Roman (1930), and Assnin and Sutejew (1934) were unable to do so.

Samek and Fischer (1929) were able to cultivate the bacillus in pure cultures from the genital ulcers, the erythema nodosum-like lesions of the skin and from the blood. Later Matras (1932) also succeeded in obtaining B. crassus in pure cultures from genital lesions, oral aphthae and the bloodstream. Fuhs (1937) reported finding it in genital, oral and skin lesions, of his patient. Yamazaki (1937) found it in genital and skin lesions, while Volavsek (1938) obtained pure cultures of B. crassus from oral, genital and skin lesions.

In addition to the lesions already mentioned, Carol and Ruys (1929), Matras (1932) and Popoff (1938) described joint manifestations in their cases.

The fact that Samek and Fischer (1929) were able to demonstrate the presence of B. crassus in the skin lesions of their patient caused Kumer (1930) to state as follows: "Es ist durch den Befund Sameks aber auch der letzte Beweis erbracht, dass der Bac. crassus tatsächlich der Erreger des Ulcus vulvae acutum ist, was bisher ja noch fraglich war und tatsächlich auch von vielen bezweifelt wurde". In his further description Kumer, however, pointed out that it is remarkable that all attempts to pass the disease on to animals and humans have met with failure. According to him, Scherber was the only one who succeeded – after numerous attempts – in showing some pathogenicity of B. crassus in rabbits. Scherber, however, did not consider his findings to be conclusive. Kumer further speculated on the relationship between ulcus vulvae acutum and the aphthosis of Neumann. He found that similarity exists, but that B. crassus could not be demonstrated in aphthosis of Neumann.

On account of the fact that B. crassus was not constantly

present in their cases, Wien and Perlstein (1932) concluded that the aphthosis of Neumann and ulcus vulvae acutum were one and the same disease.

Behçet's syndrome.

In 1937, Behçet (Turkey) described two cases under the title "Ueber rezidivierende aphthöse, durch ein Virus verursachte Geschwüre am Mund, am Auge und an den Genitalien". In smears from the oral and genital lesions of these patients, elementary bodies resembling those of a virus were repeatedly demonstrated by Braun of the Microbiology Institute in Instanbul. Behçet, therefore, considered a virus as the cause of the lesions. A year later Behçet (1938), however, considered focal infection as the possible cause only to reject it again (Behçet 1940) in favour of the virus theory. He was convinced that the triad of oral aphthae, genital ulcers and iritis constituted a definite clinical entity, and referred to it as the "Triple Symptom Complex". The great value of Behçet's observations can be summarised as follows:

1. Behçet realised that the simultaneous occurrence of oral aphthae, genital ulcers and eye lesions constituted a distinct entity, and that similar cases described by dermatologists on the one hand and ophthalmologists on the other – under a variety of names – belong to the same disease.

2. He demonstrated that B. crassus could not be found in all cases of ulcus vulvae acutum.

3. His observations stimulated others to study cases of this nature reported in literature.

Shortly after Behçet's first publication, the same triad was proposed as a new syndrome by Weekers and Reginster (1938) in Belgium. These authors pointed out that Neuschuler (1898) was the first to describe the occurrence of recurrent iritis with hypopyon.

Prior to Behçet (1937), various ophthalmologists have described cases presenting the triad of oral, genital and eye-lesions. In the Netherlands, Weve (1923) reported a case under the title of recurrent allergic staphylococcal uveitis. In Greece, Adamantiades (1931) and Dascalopoulos (1932) added three cases of this nature.

In the meantime, numerous cases suffering from Behçet's syndrome or Behçet's disease were described in literature.

Aphthosis.

Stimulated by the observations of Behcet (1937, 1938a, 1938b, 1939, 1940), Touraine (1941) looked up all the cases he could find in literature presenting features of Behçet's syndrome and, after evaluating the various symptoms, he concluded that ulcus vulvae acutum, aphthosis of Neumann, Behçet's syn-

drome and chronic recurrent aphthae were all one and the same disease. To this he referred as "L'aphtose". He based his findings on the common feature in all these conditions, namely the oral and genital aphthae.

In France, Touraine immediately received support for his concept. In other countries his work was not recognized until after the Second World War, when he received further support, especially from Curth (1946a) in the United States, and Haensch (1953) in Germany.

Touraine (1941, 1955) emphasised that aphthosis constitutes a systemic disease, caused in all probability by a virus related to herpes simplex but not identical to it.

In our atempt at a classification of aphthae in Chapter II, we have stated that Touraine was justified in considering ulcus vulvae acutum, Behçet's syndrome and the aphthosis of Neumann as belonging to the same disease entity, but that we have reservations on the matter of chronic recurrent aphthae. We also considered the name aphthosis as being more appropriate than Behcet's syndrome or Behçet's disease, on account of the fact that the triad of oral aphthae, genital ulcers and recurrent iritis was already described by Adamantiades (1931) and Dascalopoulos (1932) before 1937. To this we must add that Behçet, in a personal communication to Touraine (1955), expressed the wish that his syndrome should be considered as a part of aphthosis.

At this stage it is necessary to discuss briefly a number of terms which at some time or other have been considered as belonging to Behcet's syndrome or aphthosis.

Dermatostomatitis.

In 1925, Baader observed two patients with oral and pharyngeal lesions which showed some resemblance to diphtheria. Cultures and smears, however, proved to be negative. Both patients had a high temperature, while skin lesions, especially around the genitals, appeared in the course of the disease. Baader considered Foot and Mouth disease and Erythema exudativum multiforme in the diagnosis, but concluded that he was dealing with a new disease which he called dermatostomatitis.

Ectodermosis Erosiva Pluriorificialis.

Rendu (1916) observed a new syndrome, characterized by inflammation of the oral, nasal and genital mucosae together with conjunctivitis and a varicelliform eruption of the skin. The papulo-vesicular skin eruption showed a tendency to form confluent areas with haemorrhages. Further observations on cases of this nature were made by Fiessinger and Rendu (1917), and Fiessinger et al. (1923). The name "ectodermose érosive pluriorificielle" was applied in the description of the disease.

The patients observed by these authors showed marked prostration with a high temperature. The disease ran a course of from three to six weeks.

Klauder (1937) compared the clinical features of cases of this nature with those observed in the human form of foot and mouth disease, and concluded that he dealt here with cases of erythema exudativum multiforme.

Popoff (1938) considered ectodermosis erosiva pluriorificialis and ulcus vulvae acutum as the same disease.

Stevens-Johnson disease.

Stevens and Johnson (in 1922) described a new eruptive fever associated with stomatitis and ophthalmia. This condition became known as Stevens-Johnson disease. It is characterized by a maculo-papular eruption, purulent conjunctivitis, corneal ulceration, ulceromembranous stomatitis and fever.

Burket (1946) considered it to be a severe form of herpetic stomatitis, but in 1957 he grouped it with erythema exudativum multiforme.

Chronic Recurrent Aphthosis.

In 1933, Kerl described a case suffering from chronic recurrent aphthae where brownish-red nodules developed on the extremities, accompanied by muscle and joint pains. Löwenstein was able to isolate the bacillus of avian tuberculosis from the lesions. Kerl applied the name chronic recurrent aphthosis to the condition.

Kumer (1942) reserved the name chronic recurrent aphthosis to describe two cases of recurrent oral and genital aphthae accompanied by skin and eye lesions. No bacteria could be cultivated from the lesions. He believed these cases to be identical to those described by Carol, Weekers and Reginster, Cohen, Whitwell, Cole and Driver, etc. The case of Kerl, caused by avian tubercle bacilli, was considered by Kumer (1942) to be one of solitary metastatic aphthae.

Behçet (1940) noted some similarity between cases of his syndrome and erythema exudativum multiforme, but considered them as not identical. He also differentiated his cases from those described by Baader (1925) as dermatostomatitis. He concluded that the latter belonged to erythema exudativum multiforme.

Touraine (1941) believed that the cases of dermatostomatitis and chronic recurrent aphthosis described in literature should be considered a part of aphthosis, while those described as ectodermosis erosiva pluriorificialis should be considered as belonging to erythema exudativum multiforme. The case reported by Sato (1936) in Japan, which he considered to constitute a new disease, was rightly considered by Touraine to be aphthosis. It is interesting to note that Sato considered

his case as bearing a resemblance to the cases described by Baader, but on clinical grounds he believed it to be different.

Melczer (1946), after a study of eight patients, concluded that aphthodermatosis, dermatostomatitis and Behcet's syndrome were the same disease. On account of the severity of the lesions encountered in these patients, Melczer decided that they were different from erythema exudativum multiforme.

Proppe (1949), after an outstanding discussion of Baader's dermatostomatitis, and after having reported a case, came to the conclusion that all the cases described in literature under Stevens-Johnson disease, dermatostomatitis, ectodermosis erosiva pluriorificialis and conjunctivitis et stomatitis pseudomembranacea (Hartlev, 1921), belong to erythema exudativum multiforme.

Robinson and McCrumb (1950), after a comparative analysis of the features encountered in the various muco-cutaneous-ocular syndromes, concluded that Behcet's, Stevens-Johnson disease, ectodermosis erosiva pluriorificialis and Reiter's disease were all variants of the same disease entity: erythema exudativum multiforme.

Ruiter (1952) emphasised the fact that too many cases in literature were reported as suffering from erythema exudativum multiforme without indicating the characteristics of the disease as originally laid down by von Hebra (1860). Ruiter distinguished between an idiopathic form of erythema excudativum multiforme and a erythema exudativum multiforme syndrome sive erythema exudativum multiforme symptomaticum. According to him, the former is of unknown etiology, while the latter should be considered as a polymorph toxic exanthema due to various causes, including primary tubercular infection, streptococcal infection, hypersensitivity to medicaments etc. In his paper, Ruiter (1952) mentioned the existence of a febrile form of erythema exudativum multiforme which includes Baader's dermatostomatitis, ectodermosis erosiva pluriorificialis and Stevens-Johnson disease. Owing to their unsettled position regarding erythema exudativum multiforme, Ruiter did not include them in his discussion.

Hamminga (1956), who adopted the views of Ruiter (1952), agreed with Proppe (1949) that Stevens-Johnson disease, ectodermosis and dermatostomatitis were the same syndrome belonging to the febrile type of erythema exudativum multiforme. Hamminga (1956) concluded that it was probably advisable, for the time being, to separate these conditions from the commonly observed idiopathic form of erythema exudativum multiforme.

In our opinion, Touraine (1941) incorrectly classified dermatostomatitis under aphthosis. The distinction he made between ectodermosis erosiva pluriorificialis and dermatostomatitis is again unjustified. We agree with Proppe (1949) and

Hamminga (1956) that Baader's dermatostomatitis, ectodermosis, Stevens-Johnson disease and the pseudomembranous conjunctivitis and stomatitis of Hartlev, should be considered as cases of erythema exudativum multiforme syndrome. In these conditions one finds an acute febrile disease which either heals in about three weeks or turns out fatally. Recurrences in erythema exudativum multiforme syndrome (Ruiter, 1952; Hamminga, 1956) are rare, while the oral lesions differ from those of aphthae. Here one finds the so-called "ätzschorfähnliche", superficial haemorrhagic crusts or pseudomembranous lesions on the mucosa. To this one can add that the eye lesions usually appaer in the form of a conjunctivitis, while a rhinitis is not uncommon. When the lesions extend to the vermilion border of the lips they take on a typical haemorrhagic crust-like appearance, never observed in aphthosis.

The view held by some authors (Melczer 1946; Löffler, Martin and Babel, 1947; Robinson and McCrumb, 1950; Burket 1957) that Behçet's syndrome should be considered as part of erythema exudativum multiforme might be proven correct in future, but on account of the difference observed in the oral lesions, we feel that for the time being these conditions should be considered as two different diseases.

Robinson and McCrumb (1950) and Burket (1957) even went so far as to group Reiter's syndrome with erythema exudativum multiforme on account of common features encountered in it and other mucocutaneous-ocular syndromes, such as Behcet's syndrome. Reiter (1916) described his syndrome after observing a patient suffering from a non-specific urethritis, conjunctivitis, followed later by an iritis, and arthrosis accompanied by rheumatic pains and intermittent fever. Reiter was able to cultivate a spirochaete from the blood of this patient and called it Spirochaeta forans. Reiter's finding, however, was never confirmed by others. It is noteworthy that, in literature, only one case (that of Warthin, 1948) had been reported as suffering from Reiter's syndrome accompanied by aphthae in the mouth. The case demonstrated by Schubert (1937), and which Touraine (1941) included under aphthosis, might be considered as Reiter's disease. This patient of Schubert, a male of 41 years, suffered from a non-specific urethritis and balanitis, accompanied by unilateral conjunctivitis and recurrent aphthous stomatitis, for three years. He also presented oedema of the penis and a painful meatus. A fistula from the urethra to the frenulum was present. In the discussion that followed, Schmidt-Lebaume considered the likely etiological to be a virus.

Detailed accounts of aphthosis were published by Touraine (1941, 1955), Curth (1946a; 1956) and Haensch (1953). Touraine and Curth decided on the name aphthosis, while Haensch preferred chronic recurrent aphthosis as a name for the condition.

Schuermann (1958a, 1958b) accepted the term aphthosis proposed by Touraine, while Lindemayr (1957) adopted the name chronic recurrent aphthosis. That recurrences are important features of aphthosis cannot be denied, but – as Curth had pointed out – simultaneous recurrences of oral and genital aphthae are not essential for the diagnosis of aphthosis. It is also true, as pointed out by Kumer (1942) and Haensch (1953), that the cases of Neumann – originally referred to as cases of aphthosis – were not of uniform character. Neumann made no mention of any recurrences. Indeed, some of the cases described by this author may have been cases of erythema exudativum multiforme syndrome. It should be remembered, however, that Neumann (1895) clearly stated that oral lesions in his cases were indistinguishable from those observed in men suffering from aphthae. Curth (1946a) also emphasised that the single co-existence of oral and genital aphthae was reported by Neumann (1895), Carol and Ruys (1929) and Kumer (1930). Haensch (1953) and Lindemayr (1957) probably adopted the name chronic recurrent aphthosis from Kumer (1942). It is interesting to note that after the publications of Behçet (1937, 1938, 1940) and Touraine (1941), Kumer (1942) still considered the aphthosis of Neumann, Behcet's syndrome, ulcus vulvae acutum and chronic recurrent aphthosis as different diseases. In this, Kumer received support from Greither (1955) and Becker (1955).

With ulcus vulvae acutum being out of date, the present position is that identical cases are still referred to in literature as either suffering from Behcet's disease or aphthosis. We therefore proposed that only the name aphthosis should be used in a description of such cases.

B. THE CLINICAL PICTURE OF APHTHOSIS

A great variety of clinical manifestations were observed in cases suffering from aphthosis, but not a single one has as yet been reported which shows all these manifestations.

Touraine (1941), after considering the clinical manifestations of 274 patients described in literature, concluded that clinically aphthosis is made up of the following:

1. Mucosal aphthosis (a constant feature)
   a. Lesions of the genital mucosa (present in 262 of the 274 cases)
      Females (213 of 262 cases)
      Males (48 of 262 cases)
   b. Lesions of the buccal mucosa (present in 104 of the 274 cases)
   c. Bipolar mucosal aphthosis (present in 104 of the 274 cases)

   In this group, aphthae in the mouth appear in conjunction with genital ulcers.

2. Muco-cutaneous aphthosis (of not infrequent occurrence; present in 32 of the 274 cases)
   Aphthae of the mucosae accompanied by skin manifestations.
3. General aphthosis (aphtose généralisée or grande aphtose of Touraine).
   Observed in 79 of the 274 cases. Under this heading all the cases presenting the complete triad of Behçet's syndrome are grouped.
   Apart from oral and genital lesions, one finds:
   a. Skin manifestations.
      Erythema nodosum-like lesions
      Polymorph erythema (Erythema exudativum multiforme-like lesions)
      Macular eruptions
      Erythema induratum (Bazin)
      Purpura
   b. Ocular manifestations
      Conjunctivitis
      Iritis with hypopyon
      Neuroretinitis
   c. Joint manifestations.
   d. Systemic symptoms and signs.
      Temperature
      Headache
      Muscle pains
      Malaise
      Anaemia
      Other casual findings reported e.g. enlarged liver.

In an additional publication in 1955, Touraine added another 69 cases from literature, bringing the total to 343. In this publication, Touraine brought to attention the occurrence of various rare manifestations of aphthosis. Notwithstanding the fact that he included cases of chronic recurrent aphthae and Baader's dermatostomatis in his descriptions, we have to admit that Touraine's publications have done much to increase our knowledge of the disease.

In literature, cases presenting various combinations of the classical manifestations of aphthosis were reported. Thus one finds oral aphthae in combination with genital lesions, genital lesions together with skin lesions, oral lesions with eye lesions, or a combination of oral, eye, skin and genital lesions, etc.

The following manifestations were observed in cases described in literature:

I. Mucosal lesions.

Neumann (1895) had already pointed out that the oral lesions of his patients were indistinguishable from those obser-

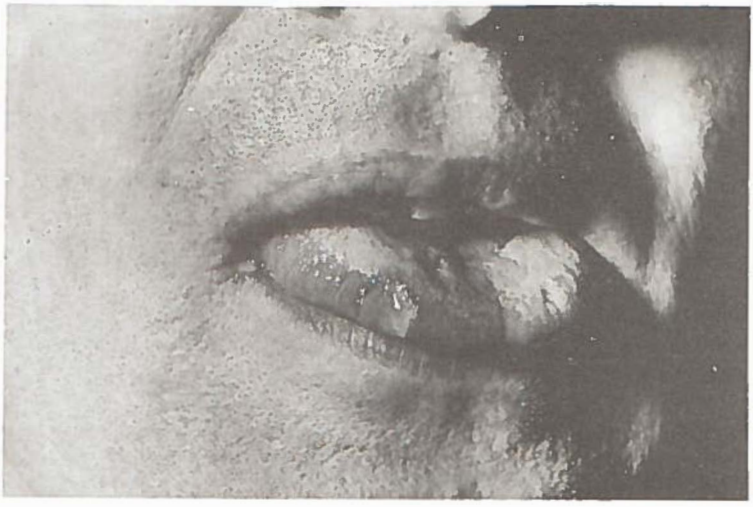

Fig. 1. Patient with aphthosis (Case B) presenting lesions on tongue and right corner of the mouth. (Photo: D.C. Dijk, Dept. of Dermatology, University Hospital, Groningen).

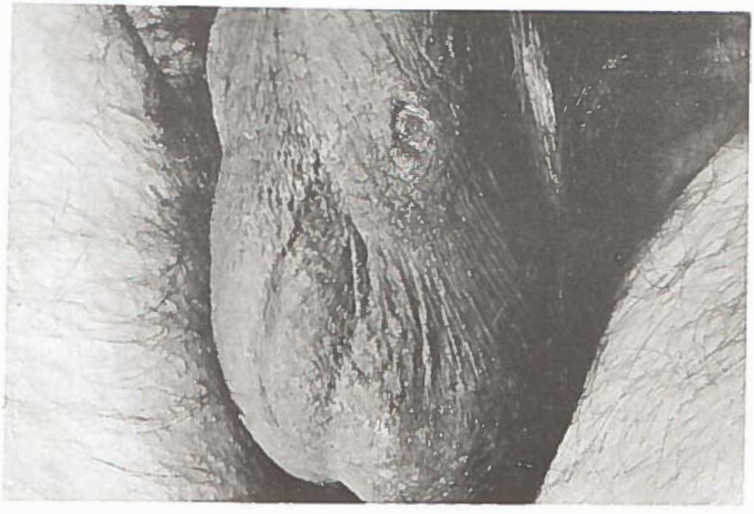

Fig. 2. Scrotal lesion of Case B with aphthosis. (Photo: D.C. Dijk, Dept. of Dermatology, University Hospital, Groningen).

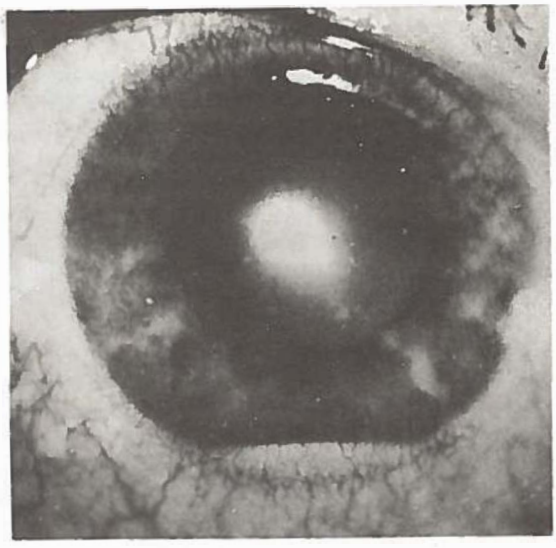

Fig. 3. Eye of Case A with aphthosis, revealing an hypopyon. (Photo: A. Lammers, Dept of Ophthalmology, University of Amsterdam).

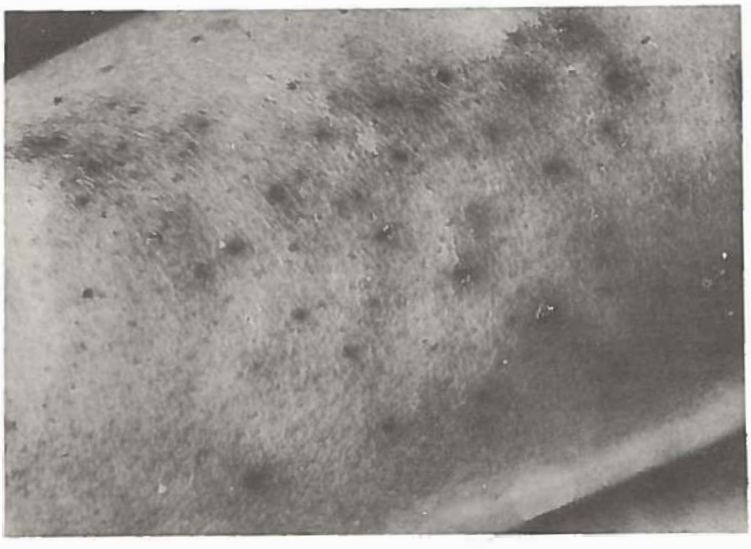

Fig. 4. Skin lesions on anterior aspect of lower extremity in Case A with aphthosis. (Photo: A. Lammers, Dept. of Ophthalmology, University of Amsterdam).

ved in cases with ordinary aphthae. Schugt (1925), on clinical and histological grounds, considered the oral and genital lesions to be identical.

Touraine (1941; 1955) based his concept of aphthosis on the presence of oral and genital aphthae. To him the aphthae in aphthosis were identical to those observed in cases suffering from chronic recurrent aphthae. He therefore considered chronic recurrent aphthae as a part of aphthosis. Touraine (1955) stated that buccal and genital aphthae were the fundamental elements of aphthosis. They proved the unity and were almost constantly present. Clinically, Touraine distinguished five types of mucosal lesions which we can summarise as follows:

a. Simple or solitary type ("forme insulaire"). They appear singly or few in number (2 to 6) and usually remain small in size (5-15 mm). According to Touraine, this form is almost constantly present in cases with aphthosis. They do not give rise to lymphadenopathy or any general disturbance and heal spontaneously in the course of a few days without scar formation. They also tend to recur over many years without any special rhythm.

b. Miliary type ("forme miliaire"). Numerous small aphthae are scattered over the oral or genital mucosae.

c. Giant type ("forme géant"). In this form round or oval lesions are found in the mucosal folds, reaching a size of from 2 to 3 cm.

d. Indurated type ("forme induré").

e. Gangrenous type (forme gangréneuse").

Haensch (1953), who, like us, considers chronic recurrent aphthae and aphthosis as being two separate diseases, stated that it is difficult to differentiate between the oral lesions of the two conditions. According to him, the oral lesions of chronic recurrent aphthae are much more painful than those of aphthosis and genital lesions are never observed together with the former.

In females, genital lesions were described on the mucosa of the vagina, labium majus, labium minus, clitoris and around the urethral opening while in males lesions were observed on the penis (Whitwell, 1934; Berlin, 1944; Sachs, 1946; Søbye, 1949; Curth, 1952) and on the scrotum (Urbach, 1929; Tagami, 1936; Curth, 1952; Zeavin et al., 1956).

Apart from oral and genital lesions, Touraine (1955) observed 20 cases where lesions were also present in the pharynx.

Pharyngeal aphthae were also observed in cases of Urbach (1929); Sachs (1946); Haensch (1953), case one; and Michel (1957).

Sore throat was present in cases of Yamazaki (1937), Fuhs (1937), Whitwell (1934), Popoff (1938), Volavsek (1938) and Nikolowski 1956).

The patient of Adamantiades (1931) revealed tonsillitis accompanied by a chronic rhino-pharyngitis, while the first case of Talalov (1934) had a slightly inflamed pharynx.

Nishimura's patient (1935) had aphthae on the uvula accompanied by swollen tonsils and reddening of the pharynx.

A case reported by Kenet (1951) suffered from ulceration of the pharynx and trachea, complicated by oedema.

The larynx was affected in cases of Bingel (1921), Gardner et al. (1950), Haensch (1953)-case 2, Laugier (1957) and Herbeuval et al. (1957).

Csonka and Duperrat, cited by Touraine (1955), reported a case of lesions on the nasal mucosa, while the oesophagus was involved in cases of Laugier (1957) and Bataille (1958).

Gastric pain was a feature in the cases of Urbach (1929), Assnin and Sutejew (1934) -case 3, Whitwell (1934) and Laugier (1957). In the patient of Laugier (1957), roentgen examination revealed a shadow in the colon. At subsequent autopsy no malignancy was found.

Aphthae were observed on the gastric mucosa after endoscopy by Chevallier and Moutier (1946), Moutier and Cornet (1949; 1951) and Bataille (1958). The patient of Bataille died after a massive intestinal haemorrhage.

Jensen (1944) observed a case of ulcerative haemorrhagic colitis, while Bechgaard's patient (1940) suffered a preceding attack of ileitis.

II. Skin lesions.

Erythema nodosum-like lesions were observed in cases by Neumann (1895; 1900), Reis (1906), Scherber (1919), Planner and Remenovsky (1922), Chauffard and co-workers (1923), Pils (1925), Katznelson (1925), Schnabl (1927), Samek and Fischer (1929), Kumer (1930), Dreyer (1932), Sicharulidze (1933), Kerl (1933), Rosenthal (1934), Whitwell (1934) -2 cases, Sato (1936), Yamazaki (1937), Behcet (1937; 1940), Weekers and Reginster (1938), Pautrier et al. (1938), Jensen (1941), Franceschetti and Valerio (1940), Mach and co-workers (1941), Ephraim (1944), Silfverskiöld (1951), Karani (1953), Freedman (1953), Norbis and Malbrán (1955)-2 cases, Zeavin et al. (1956), Sezer (1956) and Lindemayr (1957).

Erythema multiforme-like lesions were observed by Neumann (1895)-2 cases, Sibley (1899) -case two, Planner and Remenovsky (1922), Kumer (1930), Fuhs (1937), Volavsek (1938), Popoff (1938) - case one, Alm and Öberg (1945), Ramos and Peryassu (1950) and Haensch (1953).

Indurated erythema (Bazin) was observed in cases by Schindler (1926), Grütz (1926) and Bureau (1838). The patient of Schindler also showed livedo racemosa.

Maculo-pustular erythema of the face, neck, trunk and extremities were reported by many authors. Cases of this na-

ture were recorded by Neumann (1900)- pea-sized pustular nodules over breast, shoulders, lumbar region and extremities; Sibley (1899) - folliculitis leading to superficial ulceration of external genitalia; Reis (1906) - furunculosis of lip; Planner and Remenovsky (1922) - Macular and pustular exanthema; Weve (1923) – furunculosis of neck; Pils (1925) – follicular pustules around genitals; Carol and Ruys (1929) – papulo- vesicular eruption with pustules; Walter and Roman (1930) – papulo and papulo-vesicular exanthema; Matras (1932) – pustules on neck and inner surface of thighs; Talalov (1934) – case one, pustules on face, scalp and trunk together with two pea-sized ulcers in right axilla; case two, scattered acne over trunk; Whitwell (1934) – case one, papulo-pustular eruption; Assnin and Sutejew (1934) – case seven, acne on face and body; Fuhs (1937) – reddish-brown nodules with a number of pustules on chest, face, neck and interscapular region; Yamazaki (1937) – pustules on breast and loins; Curth (1946) – mild acne of face and back together with pyogenic infection of big toe; Herrmann (1953) – furunculosis, pimples and boils; Sezer (1953) – case one, papulopustular lesions on legs and arms; Haensch (1953) – papulo-vesicular erythema; Sezer (1956) – cases four and five: suffered from pustular papules; Zeavin et al. (1956) – follicular pustules on back of arms, while Laugier (1957) observed a papular erythema on the trunk, extremities, genitals and buttocks of his patient.

Abscesses were present in the patients of Weve (1923), Curth (1946a) and Andrews (1946). Weve's patient suffered from a recurrent subcutaneous abscess below the left ear, Curth's patient multiple abscesses in the axilla, while the patient of Andrews suffered from subungual abscesses.

Variuos authors reported lesions on the perineum and around the anus. Perineal lesions were observed by Carol (1935), while anal and perianal lesions were observed by Talalov (1934) – case one, Whitwell (1934) case three, Tagami (1936), Sachs (1946), Haensch (1953) – case six, Nikolowski (1956), Michel (1957), Sezer (1956) – case four, and Bataille (1958).

A peculiar skin sensitivity to all forms of trauma and injections (including physiological saline) was observed by Sato (1936), Jensen (1941), Katzenellenbogen (1950), Curth (1952), Haensch (1953), Martin (1954) and Lindemayr (1957). Carr (1957) noticed repeated attacks of thrombophlebitis and cellulitis in his patient, even after the slightest trauma. Jensen (1941) considered this reaction of the skin an important diagnostic feature, while Schuermann (1958) compared it with Köbners phenomenon (in this phenomenon, new lesions appear in linear distribution at the site of an abrasion or excoriation).

Thrombophlebitis, usually of the legs, were present in cases of Adamantiades (1946), Adamantiades and Lorando

(1949), Gray (1950) and Martin (1954). France and co-workers (1951) stated that thrombophlebitis occurred in 25% of cases.

III. Eye Manifestations.

Various eye lesions ranging from a simple conjunctivitis to optic atrophy and total blindness have been described in literature.

Conjunctivitis as the only eye manifestation was reported by Sibley (1899) – case two, Carol and Ruys (1929), Behçet (1937; 1940), Gardner et al. (1950), Haensch (1953) – case one, Sezer (1956) and Herbeuval and co-workers (1957).

Conjunctivitis in conjunction with iritis was found in patients of Planner and Remenovsky (1922), Whitwell (1934), Behcet (1937), Nishimura (1937), Gözcü (1938) and Andrews (1946).

Recurrent keratitis was present in the fifth case of Haensch (1953).

Recurrent iritis with hypopyon was reported by Reis (1906), Gilbert (1923), Weve (1923), Planner and Remenovsky (1922), Adamantiades (1931), Dascalopoulos (1932), Whitwell (1934), Blobner (1937), Behcet (1937; 1938; 1940), Weekers and Reginster (1938), Jensen (1941), Curth (1946a), Karani (1953) and others.

One patient of Norbis and Malbrán (1955) suffered from bilateral uveitis with hypopyon, while another revealed the same manifestations, unilaterally.

Optic neuritis was observed by Behçet (1940); white atrophy of the optic nerve by Gözcü (1938), and Weekers and Reginster (1938). Kemp's patient (1953) suffered from thrombophlébitis migrans and was totally blind as a result of retinal thrombosis. Haemorrhage into the vitreous was observed by Katzenellenbogen (1950). The patient of Zeavin, King and Gohd (1956) suffered from a massive haemorrhage into the right eye (vitreous?), which resulted in complete loss of vision. Subsequent examination of their patient revealed the presence of keratic precipitates and posterior synechia in the right eye and an iritis of the left eye.

Cataracts developed in cases of Reis (1906), Touraine (1955), Phillips and Scott (1955) and Jadassohn and co-workers (1957).

Glaucoma was recorded in cases of Thomas (1947), Cavara (1940), Herrmann (1953) and Sezer (1956).

Acne of the eyelids was present in cases of Gilbert (1923), and Behcet (1937), while blepharitis was recorded in cases of Andrews (1946) and Haensch (1953) – case five.

Phlyctenules developed in the patient reported by Fraser-Moodie (1953).

The course of events as far as eye manifestations are concerned can be summarised in the words of Curth (1946a): "For a while only one eye is involved; later the other eye invari-

ably shows the same changes. In a few instances the disease has started in the two eyes simultaneously. The attacks occur every three to four weeks, or about that frequently. They are characterized by intense periorbital pain and photophobia. The pericorneal reaction is usually mild; there are precipitations in Descemet's membrane. Iritis or iridocyclitis develops later. Either the anterior part of the eye, with or without involvement of the retina and choroid, shows the first pathologic changes, or the posterior parts of the eye manifest retinochoroiditis or periphlebitis. In both instances hypopyon is a late symptom. All authors have noted that the hypopyon tends to disappear rapidly (in two to three days), while the vitreous clears slowly and sometimes incompletely. After every attack the vision remaining is definitely diminished. The impairment of the vision progresses to complete blindness in both eyes".

The loss of vision, according to Curth (1946a) is attributed either to posterior synechia with occlusion of the pupil and atrophy of the optic nerve, to secondary glaucoma or to lack of transparency of the vitreous, which cannot recover during the short intervals between the frequent attacks.

IV Muscle and Joint Manifestations.

Arthralgia was reported by Weve (1923), Urbach (1929), Popoff (1938) - 2 cases, Curth(1946a), Freedman (1953), Nikolowski (1956), Herbeuval et al. (1957), Laugier (1957) and Lindemayr (1957).

Rheumatic pains were present in cases of Adamantiades (1931), Sezer (1956) - cases 3, 16 and 18, and Herbeuval and co-workers (1957).

Case 1 of Curth (1946a) suffered from myositis and fibrositis of the back, while her second case suffered from drawing pains in the legs.

More or less severe arthritis was recorded in cases of Reis (1906) - left ankle; Matras (1932) - polyarthritis. Ephraim (1944); Curth (1946a) - osteoarthritis of right ankle-joint; Norbis and Malbrán (1955) - exudative arthritis in two patients; and Sezer (1956) - eight cases with polyarthritis.

Swelling of the joints: Recurrent swelling of ankle joint (Reis, 1906); swelling of joints many years before outbrake of oral and eye lesions (Weve, 1923); hydrops of right knee joint (Andrews, 1946b); right ankle joint (Curth, 1946a); recurrent swelling of various joints (Herrmann, 1953); both ankles in the first case of Sezer (1953); three cases of Sezer (1956); spontaneous swelling of right knee (Zeavin et al., 1956); transient hydrarthrosis of wrist joints in second case of Dernoncourt (1955) and hydrarthrosis of left shoulder (Laugier, 1957).

V Lung Manifestations.

Pulmonary tuberculosis was confirmed in one patient of Bingel (1921). Both lung apices were affected in the case described by Schindler (1926).

Enlarged hilar glands were present on x-ray examination in cases reported by Samek and Fischer (1929), Adamantiades (1931) – case one, Popoff (1938), Silfverskiöld (1951) – case one, and Freedman (1953). Hilar opacity together with opacities at the left lung apex was reported by Dascalopoulos (1932).

Active pulmonary Tb was diagnosed in one patient of Assnin and Sutejew (1934), while the apices were suspect in the first case of Weekers and Reginster (1938).

Haemoptysis occurred in cases of Dascalopoulos (1932) and Jensen (1941).

One patient of Zeavin and co-workers (1956) suffered from a productive cough and marked bronchiectasis of the left lower lobe.

VI Involvement of the nervous system.

Involvement of the nervous system in aphthosis cases constitutes the gravest complication of the disease.

Cases showing neurological manifestations have been reported by Knapp (1941), Berlin (1944), Alm and Öberg (1945), Gray (1950), Magni (1951), Silfverskiöld (1951) – three cases, Curth (1952) – the same patient was later reported on by Herrmann (1953), Phillips and Scott (1955), Pallis and Fudge (1956) – two cases, Evans and co-workers (1957), McMenemey and Lawrence (1957) and Wadia and Williams (1957) – three cases.

Admirable reviews on the cases of aphthosis reported in literature and manifesting neurological complications were given by Pallis and Fudge (1956) and Wadia and Williams (1957).

Pallis and Fudge (1956) concluded that, from a clinical point of view, the neurological disorder conforms to one of the following patterns:

1. A brain stem syndrome, which, according to them may be either episodic as in the patient of Phillips and Scott (1955), or which may progress, in an irregular manner, to death from bulbar paralysis, as in the patients of Gray (1950) and Magni (1951).

2. A meningomyelitic syndrome as was observed by Silfverskiöld (1951) characterized by recurrent attacks of paraplegia or tetraplegia. In such cases the disorder is heralded by fever, headache and stiff neck. This group is further characterized by an accompanying polymorphonuclear pleocytosis in the C. S. F. Transient or terminal brain stem symptoms may occur.

3. An organic confusional syndrome, as in the patient of Chauffard et al. (1923). In these cases the manifestations may be either transient with much agitation or they may progress to dementia with fits, as in the case described by Berlin (1944).

Wadia and Williams (1957), however, consider the classification of Pallis and Fudge (1956) as inapplicable on account of the fact that none of the cases reported up to now conformed entirely to one pattern.

In order to illustrate the features of the neurological involvement, we give the following summary of a number of case histories of patients considered by Pallis and Fudge (1956) as prototypes in their classification:

1. Case of Gray (1950). Male, aged 26. First suffered from attacks of erythema nodosum-like lesions, followed by recurrent oral aphthae. Later the patient developed recurrent iritis, followed after a few weeks by night sweats, precipitancy of micturition, headaches and weakness of the left leg. Examination revealed thrombosis of a branch of the right retinal vein. Vitreous opacities. Pyramidal signs of the left leg. C.S.F.: 25 cells/cu.mm., protein 75 mg.%. In the course of a few days the patient developed right third and fourth cranial nerve palsies, palsy of the left superior rectus, vertical and horizontal nystagmus and thermoanaesthesia of the legs, one after the other. A few months later fever, occipital headache, vomiting, positive Kernig sign, left facial paralysis, paralysis of conjugate ocular deviation to the left and dysphagia were followed by death as a result of respiratory paralysis. C.S.F. before death revealed 763 cells cu.mm. (72% polymorphs) and protein 70 mg.%.

2. Case one of Silfverskiöld (1951). Male, age 38. In 1935 patient had gonorrhoea. Discharged from hospital as cured after 14 days. In 1938 purulent lesions on scrotum and then sudden failure of vision. Examination revealed exudates in the vitreous and isolated precipitates in the cornea. In 1941, hypopyon, urethral discharge, lesions on tongue, painful erythematous patches on legs. 1947: Headache, fever, disorientation, slurred speech, numbness of right arm and leg, attacks of laughter and crying. C.S.F. 5 cells/cu.mm. 1949: Paraplegia, paralysis of bladder and erythema nudosum.

3. Case of Berlin (1944). Male, aged 28. Recurrent oral and genital lesions for 3 years followed by recurrent hypopyonuveitis. Eighteen months later mental changes, apathy, headaches, dizziness and disorientation. This was followed 3 months later by fits and coma. Reflexes diminished or absent. C.S.F.: protein 49 mg.%, cells 95/cu.mm. (40 polymorphs, 55 lymphocytes). Eventually death followed four days after the onset of coma.

VII Urethritis.

We mentioned the case of Schubert (1937), a male 41 years, who suffered from a non-specific urethritis and balanitis, accompanied by a unilateral conjunctivitis and recurrent aphthae, as well as the patient of Warthin (1948) who was diagnosed as suffering from Reiter's disease and who also had aphthae in the mouth.

More cases were reported with urethral infection. In many, a diagnosis of gonorrhoea was made. From the descrip-

tions it is not possible to tell whether this diagnosis was confirmed by bacteriological methods.

Jaffe's patient (1930) was treated for gonorrhoea, while the second patient of Dascalopoulos (1932) was diagnosed as gonococcal urethritis. A diagnosis of gonorrhoea was also made in patients of Duval (1946) and Silfverskiöld (1951) - case one. In Duval's patient lesions healed within a few hours after treatment with penicillin.

The first patient of Curth (1946a) had a urethral discharge, while the patient of Assnin and Sutejew (1934) complained of of painful micturition.

Nasemann's patient (1954) gave a previous history of gonorrhoea.

VIII General malaise.

Malaise was recorded in patients of Volavsek (1938), Popoff (1938) - case 2, Assnin and Sutejew (1934) - 6th case, who also suffered from headaches, and Freedman (1953) - malaise and lassitude.

IX Asthenia.

Asthenia was present in cases described by Herrmann (1953) and Laugier (1957).

X Temperature.

A rise in temperature was observed in patients of Neumann (1900); Grütz (1926); Samek and Fischer (1929) - from 37.5°C to 38°C; Urbach (1929); Matras (1932) up to 38.7°C; Philadelphy (1933) - 39°C; Assnin and Sutejew (1934) - case one 39.9°C, case three 39.9°C, case four 38°C - 40.2°C, case five 39.0°C, case six 40°C; Rosenthal (1934) - 38.5°C; Nishimura (1935) - chills, fever and malaise; Yamazaki (1937) - sometimes temperature; Fuhs (1937) - ± 38°C; Volavsek (1938); Popoff (1938) - case one 39.5°C, case two 38.0°C; Jensen (1941); Gardner et al. (1950); Herrmann (1953) - low grade fever; Nikolowski (1956) and Lindemayr (1957) - up to 38°C.

Touraine (1941) found that 14(12%) reported cases out of 119 had no rise in temperature.

XI Lymphadenopathy.

Palpable lymph glands were observed in patients of Matras (1932), Philadelphy (1933), Whitwell (1934) - case three, Talalov (1934) - two cases, Assnin and Sutejew (1934) - one case out of seven, Volavsek (1938) - slightly enlarged, Curth (1946a) - case two, and Haensch (1953) - case one.

Cases without lymph gland enlargement were reported by Samek and Fischer (1929), Wien and Perlstein (1932), Assnin and Sutejew (1934) - six cases, Whitwell (1934) - two cases, Holzapfel (1936), Søbye (1949) and Curth (1946a) - case one.

XII Anaemia.

The patient of Pils (1925) was very anaemic, while Lindemayr's patient (1956) revealed sligt anaemia. Haensch (1953) observed no anaemia in his cases.

XIII Blood picture.

In literature the following findings were reported:

Authors	Case No.	Rbc.	Hb%	Tot. Wbc.	Eos.	Baso	Rod-forms	Segm. forms	Lymph.	Mono
Rosenthal (1930)	1	?	?	7,400			16%	49%	29%	6%
	2	4,300,000	85%	5,000	5%			62%	23%	10%
Assnin and Sutejew (1934)	3	4,710,000	55%	6,800	7%			52.5%	33.5%	7%
	4	5,400,000	82%	8,800	3%		10%	34%	40%	10%
	6	3,880,000	67%	6,600	1%			65%	32%	2%
	7	4,040,000	73%	7,600	3%	1%	5%	60%	28%	3%
Popoff (1938)	1	4,200,000	54%	10,500	1%			48%	48%	3%
	2	4,980,000	?	7,800	3%			73%	23%	1%
Curth (1946a)	1	Leucocyte count ranged between 10,000 and 16,000. Differential count normal.								
	2	4.850.000	92%	11,850-15.900				72%	27%	1%
Herbeuval et al. (1957)	1	3,840,000	?	11,200	1%			68%	26%	5%

The normal erythrocyte count, according to Wintrobe (1946), is 4.8 ± 0.6 million per cu. mm. for adult females, and 5.4 + 0.8 million per cu. mm. for adult males. From the figures above we can conclude that cases 6 and 7 of Assenin and Sutejew (1934) and the patient of Herbeuval et al. (1957) showed slight anaemia. Our case B had a normal erythrocyte count of 5,190,000. In our opinion anaemia is not a characteristic feature of aphthosis.

Burket (1957) and de Vries (1955) emphasized the fact, that little value can be attached to haemoglobin values expressed in percentages, since the amount of haemoglobin constituting 100% is subject to diversity of opinion. In Europe and America 15.6 gm. haemoglobin is usually considered 100%, while in England 14.8 gm is accepted as such.

Leucocyte counts above 10,000 per cu. mm are usually considered as leucocytosis, while counts below 5,000 point to leucopenia (Wintrobe, 1946).

According to Burket (1957) the normal leucocyte values are as follows:

Types of cells	%	Absolute numbers per cu. mm.	Total counts per cu. mm.
Neutrophils	60 --70	3,000 to 7,000	4,150 - 11,500
Basophils	0.1 - 1	0 to 100	
Eosinophils	1 - 3	50 to 300	
Lymphocytes	20 - 35	1,000 to 3,500	
Monocytes	2 - 6	100 to 600	

If one compares these figures with those reported in literature, it becomes evident that the cases of Curth (1946a) and Herbeuval et al. (1957) showed definite leucocytosis, while the differential counts were normal.

A relative lymphocytosis was present in case four of Assnin and Sutejew (1934) and case one of Popoff (1938). Both these patients had a fairly high leucocyte count.

Eosinophilia was present in the second case of Rosenthal (1930) and the third of Assnin and Sutejew (1934), while an increased monocyte count was observed in the second case of Rosenthal (1930) and in the third and fourth cases of Assnin and Sutejew (1934).

The leucocyte count in case B of our series revealed a fairly high total count (10,000 per cu.mm.) with an increased monocyte value (9%). The eosinophil count was normal.

According to Cahn (1950), the diagnosis of viral infections is frequently difficult, but the blood count is often suggestive. Cahn (1950) gave the following example to illustrate this:

Hemoglobin	12.6 gm(80%)
Red cells	4,170,000
White cells	4,500
Platelets	140,000
Polys, nonsegmented	2 per cent
Polys, segmented	55 per cent
Lymphocytes	29 per cent
Abnormal lymphocytes	6 per cent
Monocytes	8 per cent

Cahn concluded that there is a slight anaemia, leucopenia and a moderate increase in nonsegmented cells. In some viral conditions also, a rather distinctive monocyte may be found.

If we consider the abovementioned facts, it becomes evident that no definite conclusions can be reached from the blood picture in aphthosis.

XIV Erythrocyte Sedimentation Rate (ESR).

An elevation of the ESR was reported by Freedman (1953), Herrmann (1953), Zeavin and co-workers (1956) - 36 in the first hour, Sezer (1956) - 90/132, Lindemayr (1957) - 72/96 and Jadassohn et al. (1957) - 41/60.

Søbye (1949) found a normal ESR in his patient.

XV Other accompanying conditions:

Typhoid was diagnosed in two patients of Assnin and Sutejew (1934), while two cases of Rosenthal (1930) were supposed to be suffering from paratyphoid. One patient of Assnin and Sutejew (1934) suffered attacks in conjunction with influenza.

Congenital syphilis was a feature of Volavsek's patient (1938), while acquired lues were diagnosed in cases reported by McDonagh (1924), Schnabl (1927) and Matras (1932).

The patient of Pils (1925) developed an acute cholecystitis shortly after an attack of oral and genital lesions.

Nervous shock accompanied outbreaks in patients of Wien and Perlstein (1932), and Weekers and Reginster (1938).

Exacerbations followed tooth extraction in cases of Whitwell and Behçet (1938).

Case A of our series, interestingly enough, developed an attack of acute appendicitis while under treatment for his eye lesions.

C. THE ETIOLOGY APHTHOSIS.

Review of literature.

The etiology of aphthosis is still unsettled. Various theories have been advanced, among them infection, allergy, vascular disturbance, hormonal imbalance and disease of collagen.

1. Infection.

A variety of organisms in the etiology of the disease have been considered from time to time. Lactobacillus crassus at one time enjoyed a special reputation. Nowadays, many authors consider a virus to be the causative agent.

a. Lactobacillus crassus.

L. crassus was considered to be responsible for the genital lesions of ulcus vulvae acutum (Lipschütz, 1912; Carol and Ruys, 1929; Walter and Roman, 1930; Kumer, 1930; and others). The bacillus was also demonstrated in oral lesions of such patients by Ito (1931), Matras (1932), Philadelphy (1933), Rosenthal (1930), Talalov (1934), and others. Scherber (1918a, 1919) proved the identity of L. crassus with Döderlein's bacillus. From examples in literature, Touraine (1941) adequately showed that this normal inhabitant of the vagina cannot be considered the causative agent of aphthosis. According to him, autoinoculation with material from lesions or the bacillus rendered negative results in 31 out of 37 patients, while - as Kumer (1930) had pointed out - all attempts to transmit the disease from one person to another have met with failure.

Ruys (1959) no longer considers L. crassus the causative agent of the disease. According to her, too many cases present lesions without showing the presence of the bacillus. She also considers the pathogenicity of the organism not adequately proven.

b. Other organisms.

Fusospirochetal organisms were considered in cases of McDonagh (1924) and Schnabl (1927). McDonagh (1924) also attached importance in the etiology to gonococci.

Staphylococci (Adamantiades, 1931) and Staphylococcus albus (Cavara, 1940) were considered possible causes.

Evidence was given (Urbach, 1929; Kerl, 1934) that the

bacillus of avian tuberculosis might be the causative agent, while Grütz (1926) considered blastomycetes in the etiology.

Among others, pronounced signs and symptoms of lung tuberculosis were encountered in patients reported by Bingel (1921), Gilbert (1923), Schindler (1926), Samek and Fischer (1929), Adamantiades (1931) - case one, Dascalopoulos (1932) - two cases, Weekers and Reginster (1938), Popoff (1938), Jensen (1941), Silfverskiöld (1951) - case one. Signs of glandular tuberculosis were present in cases of Adamantiades (1931), Planner and Remenovsky (1922), Samek and Fischer (1929) and Talalov (1934). No proof of the tubercular nature of these cases was however given.

Sédallian, Garin and Faure, cited by Thiers and associates (1957), considered the lesions of aphthosis to be due to toxoplasma. Sircus et al. (1957) by means of complement fixation tests, found, however, that toxoplasma antibodies did not appear more frequently in cases of aphthous ulceration than in normal controls. Cases of aphthosis were included in this investigation. It therefore seems unlikely that toxoplasma can be the cause of the disease. The positive toxoplasma complement-fixation test observed in their patient by Jadassohn and co-workers (1957) was not considered to be of etiological significance.

c. Viral infection.

Behçet (1937), after having found elementary bodies in the smears of oral lesions, concluded that the disease was due to a filtrable virus.

Touraine (1941) considered the clinical manifestations of aphthosis as strong evidence in favour of a viral infection. He stated: "Il semble cependant que, par ses manifestations clinigues, l'aphtose puisse être envisagée comme due à un ultravirus assez voisin mais différent du virus herpétique. Son début brusque, ses lésions tantôt locales tantôt générales et fébrilis, sa guérison rapide, la rareté de ses complications viscérales, sa bénignité mais aussi l'absence d'immunisation et la fréquence de rechutes capricieuses pendant de longues années sont autant d'arguments qui permettent d'envisager cette hypothèse avec faveur".

Elementary bodies were also found by Melczer (1946), Haensch (1953) and Schuermann (1958a). On the other hand, Franceschetti and Valerio, 1940 (cited by Curth, 1946a), Jensen (1941) and Curth (1946b) were unable to demonstrate the presence of elementary bodies in smears made from lesions of their patients.

Unsuccessful attempts to isolate a virus from oral and genital lesions were reported by Curth (1946a; 1946b) and Katzenellenbogen (1946). Levaditi (1943), cited by Touraine (1955), was able to isolate a virus from cases which caused an encephalitis in mice.

Alm and Öberg (1945) were able to produce focal encephalitis, optic neuritis, retinitis, uveitis, keratitis bullosa and conjunctivitis in rabbits after cisternal injections of spinal fluid from patients with aphthosis. At autopsy no bacteria was found in the brain or meninges of the animals. Spinal fluid obtained from normal controls produced negative results. Alm and Öberg considered these findings evidence of the viral nature of the disease.

Sezer (1953) reported isolating a virus from the vitreous of an enucleated eye in one patient, as well as from sub-retinal serous fluid obtained by puncture from the eyes of two other patients. The virus was grown on the chorio-allantoic membranes of fertile eggs and subsequent passages made in allantoic fluid, yolk sac, mice, guinea-pigs and rabbits. Intracerebral injection of the virus in mice produced encephalitis, while intraperitoneal, intracerebral and subcutaneous injections in guinea-pigs caused a haemorrhagic lobar pneumonia. Injections into the vitreous of rabbits resulted in the development of chorioretinitis and hypopyon. Antigens consisting of allantoic fluid and mouse brain suspensions of the virus gave positive complement-fixation tests in 12 patients with aphthosis. Normal controls consistently produced negative results. Sezer obtained similar results with neutralization tests. He was, however, unsuccessful in his attempts to produce an experimental disease in the eyes of rabbits with material from the anterior chamber or from aphthae of patients. Sezer concluded that the failure of others to cultivate a virus "have been the limitation of their investigations to the fluid in the anterior chamber and the exudate of the aphthae formed on the genitalia and in the mouth".

Cavara (1954), however, was unable to isolate a virus from alleged viral material received from Sezer, while Blank and Rake (1955) did not consider Sezer's findings enough evidence of a viral etiology.

Sezer (1956) reported isolating the virus on the chorio-allantoic membranes of fertile eggs from blood of twenty patients. He concluded "that antibodies appear in the blood of the patients after a certain time, which is not yet known. When antibodies are not present, hemocultures can be of value for diagnostic purposes. The complement-fixation reaction which is as high as 1:126 during periods of remission, decreases to 1:64 and even to 1:16 during an acute crisis. The virus is liberated in the ulcerine, at least during viraemia".

In both his publications, Sezer (1953 and 1956) included photographs of the virus as observed with the electron microscope. Caution should, however, be exerted with these findings, since Blank and Rake (1955) pointed out that normal tissue components are frequently indistinguishable from viral particles.

Zeavin, King and Gohd (1956) were unsuccessful in their attempts to isolate a virus from the case they described. Since no vitreous or subretinal fluid could be obtained from the patient, Zeavin et al. (1956) conducted their experiments with aqueous humor. This material was inoculated intracerebrally in mice, into the allantoic sac and onto the chorio-allantoic membrane of embryonated eggs. Similar findings were reported by Duperrat, Kraft de Ruych and Vigneron (1955).

Evans, Pallis and Spillane (1957) reported the successful isolation of a virus from a fatal case of aphthosis. Undiluted aqueous humor (0.2 ml.) was inoculated onto the chorio-allantoic membrane of each of fifteen 10-day- old eggs. At the same time, a piece of brain tissue was homogenised and diluted to make a 10% suspension in sterile distilled water. The suspension was then inoculated in amounts of 0.2 ml. onto fifteen further eggs. Harvesting of the membranes revealed scanty pock formation with much congestion. The pocks were 5 mm. in diameter, tough and white. After 21 passages Evans et al. could transmit the virus at a titre of 10-4. In just less than half of the cases, they also observed death of the embryos on the fifth day of incubation. Attempts to adapt the virus to cultures of human embryo kidney cells, human amnion cells, and HeLa cells proved unsuccessful, while attempts failed to produce the disease in mice, guinea pigs and rabbits after intracerebral, intramuscular and intraperitioneal injections. Neutralization tests revealed a significantly raised titre of virus neutralising antibody in 11 cases of aphthosis, whereas no detectable amounts of antibody were found in 14 normal controls. Evans and co-workers, however, were unable to isolate a virus from the blood, urine, spinal fluid and aqueous humor of one of their other patients.

Fluid from the anterior chamber of the eye of their patient was submitted for viral studies by Jadassohn, Franceschetti and Golay (1957). This included inoculation of tissue cultures (HeLa- and monkey kidney cells), embryonated eggs (onto the chorio-allantoic membrane and into the allantoic cavity) and mice (intracerebrally). All these investigations had negative results.

Vendég, Ujváry and Abraham (1958) observed the occurrence of aphthosis after contact with plants. They ascribed the condition to the presence of what they called vegetal viruses and considered it a form of phyto-photodermatosis. The virus is neutralized by the serum of birds immunized with the vesicular (?) contents. Inoculated mice are arrested in their development and ultimately die, while inoculated rabbits die with characteristic symptoms. From the photograph published by Vendég et al. of the oral lesions of such a case of aphthosis it is evident that such cases cannot be considered under this heading. The photograph mentioned reveals haemorrhagic crust-like lesions on the lips.

Schuermann (1958a), in his discussion of aphthosis, concluded with: "Wenn die Konzeption Touraines sich also richtig erweist (und wie eingangs betont, spricht manches dafür), dann entfallen tatsächlich viele bisher als gesondert betrachtete Krankheitsbilder zugunsten eines einheitlichen Morbus als Infektionskrankheit viraler Atiologie, eben der Aphthosis". In the same year Schuermann (1958b) was more definite about the etiology of the disease. He then positively stated that aphthosis was caused by a virus.

It is evident from literature that uniformity of opinion exists as far as the viral etiology of aphthosis is concerned. That it is the most widely accepted theory is definite. Our investigation of this is discussed together with that of chronic recurrent aphthae (in Chapter VII).

2. Allergy.

Weve (1923) considered staphylococcal allergy in the etiology of the disorder, while Urbanek (1934) attributed the lesions to allergic signs of tuberculosis.

Weekers and Reginster (1938) called the condition "recurrent allergic uveitis".

Koch (1950) reported on a patient with aphthosis in whom allergy tests were negative. Exacerbations of lesions in this patient were accompanied by gastric discomfort in the form of colitis. Treatment with an antihistamine "antasten" led to rapid freedom of symptoms. Koch concluded that "as antasten is an anti-allergic remedy with, as far as is known, a specific effect on allergic disorders, it appears warranted to assume an allergic aetiology in the case reported". The finding of Koch, however, was not confirmed in literature.

Silfverskiöld (1951) found a blood eosinophilia of 35% in the third patient reported by him. This occurred towards the end of her illness. Eosinophilia was a feature in cases reported by Rosenthal (1930) - case two, and Assnin and Sutejew (1934) - case three.

After considering the histological picture of the lesions, Talalov (1934) concluded that the condition must be considered a manifestation of allergy. A similar view was expressed by Karani (1953).

3. Vascular disturbance.

The frequent occurrence of thrombosis and haemorrhage have led France et al. (1951) to consider a vascular basis for the disorder. They reviewed 33 cases in literature and observed thromboses of cutaneous veins in 25%.

Indeed, one is impressed by the frequency with which thromboses and haemorrhage have been recorded in literature.

Purpura was observed in patients reported by Pils (1925), Degos, Lortat-Jacob and Sainrapt (1947), and Degos (1951),

while Volavsek (1938) reported skin haemorrhages in his patient.

The patient of Thomas (1947) showed thrombosis of the inferior vena cava.

Whitwell (1934) considered emboli responsible for the eye and skin lesions of his patient. His first patient suffered outbreaks after tonsillectomy and tooth extraction.

Jebepan and Kalfayan (1946) observed thromboses of the retinal veins, while Duperrat and co-workers (1955) reported the presence of retinal haemorrhages.

Katzenellenbogen's patient (1950) revealed a haemorrhage into the aqueous humor, while thrombophlebitis migrans and retinal thromboses were observed in the patient of Kemp (1953). The patient of Zeavin et al. (1956) lost vision in the right eye as a result of massive haemorrhage.

Massive intestinal haemorrhage of a fatal nature was seen in patients of Cordonnier, Samain and Goddéris (1953) and Bataille (1958).

Thrombophlebitis was a prominent feature in cases recorded by Martin (1945) and Carr (1957).

Cerebral thrombosis occurred in the patient of Gray (1950), while necropsy revealed small brain haemorrhages in the case described by Magni (1951).

Histological investigation by Berlin (1944) of a genital lesion revealed the presence of thrombosed vessels. A similar finding was reported by Curth (1952).

4. Hormonal disturbance.

On account of a relationship between outbreaks and the menstrual period, Wien and Perlstein (1932) considered ovarain dysfunction as a possible cause of the lesions.

A relationship between attacks and the menses was reported by Sibley (1899) - case 2, Talalov (1934), Whitwell (1934) - case 3, Tagami (1936) - case 1, Dernoncourt (1955) - case 1, Phillips and Scott (1955) - 5 cases, Nikolowski (1956) and Sezer (1956) - case 12.

Moseley (1941) successfully treated a 74-year-old woman with an oral oestrogenic preparation. The finding of Moseley was not confirmed by others.

5. Disease of collagen.

Popoff (1938) observed collagen changes on histological examination of a genital lesion.

After examination of an erythema nodosum-like lesion, Karani (1953) reported finding fibrinoid degeneration of perivascular collagen in some places.

Phillips and Scott (1955) were unable to find any fibrinoid necrosis in lesions examined by them. They concluded, however, that it seems possible that the disease may eventually fall into place among the collagen diseases.

D. THE HISTOLOGICAL PICTURE OF APHTHOSIS.

In literature very few descriptions deal with the histology of oral lesions in aphthosis. Various authors, however, gave a description of the histological picture of skin, genital, eye and brain lesions, some of which were rather brief.

Pils (1925) examined a genital and skin lesion of one of his patients. The genital lesion revealed an extensive round cell infiltration with much oedema in the cutis, while a nodular lesion of the skin of the lower leg presented the typical appearance of erythema nodosum. The latter demonstrated characteristic vessel changes in the deeper layers of the cutis and at the junction of cutis and subcutis accompanied by a circumscribed small cellular infiltration, predominantly around the blood vessels. In one area of the subcutis, abscess formation with many polymorphs was found. According to Pils, the lesions which clinically had a haemorrhagic appearance did not show corresponding changes on histological examination.

Samek and Fischer (1929) also considered the histological picture of a skin nodule to be typical of erythema nodosum. Around the blood vessels (arteries and veins) they found extensive lymphocytic and leucocytic infiltration, while the walls of the vessels showed proliferation of the intima with swelling and desquamation of the endothelium. According to them, the perivascular infiltrates revealed a slight haemorrhagic character in some areas. They also observed minute abscess-like infiltration in the subcutaneous fat, while collagen fibres throughout the cutis were swollen as a result of oedema.

Monacelli (1927), cited by Touraine (1941), was of the opinion that in aphthosis one deals with an endo-perivascularitis which shows resemblance to periarteritis nodosa.

Urbach (1929) who considered the lesions due to infection with avian tubercle bacilli, found no specific changes of tubercular infection on histological investigation.

Ito (1931) observed identical changes in oral and genital lesions. These consisted of an exudative periphlebitis and arteritis.

On examination of a genital lesion, Wien and Perlstein (1932) found extensive leucocytic and lymphocytic infiltration. Numerous plasma cells and eosinophils were encountered in the cellular infiltrate, while the blood vessels in the subcutis were dilated. They also found swelling of the endothelium of the vessels with "Einwanderung" of inflammatory cells in their walls.

The histological picture of erythema nodosum-like skin lesions on the lower extremities of Rosental's patients (1934) he considered to be evidence of the haematogenic origin of the lesions. According to Rosental the lesions should be considered septic or septic-allergic foci.

Talalov (1934) described the histological picture of an ulcer in the armpit and genital lesions. The armpit lesion revealed moderate acanthosis of the epidermis around the ulcer. The intercellular interstices of the rete Malpighii were widened and infiltrated by leucocytes. He observed pronounced spongiosis and leucocytic infiltration in the epidermis adjacent to the edge of the ulcer. The dermis, covered by epithelium and surrounding the ulcer, revealed oedema of the papillary layer and dilated blood vessels with swelling of their endothelial cells. On the surface of the ulcer, Talalov found a supperating fibrinous coating below which the collagenous tissue of the papillary and subpapillary layers was markedly oedematous. In the middle and deep layers of the dermis, he observed foci of infiltration around the enlarged blood vessels, while a diffuse infiltrate partly replaced the fat tissue in the subcutis. The cells of the infiltrate consisted of leucocytes, lymphocytes, fibroblasts, histiocytes together with occasional plasma cells and fat cells. Talalov was impressed by the changes in the walls of the blood vessels (chiefly the veins). These consisted of oedematous thickening and invasion by numerous leucocytes. He found similar histological changes in the genital lesions. Talalov concluded that "apparently the condition must be considered as a manifestation of allergy by analogy with other infections".

The histological findings of genital lesions reported by Tagami (1936) and Popoff (1938) were almost identical to those of Talalov (1934). Tagami, however, considered arterioles to be affected to the same extent as the venules while Popoff observed epithelioid cells, lymphocytes, histiocytes, a few plasma cells and mast cells together with an occasional giant cell.

Assnin and Sutejew (1934) observed lymphoid cells, numerous plasma cells, stippled basophilic cells, fibroblasts as well as an occasional giant cell in the genital lesion of one of their patients.

In a genital lesion Berlin (1944) observed marked thrombosis of large vessels within areas of inflammatory infiltration. A similar finding was reported by Thomas (1947).

After histological examination of biopsy specimens from the mouth, vulva and skin Phillips and Scott (1955) found no distinctive pattern. According to them the ulcers showed granulation tissue superseded by round cells. No histiocytic proliferation or fibrinoid necrosis were observed by them.

France et al. (1951) described the histological picture of a scrotal lesion prior to ulceration. Underneath the intact epidermis they found pronounced perivascular and interstitial oedema. Interstitially they observed a diffuse infiltration with mononuclear cells. The inflammatory reaction was localized around the capillaries and venules, sparing the arterioles. France et al. considered these changes to be of an unspecific nature.

According to Karani (1953), an erythema nodosum-like lesion demonstrated a marked allergic reaction lying within the lower cutis and subcutis. He found a marked proliferation and obliteration with thrombosis of vessels, together with fibrinoid degeneration of perivascular collagen in some places.

Itô (1959) compared the histological findings in cases of aphthosis, the syndrome of Fuchs (erythema exudativum multiforme symptomaticum) and idiopathic erythema exudativum multiforme. According to him, no histological differences exist between these conditions. He concluded that the changes observed by him were in favour of an allergic etiology.

Curth (1946a) reported the pathological findings in an enucleated eye. The iris revealed marked infiltration by polymorphonuclear leucocytes, while the ciliary body, the lower portion of the choroid, the retina and the optic nerve were infiltrated by lymphocytes. The retina was completely detached, and there was detachment of the choroid and of the posterior portion of the ciliary body. She also recorded the presence of an exudate extending from the surface of the iris and across the interior lens capsule to join a lesser band of exudate from the upper ciliary process. The choroid above revealed only a slight cellular infiltration in its interior portion. The episcleral vessels over the lower portion of the globe were surrounded by inflammatory cells. Similar findings were reported by Weve (1923) and Blobner (1937).

Berlin (1944), Magni (1951), Silfverskiöld (1951), Pallis and Fudge (1956), Wadia and Williams (1957), and Mc Menemey and Lawrence (1957) reported the histological findings in lesions of the nervous system.

According to Mc Menemey and Lawrence (1957) the lesions seemed od of four types:

a. Foci of softening in relation to blood vessels with microglial activity, feeble astroglial proliferation and where grey matter was involved loss of nerve cells.

b. Perivascular cellular infiltrations with lymphocytes and occasional microglial cells, mostly in the white matter and with slight associated loss of myelin.

c. Perivascular cuffing with sudanophilic foam-cells mostly in the white matter.

d. Extensive and patchy areas of cortical infarction with consecutive astroglial proliferation.

Pallis and Fudge (1956) considered it significant that in none of the necropsy reports mention was made of occlusive changes in smaller blood vessels. They compared the histological findings in neural lesions of aphthosis with those of acute disseminated encephalomyelitis. The latter, according to them, was reported after measles, vaccination or as a sequela to non-specific respiratory infection. Miller and Evans (1953), cited by Pallis and Fudge (1956), considered acute dis-

seminated encephalomyelitis an allergic reaction of the nervous system to various antigens. On clinical and histological grounds, Pallis and Fudge considered aphthosis and acute disseminated encephalomyelitis to be distinct.

Wadia and Williams (1957) stated "In neither case was demyelination an obvious feature which suggests that these changes were not allergic, ----". On the available evidence, however, they concluded that it was possible that both virus infection and allergy are concerned in the pathogenesis of the disease.

Mc Menemey and Lawrence (1957) found that capillaries and veins were rather more affected than arterioles. According to them, this finding fits in with the view of Kahle (1957), namely that the antigen-antibody reaction in all types of allergic encephalitis is strongest on the venous side of the circulation, where the mesenchyma is most likely to become sensitised against the waste-products of brain metabolism.

Mc Menemey and Lawrence, considered the presence of swollen joints, erythema nodosum and erythema multiforme together with occasional eosinophilia further evidence in favour of a likely allergic etiology.

Our histological findings in oral lesions of aphthosis are discussed with those of chronic recurrent aphthae (in Chapter VIII).

CHAPTER V

APHTHOUS DISEASES OF UNKNOWN ETIOLOGY.

A. CHRONIC RECURRENT APHTHAE.

1. Introduction.

Synonyms: recurrent aphthae (Cahn, 1950); recurrent oral aphthae (Everett, 1950; Gottlieb, 1951; de Azevedo, 1951); recurrent aphthous stomatitis (Orban and Wentz, 1955; Strean, 1957b); Owen, 1957); secondary aphthous stomatitis (U. S. Navy, Color Atlas of Oral Pathology, 1956); recurrent gingivo-stomatitis (Dekking, 1958); secondary herpetic stomatitis (Strean, 1957a); recurrent herpetic gingivostomatitis (Benzuly, 1956); recurrent herpetic ulcers (Farmer, 1956); habitual aphthae (Flusser, 1930); recurrent painful aphthae (Langner, 1957); aphthae resistentiae (Jadassohn, 1930); solitary aphthae (Frech, 1945); recurrent habitual aphthae (Frech, 1945); periadenitis mucosa nacrotica recurrens (Sutton, 1911; Epstein, 1939; Fergusson, 1939a); habitual aphthous stomatitis (Schmidt, 1940; Wolff, 1952); aphthous ulcers (Rivin and Barton, 1955; Upton, 1951; Bergman, 1954; Silcox, 1956); Mikulicz's aphthae (Sutton and Sutton, 1939; Thoma, 1944); cyclic habitual aphthous stomatitis (Strauss, 1947); recurrent ulcerative stomatitis (Oliver, 1954; Barbash et al., 1958; Kutscher et al., 1958); habitual aphthosis (Thoma, 1944, 1954); recurrent maculofibrinous stomatitis (Fragekasten, 1940); ulcerative aphthous stomatitis (Bloom, 1954); aphtose monopolaire (Touraine, 1941); ulcus neuroticum mucosae oris (Löblowitz, 1910; Sutton and Sutton, 1939); ulcus necroticum mucosae oris (Sircus et al., 1957); dyspeptic ulcers (Fleming, 1958); vesicular stomatitis (Templeton, 1926; Scott et al., 1941); aphthous stomatitis (Rivin and Barton, 1955; Zwerling, 1957; Knoedler and Stanmeyer, 1958); canker sores (Beecher, 1928; Cheney, 1948; Fisher and Leider, 1951; Moskowitz, 1958); chronic intermittent recurrent aphthae (Baur, 1957); chronic aphthae (Besecny, 1933); recurrent herpes (Aphthae) (Tièche, 1915); neurotic ulcers (Löblowitz, 1910); stomatitis neurotica chronica (Sibley, 1899); ulcus aphthosum chronicum (Löblowitz, 1910); recurrent non-febrile aphthous stomatitis (Fisher and Leider, 1951); recurrent aphthosis multiplex mucosae oris (Die Medizinische, 1952); chronic recurrent aphthosis (Steurer, 1952); ulcus neuroticum (Jacobi, 1894; Davies, 1939); recurrent scarring painful aphthae (Sutton Jnr., 1941; Cahn and Bartels, 1942); Aphthen (Landgraf, 1933) and chronic scarring aphthous ulcers (Weichselbaum and Derbes, 1957).

If one considers the long list of names that has been used for this condition one is again reminded of the great confusion that exists as far as momenclature is concerned. It is not our intention to discuss all the names separately for that would

serve no purpose. For the sake of clarity, however, we have to refer to the origin of a few of the names because at some time or other the conditions described as such, were considered different from chronic recurrent aphthae.

We decided for the purpose of this work to adhere to the name chronic recurrent aphthae as used by Mikulicz and Michelson (1892) in their original description of the disease.

Stomatitis neurotica chronica.

Jacobi (1894) in the United States, described three patients suffering from recurrent oral ulcers in whom neurosis and insanity appeared to be prominent features. He therefore named the condition stomatitis neurotica chronica. Three more cases were added by Sibley (1899) where a neurotic background seemed to play a part. Sibley preferred the name neurotic ulcers of the mouth.

Löblowitz (1910), after having read the publications of Jacobi and Sibley, could not find a description of similar cases in German literature. He therefore reported cases of this nature, occurring in one family, under the name ulcus neuroticum mucosae oris.

In the female patient who suffered from recurrent oral aphthae in conjunction with recurrent lesions of the vulva (reported by Carol, 1935) the diagnosis would inevitably have been ulcus vulvae acutum if Carol had been able to demonstrate the presence of B. crassus in the lesions. He therefore considered his case to be similar to those described by Jacobi (1894), Sibley (1899) and Löblowitz (1910). Carol, however, was not convinced that a neurotic factor played any prominent part in the causation of the disease. The only differences that he could find between the lesions of his patient and those observed in chronic recurrent aphthae (CRA), as described by Mikulicz, were the intensity, extent and stubborn nature of the lesions present in his patient. It is obvious that Carol's patient. suffered from aphthosis. In considering his patient to be suffering from ulcus neuroticum, Carol unwittingly linked aphthosis with CRA, since, with Kumer (1942), we believe that the cases described in literature as neurotic ulcers or stomatitis neurotica chronica should be considered as identical with CRA.

Periadenitis mucosa necrotica recurrens.

Sutton (1911) rediscovered the disease first described by Mikulicz and Michelson (1892), and later by Jacobi (1894). After histological examination of the lesions, however, he came to the conclusion that it deals with an infection of the underlying mucous glands. He therefore proposed the unfortunate name of periadenitis mucosa necrotica recurrens. More cases were subsequently designated as such by Epstein (1930), Fergusson 1939a, 1939b), Davies (1939), Sobel and Eller (1954) and Weichselbaum Derbes (1957).

Jadassohn (1930), after having seen patients of this nature

in the United States, considered them to be cases of aphthae resistentiae.

Wile (1930) considered the name periadenitis mucosa necrotica recurrens a poor descriptive term, while Carol (1935) could find no histological evidence in support of the glandular involvement.

Most of the authors who described cases under this long name, differentiated their cases from CRA on account of the fact that scarring appeared to be of frequent occurrence. Pusey (1930), however, pointed out that scarring was not a prerequisite in cases of this nature, while Morrow (1930) considered the mild type of lesions indistinguishable from those of CRA.

Sutton Jnr. (1941) believed PMNR to constitute a distinct entity, but preferred calling it recurrent scarring painful aphthae, while Kerr (1952a, 1952b) still subscribed to the original views held by Sutton Snr. (1911).

It is possible that lesions of CRA occasionally extend to the vicinity of mucous glands. These glands are numerous in the oral mucosa. In this way an explanation can be afforded for Sutton's finding (1911).

We share the views of Kumer (1942), Ruiter (1950) and Sircus et al., (1957), who consider PMNR identical to chronic recurrent aphthae.

Canker sores.

The name canker sores, which is often used in Anglo-Saxon literature for cases suffering from CRA (Beecher, 1928; Everett, 1950; Queries and Minor Notes, 1956; Tuft and Ettelson, 1956; Silcox, 1956 and Moskowitz, 1958), has never been the cause of any controversy, but in our opinion it may suggest relationship to cancer to laymen. We therefore feel that this name should be completely discarded from usage.

2. The clinical picture of chronic recurrent aphthae.

Patients suffering from chronic recurrent aphthae (CRA) usually present fully developed lesions (see fig. 5), varying in number from one to as many as fifty, and in size from that of a pinhead up to that of a fingernail. Individual lesions may be round, oval or slit-like and usually appear as a shallow erosion with a slightly depressed yellow or grayish-white base and surrounded by an erythematous halo of varying width. The lesions are usually sharply defined, but occasionally the edges may have a slightly irregular or ragged appearance.

The lesions may appear anywhere on the oral mucosa, but are more frequently seen on the inside of the lower lip, the cheek mucosa, the dorsum or edges of the tongue, in the mucobuccal folds and on the floor of the mouth. Very rarely lesions appear on the hard and soft palate and in the throat.

Table 1

Patient no.		Lymphglands	Temperature	ESR	Patient no		Lymphglands	Temperature	ESR
1	♀	-	37.9°		25	♀	-	37.0°	
2	♂	-	36.9°		26	♀	-	36.8°	5/15
3	♀	-	37.1°		27	♂	+	37.0°	
4	♂	-	36.8°		28	♂	+	37.2°	
5	♀	-			29	♂	-	36.4°	
6	♀	-	37.6°	14/33	30	♀	-		4/
7	♂	-	37.0°	5/15	31	♀	+	37.3°	7/
8	♀	-	36.9°		32	♂	-		11/
9	♂	-	36.6°	4/11	33	♀	-	36.0°	
10	♀	-	37.1°	19/48	34	♀	-	37.1°	
11	♂	+	37.4°	3/11	35	♂	-	37.1°	
12	♀	-	36.9°	5/12	36	♀	-	37.5°	
13	♀	-	37.5°		37	♀	-		10/23
14	♀	-		5/10	38	♂	-		2/
15	♂	-	37.4°	3/9	39	♀	-	36.8°	10/25
16	♀	+	37.4°		40	♀	-	37.0°	11/27
17	♀	+	37.0°	4/10	41	♂	-	36.9°	3/11
18	♂	-	36.8°	4/	42	♀	-	36.8°	
19	♀	-	38.0°	15/35	43	♀	-	37.2°	1[illegible] 9
20	♀	-	36.8°		44	♀	-		
21	♀	-	36.4°		45	♂	+	37.4°	
22	♀	+	37.1°		46	♀	-		
23	♀	-	37.2°						
24	♀	-		21/49					

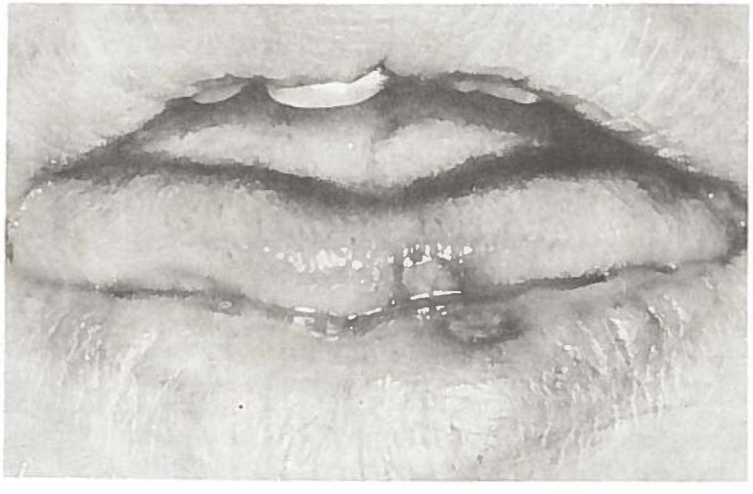

Fig. 5. Patient number 5 suffering from chronic recurrent aphthae and revealing aphthae on lip and tip of tongue.
(Photo: Schults, Dept. of Oral Surgery, University Hospital, Groningen)

The lesions give rise to intense pain, especially when eating, drinking, talking or when they are touched.

It is generally agreed that the lesions develop from short-lived vesicles, but they are not visible in the same way as for instance fluid-filled herpetic vesicles of the skin.

After the patient experiences a sudden burning sensation in a localized area of the mouth, he may feel a slight thickening by means of his tongue.

On examination, a localized area of redness is visible. Within two to six hours a yellowish or grayish-white spot appears in the inflamed area. This spot gradually changes into the characteristic shallow erosion or ulcer as described above.

In the same patient the lesions, sometimes, recur at varying intervals, while these intervals also differ from person to person. Some patients are practically never without them, since new lesions develop while others are still in the process of healing.

The lesions gradually become painless on about the fifth day, to heal as a rule within ten to fourteen days without scar formation. Rarely, scarring results from very deep lesions. The remainder of the mucosa usually has a completely normal appearance. Occasionally the area around a lesion becomes oedematous. Foetor ex oris and salivation are not features of the disease. As a rule no other complaints are encountered. Systemic changes are usually absent. The temperature is normal or may be slightly elevated (Table I).

Stark and co-workers (1954) stated that fever was usually absent or slight, except in those cases where secondary infection was present. In such cases, they occasionally observed a submaxillary adenitis.

Jordan (1933) and Kumer (1942) were of the opinion that regional lymphadenopathy is not found in the disease, while others (Greither, 1955; Nasemann, 1958; Schuermann, 1958a) considered it a prominent feature.

We observed enlarged lymph glands in only 8 of the 46 patients in our present study (Table I).

The incidence of the disease.

Jacobi (1894) who described his cases as stomatitis neurotica chronica, collected all he could find in literature and came to the conclusion that such cases must be very rare, whereas Sibley (1899) was inclined to believe that the disease was more common, but that it had been frequently overlooked.

The only statistical evidence was published in England recently by Sircus and co-workers (1957), who found that the overall incidence for all ages and both sexes amounted to 19.3%. They concluded that at some period in their lives, one in five of the population of Britain suffers from recurrent aphthous ulceration. They arrived at this figure after studying its pre-

Table II.

Patient number	Sex	Age at attendance	Duration of disorder	Intervals between attacks. No intervals	2 -8 weeks	2-3 months	longer than 3 months	completely irregular
1	♀	22	± 10yrs.		+			
2	♂	32	± 20yrs.	+				
3	♀	55	40yrs.	+				
4	♂	39	2yrs.		+			
5	♀	30	14yrs.					+
6	♀	53	38yrs.					+
7	♂	39	6yrs.	+				
8	♀	24	15yrs					+
9	♂	13	5yrs				+	
10	♀	46	±34yrs	+				
11	♂	42	1½ yrs		+			
12	♀	36	± 24yrs		+			
13	♀	32	14yrs	+				
14	♀	47	± 35yrs					+
15	♂	22	9yrs.					+
16	♀	28	8yrs	+				
17	♀	35	7yrs.	+				
18	♂	28	8yrs.				+	
19	♀	29	14yrs.		+			
20	♀	17	11yrs.		+			
21	♀	31	3 months.		+?			
22	♀	14	2yrs			+		
23	♀	42	7yrs	+				
24	♀	36	21yrs			+		
25	♀	45	14yrs.	+				
26	♀	20	5 yrs		+			
27	♂	32	5yrs.		+			
28	♂	27	1½ yrs.				+	
29	♂	33	7yrs.		+			
30	♀	24	3yrs.					+
31	♀	23	5yrs.					+
32	♂	41	± 8yrs.				+	
33	♀	36	10yrs.					+
34	♀	37	19yrs.		+			
35	♂	34	22yrs.		+			
36	♀	12	6 months				+?	
37	♀	40	± 28yrs.		+			
38	♂	22	10yrs.					
39	♀	34	20yrs.		+			
40	♀	28	10yrs.	+				
41	♂	21	9 yrs.				+	
42	♀	58	33yrs		+			
43	♀	46	28 yrs.		+			
44	♀	24	10 yrs.		+			
45	♂	28	12yrs.				+	
46	♀	25	7yrs.		+			

valence in 1587 consecutive patients attending hospitals, and 151 consecutive patients attending the surgery of a general practitioner. In the general practice group the prevalence was one in ten.

It should be noted however, that they made no clear distinction between chronic recurrent aphthae and the recurrent lesions of aphthosis.

In a leading article in the Lancet (Annotations, 1957) the view was expressed that the prevalence found by Sircus et al., in the general practice group is probably nearer to the prevalence in the general population.

We did not attempt to establish the overall incidence of the condition, bu there seems to be reason to believe that the prevalence is higher than generally supposed.

Sexual incidence.

In numerous reports on chronic recurrent aphthae (made since the original description of Mikulicz and Michelson, 1892) references were made of the fact that lesions often appear in anaemic or chlorotic women and in association with the menses or gestation (Losada, 1932; Klein, 1934; Strauss, 1947; Brachmann, 1954). Eulèr (1951) even states that it is actually a disease of women, appearing especially at the time of the menses. Baur (1957) found that it occurs more often in women than in men.

In their survey, Sircus and co-workers (1957) found that approximately 1 : 4 female subjects and 1 : 6 male subjects appear to be affected. As far as the sex ratio was concerned they obtained the following results:

	Male		Female
Sheffield Royal Infirmary	1	:	1.33
Edinburgh Western General Hosp.	1	:	1.35
General Practice	1	:	1.8

Jordan (1933) observed 24 patients in the course of seven years, of whom 14 were females, while in our own group of 46 patients, 31 were females (See Table II). The females referred to us for treatment exceeded the number of males almost twice. This is in accordance with the findings of Sircus et al. (1957), who observed that exactly twice as many women as men attended treatment in their series. We are in full agreement with Sircus and co-workers (1957) where they state that this ratio is partly a reflection of the fact that women have greater leisure for the purpose of attending the surgery and clinics.

Racial Incidence.

Cases of CRA have been described in all races, but no statistical data could be found in literature referring to the incidence in various races.

The 46 patients observed in the present series were all of Caucasian stock, born in the Netherlands.

From personal experience gained in private and hospital practice in the Union of South Africa and Tanganyika, we have gained the impression that chronic recurrent aphthae are seldom encountered among the Bantu of those parts.

Geographical Incidence.

Literature yielded no information regarding the geographical distribution of chronic recurrent aphthae. A perusal of the literature clearly indicates that cases have been reported in almost all civilized countries.

Simons (1950) stated that aphthae is of frequent occurence in the tropics. Unfortunately he did not specify the nature of the aphthae, with the result that this statement is of little value in our discussion of CRA when the high incidence of tropical aphthae is considered.

It is possible that some of the cases of aphthous stomatitis encountered by Knoedler and Stanmeyer (1958) while wintering in the Antarctic, belong to CRA, although no mention of recurrences had been made.

Seasonal Incidence.

Löblowitz (1910) could find no relationship of the disease to seasonal or climatic conditions.

Jordan (1933) attached importance to the fact that 12 of the 24 patients who reported for treatment, paid their first visit to him during the winter months (November, December, January, February), while the remainder were distributed over the other 8 months of the year. Jordan, however, did not explain why 6 of his patients reported for the first time during May.

Weisshaar (1939) observed cases at the time of year when tomatoes appeared on the market.

In our series of patients, only 3 could relate their disease to some seasonal influence. Cases 24 and 26 found that lesions were especially liable to occur in summer, while case 41 suffered more during the winter months.

From regular observations of some of our patients, we must conclude that climatic or seasonal changes have little or no effect on the course of the disease.

The age at attendace for treatment.

Jordan (1933) found that exactly half the number (12) of his patients attended for treatment between 31 and 40 years of age. The youngest patient he observed was between 16 and 20 years while two were older than 50.

Sircus and co-workers (1957) found that 65% of the 120 patients who presented themselves for treatment were between 20 and 49 years of age. As already mentioned before, twice as many women as men were observed in their series. In the

age group between 50 and 69 years, Sircus et al., found 22 women as opposed to 3 men. This led them to believe that the disease tends to burn out in males after middle age. The disappearance of lesions at the age of 50 in the two males reported by Brubacher (1926) lends support to this view.

Löblowitz (1910) considered the disease to be predominant among youth and that it tends to disappear in the years from 30 to 40. On the other hand, Greither (1955) is of the opinion that CRA only affects adults and hardly ever children.

Flusser (1930) described four children suffering from the disease. The eldest was 10 years of age, while the youngest was a boy of 4 years. Lordick (1935) observed three little patients aged between 2 and $3\frac{1}{2}$ years.

At attendence the age of our 46 patients was as follows:

	0 - 9 yrs.	10 - 19 yrs.	20 - 29 yrs.	30 - 39 yrs.	40 - 49 yrs	50 - 59 yrs.	> 60 yrs.
Fm.	0	3	10	9	6	3	0 = 31
M.	0	1	6	6	2	6	0 = 15
B.S.	0	4	16	15	8	3	0 = 46

The youngest patient in our group was a girl of 12 years and the oldest a women of 58.

The majority (67%) of our patients attended in the age group of 20 to 49 years, which is in accordance with the figure of 65% reported by Sircus and co-workers (1957).

The age at onset.

We have seen that young children as in the cases of Flusser (1930) and Lordick (1935), may suffer from chronic recurrent aphthae.

Sircus and co-workers (1957) found the highest incidence of onset in both sexes during the second decade. In more than 50% of their patients the onset was between the age of 10 and 30 years, while 10% of their female patients suffered their first attack between 50 and 59 years. They recorded no initial attacks in men of this age group.

To determine the age of onset in our series, we had to rely on the information vouchsafed by the patients themselves. This naturally has a margin of error in some instances. Six could remember that they suffered from lesions since childhood. Of the remaining 40, 30 had their first attack between 10 and 30 years of age.

The youngest age at onset was 6 years, while the oldest was 40.

Like Sircus et al. (1957) we found the highest incidence of onset in both sexes in the second decade.

The following table illustrates our findings:

Age at onset	0 - 9 yrs.	10 - 19 yrs.	20 - 29 yrs.	30 - 39 yrs.	40 - 49 yrs	> 50 yrs.
Fm.	2	16	5	3	0	0 = 26
M.	1	5	4	3	1	0 = 14
B.S.	3	21	9	6	1	0 = 40

The frequency of attacks.

The rhythmical periodicity with which attacks occur was first observed by Mikulicz and Michelson (1892). In the patient recorded by them they found new lesions after a varying interval of four to six weeks. A case of sibley (1899) suffered from lesions at varying intervals.

Loblowitz (1910) observed a difference in the frequency with which lesions occur in females and in males. In the former he noticed the appearance of aphthae at approximately monthly intervals, while the latter suffered attacks once or twice a year.

Epstein's case (1930), a woman of 37 who had aphthae since early childhood, first observed lesions occasionally, but since the age of 20 she suffered almost continuously. Other cases, never free from lesions, were described by Sutton (1941)- one female, Weichselbaum and Derbes (1957)- one female, and Truelove and Morris-Owen (1958)- two females and one male. One of the female cases described by the latter bears a resemblance to the case of Epstein (1930). She also suffered since early childhood, the lesions first appearing occasionally but since her fourteenth year they were continuously present.

Completely irregular intervals were present in the cases of Mann (1954)- one female, Weichselbaum and Derbes (1957)- one female, and Truelove and Morris-Owen (1958)- one male.

Intervals of from two to eight weeks were observed by Flusser (1930)- one male child, Grace (1936)- one female, Mann (1954)- one female, Laugier (1957)- one female, and Truelove and Morris-Owen (1958)- two females.

Three male patients (one of Sutton 1941, and two of Claus et al., 1957) had attacks after regular intervals of two to three months, while a demale patient of Davies (1939) suffered from lesions every six months.

Sircus et al. (1957) found that nearly 40 per cent of their female patients suffered crops of ulcers at intervals of less than eight weeks, and usually with intervals of less than a month. The majority of their male patients (45 per cent) experienced new crops at three to four month intervals, or otherwise are never without lesions in the mouth. Sircus and coworkers also found that 17. 5% of males against 3% offemales, show no periodicity, with completely irregular intervals between attacks.

The frequency of attacks as related by our patients (see also Table II) were as follows:

	No periodicity lesions appear continuously	Intervals 2 - 8 wks.	Intervals 2-3 mnths.	Intervals longer than 3 months.	Completely irregular
Females	8	12(+1?)	2	1?	7
Males	2	5	0	7	1
Both Sexes	10	17(+1?)	2	7(+1?)	8

The duration of the disorder.

In the cases studied by Rosenstein and Ziskin (1942) the duration of the disorder varied from several months up to six years.

Sircus et al. (1957) found no significant difference between the sexes in respect of the length of time the malady had persisted. 65 to 70 per cent of their patients had the disease from one to fourteen years, while 30 per cent suffered from it for fifteen to forty years.

In the following table the duration of the disease as observed in our cases are given:

	0-11 months	12-23 months	2-4 yrs.	5-9 yrs.	10-14 yrs.	15-19 yrs.	20-29 yrs.	30-39 yrs.	40-49 yrs.	50 yrs. or longer	
Females	2	0	2	6	9	2	5	4	1	0	=31
Males	0	2	1	8	2	0	2	0	0	0	=15
Both sexes	2	2	3	14	11	2	7	4	1	0	=46

Even in this small number of patients observed by us, similar results to those reported by Sircus et al. (1957) were encountered. Thirty (65%) of our cases had the disease from one to fourteen years, while fourteen (30%) suffered from CRA from 15 to 40 years.

The distribution of lesions.

Sircus et al. (1957) found, that the sites of election in 120 patients examined by them 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. They also found that 15% of their female patients (12 out of 80) suffered periodically from genital lesions. It is therefore obvious, that the distribution of the oral lesions as observed by Sircus et al. included those of aphthosis.

We recorded the distribution of 162 consecutive lesions in our patients and obtained the following results:

side lower lip	51x	=	31.48 %
Tongue	38x	=	23.45 %
Inside upper lip	17x	=	10.49 %
Lower buccal sulcus	15x	=	9.25 %
Cheek mucosa	13x	=	8.02 %
Upper sulcus	13x	=	8.02 %
Gi giva	9x	=	5.55 %
Palate	4x	=	2.46 %
Floor of mouth	2x	=	1.23 %

3. The etiology of chronic recurrent aphthae.

Is Chronic recurrent aphthae due to a bacterial infection?

Review of the literature.

Löblowitz (1910) observed pyogenic bacteria in his patients from oral lesion smears. This included staphylococci, streptococci, short thick rods, occasionally longer, slightly

bent rods and large spirochaetes with few and irregular spirals. From his patients with foetor ex oris Löblowitz was able to cultivate Vincent's organisms in pure culture. He considered the bacteria found to be of secondary nature.

Goadby (1925), cited by Colyer and Sprawson (1946) found a streptococcus of the nature of streptococcus faecalis in 6 out of 10 patients suffering from aphthous stomatitis. From the description of Colyer and Sprawson it can however, be gathered that some of Goadby's patients suffered from acute aphthous stomatitis.

Jordan (1933) found that bacterial investigations done on patients with chronic recurrent aphthae produced negative results in some, but that diplococci and streptococci were present in the majority. Jordan also mentioned the presence of pseudodiphteria bacilli in one patient with neurotic ulcers, and that Matras (1932) was able to show the presence of B. crassus in the oral lesions of his patient. This patient of Matras should, however, be excluded from a discussion on CRA, since she actually suffered from aphthosis. Jordan stated that altnough the mouth picture revealed a mixed flora, the bacteria mentioned above do not appear in all persons. According to him they are harmless in the majority of people but may sometimes become dangerous when the resistance of the body is lowered by gastrointestinal disturbance, diseases of the nervous system or trauma.

Lordick (1935), on the other hand, quite definitely stated that chronic recurrent aphthae is not an infectious disease.

Lempke (1941) considered CRA an infectious disease with a hereditary or acquired constitutional background. In five patients he examined the bacteriological findings were fairly constant. All of them showed the presence of fusiform bacilli and spirochaetes. He also obtained good results with arsenical treatment. He therefore suggested the possibility that these normal inhabitants of the mouth may become pathogenic under certain circumstances. Lempke, however, concluded that further research was necessary to prove this hypothesis. From the lesions in their patients, Weichselbaum and Derbes (1957) and Vest (1957) could only obtain the normal oral flora. Special cultures for fungi and tubercle bacilli in one case observed by Weichselbaum and Derbes (1957) were negative.

In favour of a possible infectious genesis for CRA would be the presence of regional lymphadenopathy, a rise in temperature and an increased erythrocyte sedimentation rate (ESR).

Sibley (1899) could find no rise in temperature in his cases, and considered it an important feature in the differential diagnosis of CRA from pemphigus.

Jordan (1933) observed no enlarged lymph glands or rise

Table III.

Pat. No.	Microscopical Findings	Pat. No.	Microscopical Findings
1	Few Gram + cocci. Few pseudodiphtheria-like Gram + rods. No yeast forms Wa R-, VDRL-.	19	Few Gram- rods. No yeast forms. WaR-, VDRL-.
2	Few Gram + cocci arranged in chains No yeast forms present. Luetic reactions not done.	20	Many epithelial cells. On cells numerous Gram + diplococci. No yeast forms. WaR-, VDRL-.
3	Few Gram + diplococci. Not suspect of Vincent's infection. No yeast forms. WaR-, VDRL-.	23	No spirochaetes or other bacteria. No yeat forms. Luetic reactions not done.
5	Few Gram-rods. Few Gram + diplococci. No yeast forms. Bacteria on epithelial cells. Luetic reactions not done.	24	Few squamous epithelium cells. No bacteria or yeast forms. WaR-, VDRL-.
6	Few pseudodiphtheria bacillu. Few Gram + diplococci, Gram-diplococci, Gram-rods. Bacteria on epithelial cells. No yeast forms. WaR-, VDRL-.	26	Few epithelium cells. No spirochaetes or other bacteria. No yeast forms. WaR-, CDRL-.
7	Few Gram + cocci arranged in groups. WaR-, VDRL-.	27	Few pseudodiphtheria bacilli. No yeast forms. Luetic reactions not done.
8	Few epithelial cells. Various Gram + cocci arranged in duplo. Few Gram-diplococci and Gram-rods. No yeast forms. Luetic reactions not done.	30	Cells loaded with pseudodiphtheria bacilli, Gram-diplococci, Gram + diplococci, Gram-rods. Few bacteria scattered amongst cells. Luetic reactions not done.
9	No spirochaetes or any other bacteria. No yeast forms. Luetic reactions not done,	31	Many pseudodiphtheria bacilli on cells. No free bacteria. Luetic reactions not done.
10	A number of Gram + diplococci. WaR-, VDRL-.	32	Few Gram + diplococci Few Gram-rods, Few yeast cells. Bacteria predominantly on cells. WaR-, VDRL-.
11	Many Gram + cocci arranged in duplo. Few Gram-rods, Gram + pseudodiphtheria -like rods, No yeasts. Bacteria on epithelial cells. WaR-, VDRL-.	34	Few Gram-rods. No rods of the type B.crassus. Luetic reactions not done.
12	Mixed oral flora. Pseudodiphtheria bacilli. Gram + diplococci, Gram-rods, leptotrichialike threads, actinomyces-like threads, B. fusiformis. WaR-, VDRL-.	35	No bacterial examination performed. WaR-, VDRL-.
14	Many large round cells with round nuclei and vacuolated protoplasma. Few leucocytes, Few Gram + diplococci and Gram-rods WaR-, VDRL-.	37	Few epithelial cells. On cells pseudodiphtheria bacilli. Few Gram-rods and pneumococci. No yeasts. No free bacteria. WaR-, VDRL-.
15	Few Gram + pseudodiphtheria-like rods Few Gram + cocci in duplo and in groups. WaR-, VDRL-.	38	No bacterial examination done, WaR-, VDRL-.
16	Few Gram + cocci in duplo and in groups, Few Gram-cocci and Gram-rods. WaR-, VDRL-.	40	Few epithelial cells. Few Gram + cocci in duplo, pseudodiphtheria-like Gram + rods. No yeast cells or mycelia. WaR-, VDRL-.

Table III (continued)

Pat.No.	Microscopical Findings	Pat.No.	Microscopical Findings
17	No bacteria or yeast orms. Luetic reactions not done.	41	Few Gram + diplococci. Not suspect of Vincent's infection. No yeast forms. WaR-, VDRL-.
18	On epithelial cells numerous Gram + diplococci. Few pseudo-diphtheria-like rods. Few Gram-rods and fusiform bacilli. WaR-, VDRL-.	43	Few epithelial cells. Few Gram + diplococci, Not suspect of Vincent's infection. No yeast cells or mycelia. Luetic reactions not done.

of temperature in his patients. Similar findings were recorded by Kochs (1940), Kumer (1942) and Strean and co-workers (1958).

Hirsekorn (1935) found that patients with CRA develop a high temperature, often higher than 40°C. In one of the cases recorded by him there was an additional submaxillary lymph gland enlargement. Others to support the idea of painful, enlarged lymph glands were Greither (1955) and Schuermann (1958a).

On the other hand, Lordick (1935) stated that painful enlarged regional lymph nodes were often encountered in many cases of CRA, but that this was due to secondary infection.

Personal observations.

In order to gain an impression of the nature of the bacteria present in the oral lesions of our own cases, scrapings of lesions were obtained from 30 patients with CRA. Smears made from this material were examined microscopically by Dr. E. A. Beute of the Bacteriological Serological Laboratory of Groningen (Head: Prof. Dr. A. B. F. A. Pondman). At the same time blood specimens from 20 of our patients were examined serologically to rule out lues.

The results of these investigations are given in table III.

Conclusion: On microscopical examination of oral smears from 30 of our patients suffering from chronic recurrent aphthae a variety of organisms were found. Since these bacteriac are commonly found in normal mouths and none of them were constantly present, we have to conclude that none of them can be considered the cause of the lesions.

At the same time, lues can be ruled out in the etiology of the disorder.

Is chronic recurrent aphthae due to a neurosis?

It was Jacobi (1894), in the United States, who first observed a relationship between the oral lesions and mental

disorder in three of his patients. Insanity and neurosis were prominent features in these cases. He therefore applied the name stomatitis neurotica chronica to the disease.

Sibley (1899) observed three patients suffering from oral lesions and compared them with those of Jacobi (1894). Sibley stated: "The cases I am about to describe I have met with during the last few years - two in private, and one in hospital practice, all being women. The patients were rather more of the hysteroid or neurotic than the insane type, as those described by Jacobi, two of whose cases were men". He continued: " Such cases are often classed as simple catarrhal or dyspeptic ulcers, whereas I consider they are the direct result of a trophoneurosis, of which dyspepsia in some form or other may be, and often is another expression". He called the lesions "neurotic ulcers". The second patient of Sibley also had genital and eye lesions and should therefore be considered as a case of aphthosis.

In Germany, Löblowitz (1910), observed a neurotic family, various members of which suffered from lesions in the mouth. The lesions were similar to those reported by Jacobi and Sibley. According to Loblowitz the lesions were due to a neurotic mucosal gangrene analogous to the so-called neurotic skin gangrene of Kreibich. The latter postulated that the vasodilator centre shows an increased sensitivity to functional (hysteria) and organic (tabes etc.) diseases of the central nervous system or even to auto-intoxication (from the ovaries) reacting with increased central or peripheral stimuli. This increased reaction is characterized by a sudden hyperaemia and transudation with subsequent pressure on the blood vessels, resulting in anaemia, necrosis and exudation.

Jordan (1933) could find no evidence of any nervous or hysterical factor in his patients.

Hirsekorn (1935) described one patient who suffered from psychic depression. He concluded, however, that the patients suffer psychologically as a result of the frequent recurrences and ultimately become neurasthenics. A similar view was expressed by Lempke (1941). Lempke found that many CRA patients could not eat because of severe pain. This resulted in their physical and psychical condition deteriorating. These patients were then subject to spells of depression while doubts as to their capacity for work had to be entertained.

After observing 11 cases of CRA in a psychopathic family Lordick (1935) concluded that he dealt with a constitutionally linked mucosal disease more or less secondarily infected.

Haymann (1940) stated that two possibilities were chiefly considered in the etiology of chronic recurrent aphthae, namely an infection and a neuro-reflex origin. According to him, none of these theories were ever proved with the result that the etiology was still unknown.

Kochs (1940) emphasized the fact that it is very difficult to prove a nervous factor in cases with CRA, since the differentiation between normal and abnormal is purely subjective and depends solely on the degree of judgement in these cases. In the family suffering from CRA he described, Kochs observed no neurotic or psychopathic background. On the contrary, he considered the members to be exceptionally robust and healthy.

Wolff (1952), himself afflicted with the disease, considers the oral lesions analogous to gastric ulcer formation. According to him, one usually finds CRA in persons with a labile vegetative nervous system such as constitutionally linked neurodystrophic mucosal damage.

In the Journal of the American Medical Association (Queries and Minor Notes, 24th Sept., 1949) a case of CRA was described in which psychic trauma seemed to play a part. On account of the chronic duration of the disease a constitutional element was considered important. According to the author of this article, it was reported that in certain persons the lysozyme content of various secretions increases during times of mental stress. The lysozyme, which is mucolytic, leaves the mucosa without its natural projection, thereby predisposing the individual to upper and lower intestinal ulceration. He concluded that such patients should consult a neuropsychiatrist.

Bennee (1954) obtained permanent and prolonged benefit in some of his patients after the intravenous administration of a 2% procaine solution. He ascribed these results to the suppressive action of procaine on the sympathetic nervous system. According to Bennee, many patients date back their symptoms to some previous emotional experience. In cases where this form of treatment is unsuccessful, he considers it to be important that the cause of the sympathetic predominance be determined with the aid of psycho-analysis.

Strean (1957a), who placed chronic recurrent aphthae under secondary herpetic stomatitis, stated that patients with this disease usually suffer from emotional stress, and that reference to a psychiatrist may be advisable. According to him, long periods of remission followed psychiatric treatment when the patient had learned to adjust himself to emotional disturbances.

In describing their third patient, Weichselbaum and Derbes (1957) remarked: " Psychiatric consultations revealed that the patient had a very unsatisfactory family background and that the main oral pathology began during the patient's sixth pregnancy, when her husband threatened her with a gun and knife ". In this respect no further comments were made by them.

The most comprehensive psychiatric study on the relation of oral ulceration to mental illness and stress to date is that of Sircus, Church and Kelleher (1957). After close investigation of 55 patients these authors could recognize mental illness in

18 (33%) of the cases. Both sexes were found to be equally affected (31% of male and 35% of female patients). The diagnosis made in the 18 cases included chronic anxiety state, hysteria, obsessional state, hypochondriasis, paranoia and epilepsy. In the remainder of the group observed by Sircus et al., there appeared to be a strong tendency to neurosis (71% were anxious, 51% experienced depressed moods, 38% hypochondria and 35% showed some form of obsession). In the majority (71%) of their patients was a history of unfavourable early environment. Onset of ulceration was preceded by severe environmental or emotional stress in 63% of their female patients and 59% of their male patients. Important factors observed by them were death in the family, marital maladjustment and stresses of social environment. Sircus and co-workers (1957) concluded: "The overwhelming association seen so often in our subjects between mental stress, psychopathological disturbance, and the onset and fluctuations of the disease, underlines these factors as the main aggravating or precipitating mechanisms, though not the cause, of the disease".

Personal observations.

No neuropsychiatric investigations were conducted for this study. However, from information given by our patients as well as from regular contact with some of them, we gained the impression that a nervous element plays an important part. The majority of our patients (26 of the 46) related the outbreaks to times of stress. Two (cases 6 and 11) were at some time or other treated for nervous breakdowns. Our case 1 suffered severe attacks shortly before college examinations, while case 2 vouchsafed the information that lesions were apt to occur when things went wrong at his work. Two other patients of our series (Cases 3 and 34) were very unstable emotionally. They often visited the clinic to relate one or other personal worry. During these conversations the patients often cried.

We agree with Sircus et al. that nervous factors aggravate or precipitate attacks, but that they do not cause the lesions. Too many patients without symptoms suffer from it.

Is chronic recurrent aphthae a hereditary disorder?

The familial character of chronic recurrent aphthae (CRA) was first observed by Löblowitz (1910) when he recorded the disease in a father and his children. A sister of the man and her two daughters were likewise afflicted since childhood.

Strandberg (1911) reported a family where eight members suffered from repeated attacks of oral ulcers. One of Strandberg's patients, however, also gave a history of scrotal lesions.

Ullmann (1927) described another family where more than one member suffered from lesions.

Lordick (1935) was unable to find a positive family history

in the majority of his patients suffering from CRA, but in a proportion of them there was indeed a striking familial incidence. In conjunction with the oral lesions in this latter group Lordick found psychopathic symptoms in the patients or in their relatives. In a family counting 36 members, he observed aphthae in 11, while 19 of the 36 were psychopaths of whom 9 were afflicted with oral lesions.

Kochs (1940) examined 49 members of one family and recorded CRA in 17 of them. The fact that in none of his cases the disease was transmitted from father to son and the preponderance of females over males (13 females as opposed to 4 males) suggested to Kochs the possibility of a sex-linked dominant inheritance.

Schmidt (1940) observed CRA in four generations, and concluded that he dealt with a superficial constitutionally-linked mucosal infection of neurotrophic nature. He was subsequently (Schmidt, 1958) able to add a further generation to the existing four.

In the survey of Sircus and co-workers (1957) a positive family history was obtained from 55 of 120 patients (45.8%). In 18.3% of their cases one or both parents were known to suffer from oral aphthae, while in 15% one or more siblings were affected. In 17.5% of cases one or more children, and in 4.1% the husband or wife suffered from lesions. Sircus and associates also observed that in several cases where children were affected, anticipation appears to have occurred, the disease appearing in the child at an earlier age than it did in the parent. They concluded that in relationship to the overall incidence of the disorder, factors of inheritance only play a minor part in the etiology.

Personal observations.

In 24 (52%) of our patients there was a history of lesions in close relatives. On two occasions we personally observed a mother child relationship. Case 9 is the son of our case 10, while case 26 is the daughter of case 25. Case 17 and her niece (case 22) attended for treatment. On no occasion did we find a father son relationship. It therefore seems possible, that a sex-linked dominant inheritance plays a part in the development of lesions.

Is chronic recurrent aphthae a manifestation of an avitaminosis?

Introduction.

Diseases due to an inadequate intake of nutrients are generally spoken of as deficiency diseases.

The essential nutrients can be divided into the following groups: a. water; b. electrolytes and minerals; c. proteins; d. carbohydrates; e. fats; f. vitamins.

A deficiency of a vitamin is also referred to as an avitaminosis.

The reasons for an avitaminosis can be shortly summarised as follows:

1. Deficient intake of the vitamin.
2. Disturbed absorption.
3. Defective storage in the body.
4. Deficiency as a result of increased requirements.
5. Deficiency through abnormal loss from the body.
6. Deficiency as a result of antagonistic action of enzymes, present in the diet.
7. Deficiency as a result of disturbed utilization in the tissues.

Nieweg (1958a) considers deficiency diseases to be rare in the Netherlands, but concluded that because of the low incidence a possibility that sporadic cases sometimes escape notice may exist.

Experience has taught that a deficiency in one vitamin is often accompanied by the deficiency of others. This is especially true of the members of the vitamin B complex.

Review of the literature.

In a discussion on herpetic, aphthous and ulcerative stomatitis, Gerstenberger (1923) stated that "recent clinical experiences have led us to believe that the underlying factor in these conditions is a disturbance of metabolism or nutrition; in other words that any part that bacteria ot similar agents may play in developing the different types of lesions is of a secondary nature". Gerstenberger observed a remarkable therapeutic effect of vitamin B in cases of chronic recurrent aphthae. In an attempt to explain the nature of these disorders, he used herpetic stomatitis as an example: "It may be that it is not so much a more or less absolute deficiency in the diet of the water soluble B vitamin that is responsible for the development of herpetic stomatitis, as it is the intake of a diet that speeds up metabolism. The common occurrence of herpes labialis in women whose metabolism, as a result of pregnancy, lactation, menstruation and thyroid disease, is so much more frequently operated at a higher rate than is that of men, suggests such an interpretation."

Danziger (1934), on the other hand, considered a deficiency of vitamin A as of prime importance in the causation of chronic recurrent aphthae. According to Danziger a deficiency of this vitamin leaves the oral mucosa more vulnerable to the pathogenic action of otherwise harmless bacteria in the mouth. The importance of a vitamin A deficiency in the etiology of aphthae was also considered by Roller (1939).

Stepp (1936) considered a number of vitamins in the etiology of the lesions. According to him a deficiency of vitamins A, B_2

and C predispose the individual to attacks of aphthae. Where it concerns vitamin B_2 the oral lesions are accompanied by signs of a colitis. Stepp suggested the intravenous administration of vitamin C for a couple of days to affect a cure.

Müller (1938) reported a female patient, who suffered from chronic recurrent aphthae for many years. All forms of treatment were of no avail. Further examination revealed that the patient suffered from a vitamin C deficiency. After daily treatment with vitamin C tablets (Redoxon) rapid healing followed. Cessation of treatment caused a return of lesions, which again disappeared after treatment was re-continued.

The findings of Müller (1938) were corroborated by Marti (1940, 1941). The latter concluded as follows: "Nicht geklärt ist noch die Frage, die wir auch anderseitig offen liessen, ob die Stomatitis als einfache Karenzerscheinung des Vitamindefizites aufzufassen ist oder ob die Hypovitaminose nur einen für das Auftreten der Stomatitis günstigen Boden schafft, oder aber, ob die infektiöse Komponente der Stomatitis, die wir auch nicht ausschliessen können, als primäre Ursache den Vitaminhaushalt des Körpers stört. Wenn die chronisch rezidivierende Stomatitis Aphthosa nur eine reine Karenserscheinung des C vitamins ist, wie wir es selbst annehmen, dann sollte es uns unter ständiger Kontrolle des C-vitamin-Stoffwechsels möglich sein, weitere Schübe bei diesen Kranken auch in späteren Jahren ganz verhindern zu können."

Burket and Hickman (1942) and Burket (1946), reported the successful treatment of cases with recurrent oral aphthae by means of the vitamin B complex. Burket (1946), in his celebrated textbook Oral Medicine, stated that in certain cases as little as 1 mg. of thiamin chloride per day would prevent lesions. That this observation by him and Hickman, however, proved to be of little value, can be inferred from the fact that it was completely ignored by the author in the latest edition of his textbook (1957).

Griebel (1939) considered vitamin B_2 deficiency an important cause of aphthae in the mouth. According to him such a deficiency may arise, either as the result of an inadequate intake in the diet, or as a result of defective absorption. The latter occurs in the case of disease of the gastro-intestinal tract.

According to Rosenstein and Ziskin (1942), they were able to rule out vitamin B-deficiency as the cause of lesions in four female patients observed by them. Careful histories of the patients' diet indicated an adequate intake of the vitamin, while the administration of large dosis of B-complex vitamin had no effect on the outbreaks. These authors, however, did not consider the possibility of impaired resorption of the vitamin.

Strauss (1947) observed a striking relationship between the outbreaks and the menstrual periods in 43 out of 45 female pa-

tients. According to him, this relationship pointed to a possible endocrine factor. The anterior lobe of the pituitary was considered important. On the basis that a certain level of vitamin B intake is essential to maintain a normal function of his gland, Strauss instructed his patients to take one tablespoonful of Marmite daily.

He found that the therapeutic effect of Marmite appeared to be better than that of pure vitamin B_1. The results of this treatment were that the aphthae all but disappeared; the few which did occur occasionally in rudimentary form were so attenuated as to be painless. Strauss concluded that the vitamin B_1 or B-complex did not cure the aphthae themselves, but that it served to prevent the chain of events which eventually would have led to their formation from starting.

The male patient of Distelheim and Sulzberger (1949), diagnosed as a case of periadenitis mucosa necrotica recurrens, received various treatments (among them vitamin B_1) without any benefit.

Van Krimpen (1948) reported a patient who failed to respond to a variety of remedies, but who was completely cured after the daily administration of vitamin B (a spoonful of brewers yeast) together with vitamin C (100 mg. three times a day).

Afonsky (1950) stated "I have not been very successful in my attempts to cure the cases of recurrent aphthosis by vitamin B complex preparations. Many of the girls of adolescent age afflicted by this condition also had menstrual disturbances, predominantly dysmenorrhoea. Biskind et al. (Surg. Gynaec. and Obstet. 78:49,1944) claimed a relationship between Vitamin B complex and estrogens. They stated that women with nutritional deficiency often give a history of menstrual disorders which can be cured successfully with Vitamin B complex".

Mann (1954) reported excellent results in three patients suffering from chronic recurrent aphthae who were given vitamin B12 injections. Unfortunately Mann did not state whether pernicious anaemia was ruled out in these cases. Leemans (1951) achieved similar results with folic acid (5 mg. three times a day per os).

In Queries and Minor Notes (1956), however, one finds the following statement: "Nothing is known about the nature of canker sores or aphthous stomatitis, and there is no evidence whatsoever to support the assumption that it is connected with nutritional deficiency of any kind".

Personal observations.

Signs of vitamin deficiency were not observed in any of our patients.

To find out whether possible sub-clinical deficiencies exist in CRA patients, serum vitamin A and E, blood vitamin C and

the 24-hour excretion of vitamin B_1 were determined. With the exception of vitamin C all determinations were carried out at the State Institute of Public Health, Utrecht (Dr. A. H. Holtz). The blood vitamin C was determined at the Central Laboratory, Groningen (Dr. A. Groen).

The results are given in the following table:

Case No.	Age	Sex	Serum Vit. A. (N. 80 > IU/100 ml.)	Serum Vit. E. (N. ± 1 mg.%.)	Blood Vit. C. (N. 0.8 - 1.2 mg.%)	Urine Vit. B (N.♀ 60-150 µg/24 hrs.) (N.♂ 100-250 µg/24 hrs.)
3	55	♀	-	1.0 mg.%	0.23 mg.%	450 µg.
6	53	♀	-	-	0.48 mg.%	-
8	24	♀	120 I.U.	0.75 mg.%	-	-
10	46	♀	50 I.U.	0.35 mg.%	0.35 mg.%	55 µg.
13	32	♀	80 I.U.	0.55 mg.%	0.30 mg.%	-
16	28	♀	100 I.U.	0.55 mg.%	0.40 mg.%	20 µg.
17	35	♀	110 I.U.	-	0.55 mg.%	-
19	29	♀	90 I.U.	0.55 mg.%	0.70 mg.%	-
24	36	♀	140 I.U.	0.40 mg.%	0.23 mg.%	45 µg.
26	20	♀	100 I.U.	0.60 mg.%	-	145 µg.
39	34	♀	100 I.U.	-	0.34 mg.%	-
40	28	♀	140 I.U.	-	-	60 µg.
2	33	♂	130 I.U.	0.75 mg.%	-	-
7	39	♂	-	-	0.20 mg.%	-
9	13	♂	-	-	0.70 mg.%	-
11	42	♂	130 I.U.	0.70 mg.%	0.45 mg.%	460 µg.
27	32	♂	170 I.U.	0.50 mg.%	-	65 µg.
35	34	♂	160 I.U.	0.55 mg.%	0.50 mg.%	25 µg.
41	21	♂	130 I.U.	0.40 mg.%	0.50 mg.%	-

Conclusions:

Fourteen out of 15 patients had a normal vitamin A level in the serum. A vitamin A deficiency can therefore be ruled out in the etiology of CRA.

The normal vitamin E content of serum is considered to be approximately 1 mg %. According to Holtz (1959), however, the normal value is in the neighbourhood of 0.8 mg.%. A lowered vitamin E content was found in 12 out of 13 patients with CRA. The function of this vitamin in man is not known. In female rats a deficiency leads to abortion while in male rats the vitamin plays a part in spermatogenesis. According to Burket (1957), no dental or oral changes have been reported in association with vitamin E deficiency. Low blood levels were observed in cases with a disturbed fat resorption and in patients with cirrhosis of the liver (Nieweg 1958 a). No explanation can be offered for the low vitamin E values in serum of CRA patients.

Blood vitamin C levels were determined in 14 patients with CRA. All of them gave low values. No value can be attached to this finding since 4 normal persons used as controls gave similar results. These low values of vitamin C in the blood may be ascribed to the fact that the determinations were made during the winter months when fresh fruit and vegetables are scarce. A diminished excretion of vitamin B_1 in the urine is no proof of a deficiency of this vitamin. It may, however, suggest such a possibility.

From the fact that 5 out of 9 patients in our series had a normal excretion of vitamin B_1 in the urine we may conclude that CRA is not caused by a deficiency of vitamin B .

Is chronic recurrent aphthae a manifestation of gastro-intestinal disease?

Sibley (1899) stated that the lesions of CRA were often classed as dyspeptic ulcers. After this statement by Sibley, various authors mentioned dyspepsia or other gastro-intestinal affections in connection with the disease. Tiscornia (1927), Pusey (1930), Lombard and Rochette (1935) and Silcox (1956) considered gastro-intestinal disturbances of great importance in the causation of the disorder. Kochs (1940) and Wolff (1952) considered the lesions to be analogous to gastric ulcer formation.

Oliver (1954) reported the following interesting case: A 56 year old woman suffered from intermittent indigestion with epigastric pain related to the meals. According to Oliver, she presented the typical picture of peptic ulceration. The family history was also positive for intestinal ulceration. Her father had a gastro-enterostomy for duodenal ulcer, a paternal uncle died of a perforated duodenal ulcer, while two paternal cousins had duodenal ulcers. On the other hand, a paternal grandfather died of pernicious anaemia. She developed oral and tongue ulcers 18 months previously. These were first intermittent, but later the exacerbations became so frequent that she was never entirely free. The patient could not eat with comfort and indigestion became worse. The blood count revealed no abnormality. After a barium meal, X-ray examination was negative, but gastric analysis showed a complete achlorhydria. Oliver was able to cure her condition by means of Vit. B12 injections (50 μg twice a week).

In Queries and Minor Notes (J. A. M. A. 161:300, 1956) an almost similar case to the one of Oliver (1954) was reported. The patient, a 50 year old woman, had a cholecystectomy, followed one year later by subtotal gastrectomy and gastro-enterostomy, the latter for recurrent duodenal ulcers. Within 6 weeks after the second operation, the patient lost 22 lbs (10 Kg) in weight and began to have aphthae in the mouth. According to the author of this communication, all treatment were ineffective.

Blum's patient (1954) suffered from recurrent aphthous ulcers concurrently with a duodenal ulcer. On the other hand, Truelove and Morris-Owen (1958) found that aphthous ulceration frequently accompanied ulcerative colitis. Warren and Sommers (1949), however, studied 180 cases of ulcerative colitis without mentioning the presence of oral lesions.

In our discussion on the clinical picture of aphthosis, we

mentioned that Chevallier and Moutier (1936) and Moutier and Cornet (1949) reported finding aphthae on the gastric mucosa after endoscopical examination.

In our opinion, the simultaneous finding of recurrent oral aphthae and ulcerations in other parts of the digestive tract may prove to be either CRA appearing co-incidentally with these ulcerations or manifestations of aphthosis.

Apart from ulcerative colitis, other conditions characterized by diarrhoea were described in association with oral aphthae. Van Steenis (1942) observed CRA in 5 patients out of 21 suffering from pancreatogenic diarrhoea. Examination of the faeces revealed steatorrhoea consisting mainly of neutral fat. According to Van Steenis, an important diagnostic feature was a deficiency of lipase in the duodenal juice. De Langen (1942), however, considered cases of this nature to be rare in the Netherlands. Those observed by him all previously lived in the Tropics. Cooke (1953) found aphthae in 100% of patients with non-tropical sprue.

Personal observations:

All our patients with CRA gave a negative history of gastro-intestinal disease.

An interesting fact was related by case 42, namely that her son developed CRA two years previously for the first time, after an operation for gastric ulcer. This seems to be in accordance with the description of the cases reported by Oliver (1954) and in Queries and Minor notes (1956).

No fat balance studies were done in our cases. Qualitative examination of the faeces in eight of our patients revealed nothing of importance. Except for traces of fat, no fatty acids, amylum or muscle fibres were observed.

Xylose tolerance tests performed on three of our patients gave normal results. This is evidence against a disturbance of resorption. In this test the patients were given 25 gm. of D-xylose in 500 ml. of water on an empty stomach. The amount of xylose excreted in the urine after five hours was then determined chemically. An excretion of less than 4 gm. is considered evidence of disturbed intestinal resorption. It should be noted that this test is only of value in patients with a normal kidney function.

Witts (1956), in his Sydney Watson Smith lecture to the Royal College of Physicians of Edinburgh, discussed the relationship between anaemia and the alimentary tract. Witts pointed out that recent studies of the functions of the alimentary tract in steatorrhoea and in megaloblastic anaemias, other than pernicious anaemia, have revealed disturbances of the duodenum and the small intestine. To the question which comes first, the anaemia or the alimentary tract lesion, he concluded that it is generally accepted that in pernicious anaemia and

the other megaloblastic anaemias the alimentary tract lesion appears first and that the anaemia is due to the consequent failure of absorption of essential haematinic factors, whereas in the iron-deficiency hypochromic anaemias the lesions of the alimentary tract is secondary to the lack of iron. He concluded that the present view is that iron loss caused by menorrhagia, pregnancy, or even bleeding piles, or a diet lacking in iron, leads to iron deficiency in the body as a whole, and this in turn causes the anaemia, and the poor development and loss of function of the rapidly renewed gastro-intestinal mucosa. Witts also referred to the fact that it has been long known that achlorhydria is always present in pernicious anaemia and often in iron-deficiency anaemia as well.

We already mentioned the fact that iron-deficiency anaemia was found in some of our CRA cases. To determine whether achlorhydria was present in cases of CRA we subjected eight of our patients to fractional gastric analysis.

The patient had to swallow a Ryle's tube on an empty stomach. After aspiration of the fasting gastric contents the test meal consisted out of 300 ml. of a 5% alcohol solution. Subsequent aspiration was done every 15 minutes and the contents on each occasion was collected in a test tube containing Congo Red paper. Ten test tubes were employed. If no acidity was present in the fourth tube, the patient was given lmg. of histamine subcutaneously. The acid values were determined at the Central Laboratory (Dr. Groen).

A histamine refractory achlorhydria was observed in two of the eight patients (cases 3 and 16). Low values were found in case 10. Cases 17, 19, 27, 35 and 39 showed normal gastric acidity.

Pancreatogenic diarrhoea was not observed in any of our cases. Blood and urine diastase values in 20 out of our patients were normal (between 8 and 16 units in the case of blood, and between 16 and 64 units in the case of urine).

Is chronic recurrent aphthae a disease of the blood or blood-forming organs?

Review of literature.

Mikulicz and Michelson (1892) mentioned that their patient was a chlorotic young woman.

One of the patients described by Jordan (1933) was considered to be slightly anaemic. This was a male of 33 years.

Kutzleb (1944) reported a 26 year old female with CRA in conjunction with pernicious anaemia. After treatment with liver injections the oral condition was completely cured.

Kranz (1949) and Brachmann (1954) considered anaemic looking women to be more affected.

Weichselbaum and Derbes (1957) found no evidence of anaemia in the three patients reported by them.

In his classification Marti (1941) mentioned aphthae accompanying a serious general disturbance such as pernicious anaemia. Oliver (1954), Mann (1954) and Brachmann (1954) reported excellent results in their patients after treatment with Vit. B12, while Leemans (1951) considered folic acid the best treatment of CRA. These authors, however, did not state whether their patients had signs or symptoms of a macrocytic anaemia.

In literature we found no detailed study related to the blood picture in chronic recurrent aphthae.

Personal observations:

Two of the 46 patients gave a history of anaemia (cases 6 and 13) for which they received liver injections.

The histories of these patients, as well as the fact that one may gain valuable information from the blood picture, led us to an investigation of the following:

1. Erythrocyte count.
2. Haemoglobin.
3. Diameter of Erythrocytes.
4. Leucocyte count and differential leucocyte count.
5. Thrombocyte count.
6. Erythrocyte Sedimentation Rate (ESR).
7. Serum iron content and the serum iron-binding capacity.

1. Erythrocyte count.

Normal values (Wintrobe, 1946):

Adult males 5.4 ± 0.8 million per mm^3.

Adult females 4.8 ± 0.6 million per mm^3.

The results obtained in 20 females and 11 males are recorded in table IV.

Conclusions: Slight anaemia was present in 9 of the 31 patients (4 males and 5 females).

2. Haemoglobin.

Normal values (Wintrobe, 1946):

Adult males 16.0 ± 2.0 gm per 100 cc.

Adult females 14.0 ± 2.0 gm per 100 cc.

The results obtained in 19 females and 11 males are given in table IV.

Conclusions: In the majority of patients the Hb values were within normal limits. Three out of 11 males, and 3 out of 19 females had a lowered heamoglobin.value.

3. Diameter of Erythrocytes:

Normal diameter (6.9μ - 7.8μ).

The diameter of the erythrocytes was determined in 13 patients (3 males and 10 females). No macrocytosis or microcytosis were found (see table IV).

4. Leucocyte count and differential leucocyte count.

Normal values (Sampson Wright, 1952): Total count: values above 11,000 per mm are considered as leucocytosis, while

Table IV

PAT.	Erythrocytes	Hbgm%	Diameter	ESR	Thrombocytes
1 ♀	4.400.000	13.2			
3 ♀	4.470.000	11.6	7.1		
6 ♀	3.640.000	13.4	7.2	14/33	279.000
8 ♀	4.170.000	13.3			221.000
10 ♀	4.620.000	11.8	7.1	19/48	301.000
12 ♀	4.590.000	14.7		5/12	
13 ♀	4.910.000	14.6			194.666
14 ♀	4.470.000	14.5		5/10	
16 ♀	3.500.000	13.1	7.3	7/	
17 ♀	4.420.000	14.2	7.2	4/10	222.000
19 ♀	5.050.000	14.9	7.5	15/35	240.000
20 ♀	4.280.000	14.0			212.000
24 ♀	3.020.000	-	7.5	21/49	
26 ♀	3.480.000	15.5	7.2	5/15	202.000
30 ♀	4.300.000	18.4		4/-	
31 ♀	4.400.000	13.2		7/-	
37 ♀	3.640.000	11.8		10/23	
39 ♀	5.310.000	14.4	6.9	10/25	279.000
40 ♀	4.400.000	13.8	7.8	11/27	212.000
43 ♀	4.270.000	12.6		15/39	273.000
2 ♂	4.970.000	14.8		3/7	220.000
7 ♂	4.980.000	14.2		5/15	
9 ♂	3.980.000	12.9		4/11	255.000
11 ♂	4.160.000	16.6	7.2	2/6	240.000
15 ♂	4.890.000	16.3		3/9	
18 ♂	4.450.000	13.1		4/	
27 ♂	4.300.000	14.0	7.4	2/	
32 ♂	4.220.000	14.8		11/	
35 ♂	5.450.000	10.8	6.9		
38 ♂	4.780.000	14.0		2/	
41 ♂	4.590.000	15.8			227.000

Table v

Pat		Total Wbc	Baso	Eos	Myeloc.	Youth Forms	Rod Forms	Segm. Forms	Lymph.	Mono	% Eos.
1	♀	7600	-	-	-	-	-	83	10	4	0.17
3	♀	5500	1	3	-	-	-	62	31	3	0.5
6	♀	6300	-	1	-	-	2	72	15	10	
8	♀	5000	-	1	-	-	-	58	38	3	1.0
10	♀	8400	-	1	-	-	-	74	21	4	0.5
12	♀	5600	-	4	-	-	-	62	32	2	
13	♀	4700	-	-	-	-	-	63	36	1	0.0
14	♀	5600	-	2	-	-	-	59	33	6	
16	♀	5800	-	-	-	-	1	60	35	4	1.4
17	♀	6100	-	1	-	-	-	74	24	1	0.0
19	♀	7900	-	1	-	-	-	68	29	2	0.0
20	♀	4700	-	3	-	-	-	54	39	4	9.4
24	♀	4100	-	1	-	-	-	75	23	1	1.9
26	♀	6700	-	-	-	-	1	59	37	3	1.8
30	♀	2100	1	7	-	-	-	35	54	3	
31	♀	7400	-	1	-	-	-	79	15	5	
37	♀	6600	-	7	-	-	-	57	34	2	
39	♀	8300	-	2	-	-	1	60	36	1	3.0
43	♀	6200	-	4	-	-	-	56	32	8	0.5
2	♂	5200	-	-	-	-	1	56	45	4	2.11
7	♂	6300	-	5	-	-	1	68	22	4	3.8
9	♂	3300	-	2	-	-	4	40	54	-	0.3
11	♂	3300	-	1	-	-	-	55	42	2	2.0
15	♂	4900	-	1	-	-	2	58	37	2	0.0
18	♂	4400	-	-	-	-	-	29	68	3	
27	♂	4200	1	4	-	-	-	68	26	1	
32	♂	5500	1	2	-	-	-	60	36	1	
35	♂	5300	2	1	-	-	-	68	26	3	1.0
38	♂	4600	-	3	-	-	-	52	43	2	
41	♂	5600	1	6	-	-	1	44	48	-	1.5

values below 4,000 are considered as leucopenia. Differential leucocyte count: Neutrophils 50-70%, eosinophils 1-4%, basophils 0-1%, lymphocytes 20-40%, monocytes 2-8%.

Leucocyte and differential leucocyte counts were performed on 30 patients with CRA. The results are presented in table V.

Leucocytosis was not found in any of our patients, while three (cases 9, 11 and 30) revealed a leucopenia. The differential counts revealed no "shift to the left", but a relative lymphocytosis was present in 7 of the 30.

The percentage eosinophils was determined by the method of Zollikofer in 20 patients. Eosinophilia was present in one case (case 20).

5. Thrombocytes.

In literature no uniformity of opinion exists as far as the normal thrombocyte count is concerned. Burket (1957) considers 250,000 to 500,000 per mm^3 as the normal range, while De Vries (1955) found a range of 72,000 to 313,000 per mm^3 (average 174,000) in 100 healthy males.

Thrombocyte counts in 15 of our patients with CRA ranged from 194,000 to 301,000 per mm^3 (Table IV).

6. Erythrocyte Sedimentation Rate (ESR).

Normal values (method of Westergren) according to Lubsen, Bekker and De Vries (1955): Males 1-7 mm, females 3-12 mm at the end of one hour. They consider an increased ESR in the following conditions:

a. Anaemia.

b. Conditions accompanied by the destruction of tissue e.g. fractures, after operation, after X-ray treatment of infections and malignant tumors.

c. In cases where the globulin content of the blood is increased.

d. Pregnancy.

e. Uraemia.

f. Old age.

A diminished ESR is found in polycythaemia rubra vera.

The ESR was determined in 24 of our patients (9 males and 15 females). In five of the female patients there was an increased ESR, while none of the males showed any increase (Table IV).

7. Serum iron-binding capacity.

Determination of the serum iron content. the total iron-binding capacity and the iron saturation percentage in patients may give important clues to any possible iron deficiency anaemia.

Van Beugen (1957) found the following average values in normal persons:

Serum iron content: 142γ/100 ml. (extreme values 64γ and 216γ/100 ml).

Total iron-binding capacity: 378γ/100ml.

Iron saturation percentage: 37 (extreme values 22 and 59).

Laurell (1952), cited by Van Beugen (1957), considered serum iron values below 70γ and above 220γ/100 ml. to be rare in normal males. In females the corresponding figures are 60γ and 200γ/100 ml. respectively. According to Laurell the normal serum iron content in males range between 118γ/100 ml. and 142γ/100 ml., while in females the normal range was from 90γ/100 ml. up to 123γ/100 ml.

The sum of the serum iron content and the latent iron-binding capacity constitutes the total iron-binding capacity.

The iron saturation percentage is determined as follows:

$$\frac{\text{serum iron content}}{\text{total iron-binding capacity}} \times 100$$

Van Beugen (1957) observed normal serum iron values in 4 out of 21 patients with an iron deficiency. The latter was only discovered after determination of the total iron-binding capacity and calculation of the iron saturation percentage. In such cases the total iron-binding capacity is high, while the iron saturation percentage is below the normal average.

At the Central Laboratory, Groningen (Dr. A. Groen) the serum iron content was determined (with the method of Heilmeyer and Plötner) in 13 patients with CRA (9 females and 4 males).

In 6 of these patients (4 females and 2 males) the latent iron-binding capacity was determined by means of the spectrophotometric titration method of Rath and Finch. The total iron-binding capacities and the iron saturation percentages were subsequently calculated. The results are given in the following table:

Patient no.	Sex	Serum iron	Latent iron-binding capacity	Total iron-binding capacity	Iron saturation percentage
10	♀	53γ/100ml	420γ/100ml	473γ/100ml	11
13	♀	94γ/100ml			
16	♀	123γ/100ml			
17	♀	156γ/100ml	200γ/100ml	356γ/100ml	43
19	♀	82γ/100ml			
24	♀	106γ/100ml			
26	♀	190γ/100ml	210γ/100ml	400γ/100ml	47
39	♀	141γ/100ml			
40	♀	144γ/100ml	280γ/100ml	424γ/100ml	34
11	♂	168γ/100ml	220γ/100ml	388γ/100ml	20
27	♂	250γ/100ml	330γ/100ml	580γ/100ml	43
35	♂	124γ/100ml			
41	♂	159γ/100ml			

Conclusion: Serum iron values in 13 patients revealed an iron deficiency in two (cases 10 and 19). The iron saturation percentage was determined in only one of them (case 10). The value obtained was far below normal. The serum iron content was normal in the four males, but after calculation of the iron saturation percentage in two of them, one was found to have an iron deficiency. It is evident that hypochromic anaemia are present in a number of cases with CRA. The majority, however, show a normal erythrocyte count, serum iron content and iron saturation percentage. We may therefore conclude that iron deficiency is not the etiological factor in CRA.

Is chronic recurrent aphthae a manifestation of endocrine disturbance?

Review of the literature.

Aphthous lesions in the oral cavity are not generally recognized as manifestations of endocrine disorders. On a few occasions, however, authors suggested a possible relationship between lesions of CRA and endocrine disturbance. Kirk (1899), for instance considered thyrotoxicosis an important etiological factor. Ullmann (1927) stated only that endocrine influences might play a part in the causation of the disease.

A relationship between lesions and the menses was observed by Port and Euler (1920), Tiscornia (1927), Klein (1934), Hirsekorn (1935), Prinz and Greenbaum (1939), Kochs (1940), Schmidt (1940) and Strauss (1947).

Port and Euler (1920) found that lesions were apt to occur during, or shortly after, the beginning of the menstrual period. In some women, however, they appear with such regularity before each period that these patients can exactly predict the time of its onset. Similar views were expressed by Tiscornia (1927), who considered the relationship to the menses to be a result of malfunction of the ovaries, Klein (1934) and Schmidt (1940).

Kochs (1940) observed two multiparae who could tell exactly when they were pregnant, even before cessation of the menses, from the fact that lesions did not make their usual monthly appearance.

Misch (1914), cited by Klein (1934) found that after complete cessation of the menses, the lesions completely disappeared. In this connection, Klein (1934), also referred to a patient of Davies (1898), who suffered so severely from CRA that a decision was taken to remove the adnexa. At the operation cysts were found in the ovaries. After the operation the patient was completely cured of the oral lesions.

Hirsekorn (1935) found that CRA was especially liable to affect woman during the various expressions of their sex life, puberty, menstruation, pregnancy, etc. According to Hirsekorn, however, these factors predispose the individual to the action of certain bacteria.

A different time-relationship to the menses was observed by Strauss (1947) in a group of 45 patients. In 43, the oral lesions appeared 16 days prior to the onset of the next menstrual period. In the other two patients the lesions developed, 18 and 23 days, respectively, before the next period.

Vest (1957) considered hormonal disturbances in the causation of CRA, while a casual statement was made by Nieddu Del Rio (1958) to the effect that the disease is sometimes observed during pregnancy.

A difference in incidence between males and females after middle age was observed by Sircus et al. (1957). In males the disease tends to burn out after the age of 50, whereas first attacks were not uncommon in women of the menopausal age-group. From this observation Sircus et al. drew the following conclusion: "That there may be important endocrine factors in the resistance of the individual to mucosal ulceration of this kind is suggested not only by this menopausal group of cases, but also by the observation, repeated and confirmed in several of our female patients, though not in all, that the ulcers tended to disappear entirely throughout pregnancy, only to return in the post-partum period".

Personal observations.

Outward signs of endocrine disturbance.

None of the 46 patients with CRA in our series revealed the presence of external signs that could be attributed to any endocrine disorder.

Relationship of lesions to the menstrual period.

In one of the female subjects in our series (case 36) the menses had not yet begun, while three of them (cases 3, 6 and 42) were already in the climacterium. Of the latter, only case 6 could relate a previous relationship between the lesions and the menstrual period. The lesions always developed during this period. Her periods were otherwise regular and never at any time did she suffer from dysmenorrhoea, menorrhagia or amenorrhoea. Case 3 stated that she suffered from irregularity, dysmenorrhoea and menorrhagia. Her periods lasted for from 7 to 8 days, while at the age of 26 the menses ceased for a whole year. Case 42 gave a history of very irregular periods, but was otherwise normal.

The remaining 27 females in our series were all in the reproductive period of their lives. Fifteen of them related completely normal periods, while three of the fifteen (cases 19, 26 and 31) observed a relationship between the outbreaks of lesions and the periods. Cases 19 and 31 found that the lesions appeared a few days before the onset of each period, while in case 26 the aphthae appeared during menstruation.

Twelve of the 27 cases in the reproductive period suffered from menstrual disorders. In four of them (cases 8, 16, 34

and 43), the periods were completely irregular. Menorrhagia was a feature in cases 13, 17, 34 and 39, while dysmenorrhoea was a complaint of cases 10, 13, 14, 17, 24 and 34.

Case 8, who gave a history of a normal menstrual cycle, observed that lesions completely disappeared during both her pregnancies, only to return after the confinements.

Conclusion.

If we consider the findings reported in literature as well as our own observations, it becomes obvious that in some case of CRA a definite relationship exists between attacks and the menstrual periods. The fact that the majority (15 out of 27) of our female patients had completely normal menstrual histories, however, makes it unlikely for this to be the real cause of the lesions. In our opinion, therefore, any effect of gonadal origin on CRA must be regarded as of secondary nature (Andermatt 1950; Schreus et al. 1953; Scholdgen 1955; Boorsma 1956; Zeiser 1957) we gather that the oral mucosa in women during the reproductive period is subject to cyclical changes under the influence of the sex hormones. These changes can be studied with the aid of oral smears, as suggested by Papanicolaou (1933) in the case of vaginal smears. These authors found that the mucosal epithelium is characterized by marked "keratinization" and the presence of many pyknotic nuclei during the follicular phase of the menstrual cylce. In the luteal phase, exfoliation of the epithelial cells dominates. The cells are clumped together in irregular groups while their edges show curling and folding. During the menstrual periods, the cells are pale and stain basophilic with the presence of large nuclei, while leucocytosis may be a prominent feature. From these findings we may infer that a diminished production of oestrogen leads to an increased exfoliation in the premenstrual and menstrual phases. This decreased "keratinization" then leaves the mucosa subject to injurious influences. In this way, it may be possible to explain the aese with which lesions of CRA appear in these phases (premenstrual and menstrual) of the cycle. To this one can add the observation of Mühlemann (1952) that a diminished production of oestrogenic hormone leads to a disturbed peripheral circulation which in turn leaves the gingiva more susceptible to infection. In this respect, it should be remembered that skin and mucosal infections, such as labial herpes and acne vulgaris, are often found in conjunction with the menstrual period.

The secondary part played by menstruation in the causation of CRA can finally be attributed to the mental stress which often accompanies this burden of women.

The thyroid gland and chronic recurrent aphthae.

The finding of Kirk (1899) that CRA accompanies hyperthyroidism has not been confirmed by other authors.

None of our patients revealed any signs or symptoms that

could suggest the possibility of either a hyper or hypo function of the thyroid gland.

The basal metabolic rate (BMR) was determined at the Department of Internal Medicine, Groningen University, in 6 of our CRA patients. The results were as follows:

Patient no.	Sex	Age	Weight	Length	BMR
1	♀	22	55 kg.	171 cm	0%
3	♀	55	77 kg.	153 cm	0%
16	♀	27	48 kg.	169 cm	+2%
17	♀	35	59 kg.	166 cm	+1%
19	♀	29	62 kg.	165 cm	+2%
39	♀	34	84.5 kg.	169 cm	-2%

According to Lips (1953), the normal BMR ranges between -10% and +15%. The results obtained from the six patients are therefore evidence against a disturbance of the thyroid gland as a possible etiological factor in chronic recurrent aphthae.

In addition, blood cholesterol determinations were performed on 15 patients at the Central Laboratory (Dr. A. Groen).

The results are given in the following table:

Patient no.	Sex	Age	Total cholesterol	% Cholesterol esters
3	♀	55	297.9 mg.%	68%
6	♀	53	266.7 mg.%	73%
7	♂	39	244.0 mg.%	66%
9	♂	13	300.0 mg.%	62%
10	♀	46	184.5 mg.%	71%
11	♂	42	236.7 mg.%	67%
13	♀	32	224.5 mg.%	69%
16	♀	28	176.0 mg.%	76%
17	♀	35	155.6 mg.%	71%
19	♀	29	217.8 mg.%	61%
24	♀	36	192.0 mg.%	71%
26	♀	20	165.0 mg.%	67%
27	♂	32	232.6 mg.%	57%
35	♂	34	186.0 mg.%	69%
39	♀	34	240.0 mg.%	65%

Normal serum cholesterol values: Total cholesterol 150-250 mg%
Cholesterol esters 60% - 70% of total cholesterol

(The method of Liebermann-Burchard was employed in the determination of the serum cholesterol in this study).

An increase in the total cholesterol value of serum is found in myxoedema, while a decrease is found in 40% of cases with hyperthyroidism (Verschure, 1953).

In our patients three (cases 3, 6 and 9) showed increased total cholesterol values. No decrease was observed in any of our patients.

The normal serum cholesterol values observed in 12 out of 15 patients are further evidence against thyroid dysfunction as a possible etiological factor in CRA.

Suprarenal function.

More than 20 years ago (in 1935) Koster and Heeres sug-

gested a diagnosis of Cushing's disease in one of our patients (case 3). This made us curious to know whether any relationship exists between disturbed function of the suprarenal gland and CRA.

Physical examination of this patient (case 3) provided us with no evidence in favour of disturbed pituitary or suprarenal function.

Chemical determinations of hormones in the urine may provide us with valuable facts relating the endocrine status of patients.

17-Ketosteroids. A determination of the 17-Ketosteroids (17-ketos) in the urine may reveal disturbances in the suprarenal cortex and gonads. High values are found in hyperplasia and tumors of the cortex.

Normal values (Huis in 't Veld and Louwerens, 1958):

Normal values (Huis in 't Veld and Louwerens, 1958):
Females (15-50 yrs): 5.0 -17.5 mg/24 hours (average 10.0 mg)
Males (15-50 yrs): 10.0 -33.5 mg/24 hours (average 20.0 mg)
Females (> 50 yrs): 1.5-11.5 mg/24 hours (average 5.0 mg)
Males (> 50 yrs): 5.0-15.0 mg/24 hours (average 9.0 mg)

The 17-ketosteroid excretion in the urine is changed in liver disease, hyperthyroidism, hypothyroidism, diabetes, carcinoma, rheumatism and hypertension, infectious diseases etc. (Lubsen, Bekker and De Vries, 1955).

17-Hydroxycorticosteroids.

In Addison's disease and pituitary destruction low values of 17-hydroxycorticosteroids are found in the urine. In the presence of tumors and hyperplasia of the suprarenal cortex excretion of 17-hydroxys may be increased.

Normal values (Huis in 't Veld and Louwerens, 1958):
Females 4.0 - 16.0 mg/24 hours (average 10.0 mg.)
Males 6.0 - 24.0 mg/24 hours (average 14.5 mg.)

Oestrogenic substances.

The excretion of oestrogenic substances in the urine may be increased in ovarial and suprarenal tumors. Tumors of the testes may give rise to increased excretion in males. Low values in adult females before the menopause are evidence of a decreased function of the ovaries. The amount excreted varies considerably in different individuals as well as in the same individual. According to Lubsen, Bekker and De Vries (1955) only gross deviations from the normal have any clinical importance.

Normal values (Huis in 't Veld and Louwerens, 1958):
Females (from puberty up to the time of the menopause): 75 - 500 I. U. /24 hours
Females in the menopause : 20 - 100 I. U. /24 hours
Males : 20 - 300 I. U. /24 hours

Gonadotrophins.

High values of gonadotrophins are observed in hyperfunction of the pituitary gland. Low values are observed where the amount of oestrogenic substances in the blood are diminished

as a result of disease in the ovaries or in the climacterium. The excretion of follicle stimulating hormone (FSH) by the pituitary is controled by the amount of oestrogenic substances produced by the ovaries. In the absence of the latter the amount of FSH excreted by the pituitary is increased.

Normal values (Huis in 't Veld and Louwerens, 1958):
Females (between the time of puberty and the menopause): < 10 U. /24 hours.
Females (after the menopause): >20 and <150 U. /24 hours
Males: < 10 U. /24 hours.

Pregnandiol.

The presence of pregnandiol in the urine is proof that progesterone is produced by the corpus luteum.

Normal values (Huis in 't Veld and Louwerens (1958):
Women in first half of menstrual cycle: 3 mg. /24 hours
Women in second half of menstrual cycle: 3-8 mg. /24 hours.

The urinary steroids were determined in ten patients with CRA (9 females and 1 male) at the Central Laboratory, Groningen (Dr. A. Groen).

The results are given in the following table:

Patient No.	Sex	Age	Urine 17-Ketosteriods. (mg/24 hours)	Urine 17-Hydroxycorticosteroids (mg/24 hours)	Oestrogenic Substances. (I.U./24 hours)	Gonadotrophins (Mouse Units in 24 hours)	Pregnandiol. (mg/24 hrs.)
1	♀	22	16.6	9.1	24-48	11	
3	♀	55	11.6	20.9			5.8
13	♀	32	6.8	5.4			5.4
16	♀	28	13.1	4.6	24	6	4.6
17	♀	35	13.2	25.8	< 24		
19	♀	29	18.8	8.3	48-88	6	16.0
24	♀	36	21.0	12.9			5.1
26	♀	20	9.7	5.4			20.5
39	♀	34	12.4	8.0	48-88		- 4.5
11	♂	42	13.9	7.5			

Discussion. 17-Ketos determined in 9 patients with CRA revealed normal values.

17-Hydroxys were slightly increased in 2 of the 9 patients. This included Case 3 and Case 17. Normal values were recorded in the other 7. Oestrogenic substances were determined in 5 of the female patients. Low values were recorded in 2 cases. In these 3 the amount of gonadotrophins in the urine was determined. Case 1 had a slight increase. The other two gave normal values. The pregnandiol valued in 7 females gave increased values in 2 cases (both of them were examined during the second half of the menstrual cycle.)

Intravenous ACTH test (Thorn test).

The intramuscular ACTH test described by Thorn and associates (1948) is based on the fact that administration of ACTH stimulates the adrenal cortex. In response to this stimulation normal persons react by showing a fall in the blood eosinophil count of from 80 to 100%, and a mean rise in urine 17-ketosteroids of 4.4 mg in 24 hours. The usefulness of the intramuscular test was limited on account of a significant loss of activity suffered by some ACTH preparations when injected in this way. Thorn and co-workers (1953), however, have shown that this difficulty could be overcome by intravenous administration of ACTH. In the meantime, Reddy, Jenkins and Thorn (1952) showed that the determination of the 17-hydroxycorticosteroid excretion in urine after administration of ACTH was a sensitive index of adrenal function.

In five of our patients (case 3, 16, 17. 19 and 39) the intravenous ACTH test was done. The same procedure was adopted as described by Thorn et al. (1953). The steroid excretion was determined in a 24 hour specimen of urine. After this the patient received 25 units of ACTH (corticotrophine, "Organon") by intravenous drip over a period of eight hours. The ACTH was dissolved in 500 ml. 5% dextrose solution. Before the drip was started the number of eosinophils was counted. Repeated counts were made subsequently every 2 hours for 8 hours. A second specimen of urine was collected after 24 hours, including the period of the infusion and was analysed for steroids.

Thorn et al. (1948) stated that a fall in eosinophils of 50% or more of the initial level indicates a satisfactory adrenal cortical response and in all probability eliminates the possibility of adrenal cortical insufficiency.

In normal persons, these authors found a rise of 0.9 to 19 mg. 17-ketosteroids in a 24 hour specimen after ACTH infusion. The 17-hydroxys were increased by about 10 to 20 mg.

The results in our patients are given in table VI on page 109.

Glucose tolerance test.

A flat blood sugar curve is found in Addison's disease and in disturbed intestinal resorption. A high carbohydrate diet a few days prior to the test may also give rise to a flat curve.

The normal fasting blood sugar value is 60-90 mg/100 ml.

After oral administration of 1 gm. of glucose per Kg. of bodyweight (dissolved in 250 ml. of water) the blood sugar values are recorded every 30 minutes. In normal persons there are a maximum rise in the blood sugar value within 60 minutes, which is not higher than 180 mg.%. Within two hours the original fasting value is again reached. At the same time no glucose is excreted in the urine.

Patient No.	Sex.	Age	17-ketos before ACTH infusion	17-ketos after ACTH infusion	17-hydroxys before ACTH infusion	17-hydroxys after ACTH infusion	Eosinophil count before ACTH infusion	Eosinophils 2 hours after infusion started	Eosinophils 4 hours after infusion started	Eosinophils 6 hours after infusion started
3	♀	55	12.4 mg.	11.6 mg.	8.3 mg.	20.9 mg.	242	110	77	44
16	♀	28	13.1 mg.	18.5 mg.	4.6 mg.	17.2 mg.	33	22	0	0
17	♀	35	8.2 mg.	13.2 mg.	4.6 mg.	25.8 mg.	33	33	22	0
19	♀	29	18.8 mg.	20.5 mg.	8.3 mg.	9.2 mg	165	77	22	0
39	♀	34	12.4 mg.	18.7 mg.	8.4 mg.	21.2 mg.	451	253	81	22

Conclusions: With the aid of the intravenous ACTH test no disturbed function of the suprarenal gland could be found in 5 patients with CRA.

Glucose tolerance tests performed on 5 of our CRA patients (cases 3, 16, 17, 19 and 39) revealed normal blood sugar curves.

Urinalysis in cases of chronic recurrent aphthae.

Qualitative urine analysis of 21 cases with chronic recurrent aphthae gave negative results. In none of the cases was albumin, glucose or urobilin found. Except for the presence of an occasional leucocyte or erythrocyte examination of the urine sediment revealed nothing of importance.

Liver function in chronic recurrent aphthae.

To gain an impression of the liver function in cases with CRA the results of a number of tests that are usually employed for this purpose are given in the following table.

Pat. no.	Alk. phosphatase (N. Adults 5-10 units)	Bilirubin direct.	Bilirubin indirect. (N. 0.2-1.5)	Thymol turbidity test (N. 2-5 Units)	Urobilin in urine
3	7.4	-	0.9	2.8	
7	7.3	-	0.9	4.6	Trace
10	9.0	-	1.4	3.8	+
16	7.3	-	1.5	5.0	-
17	3.9	-	0.9	3.2	-
24	5.6	-	0.9	5.8	-
26	5.5	-	1.6	5.0	Trace
27	6.5	-	1.5	2.1	-
39	7.9	-	0.9	5.0	-
41	6.7	-	1.2	1.8	-

(Alkaline phophatase was determined according to the method of King and Armstrong).

Conclusion: Liver function tests in ten patients with chronic recurrent aphthae gave normal values. We may therefore assume that CRA is not due to a disturbance in liver function.

Is chronic recurrent aphthae a manifestation of allergy?

Introduction.

Attention was first directed to the phenomenon of hypersensitiveness by the observations of Portier and Richet in 1902. In a study of the toxic properties of Actinaria, Richet and his of the tentacles of this sea anemone into dogs, definite symptoms were so severe that death ensued. To this altered reaction shown by the dogs, Richet applied the name of anaphylaxis.

Shortly after the discovery of Portier and Richet, Arthus (1903), while studying the effects of successive injections of foreign serum into rabbits, observed that with the first injection no sign of injury occurred, but that with subsequent injections of the same serum a marked local reaction developed.

This reaction or local anaphylaxis has been named the Arthus phenomenon.

In 1905, Von Pirquet and Schick correlated their observations made on serum sickness with the findings of Richet and Arthus. For the acquired state of hypersensitiveness, Von Pirquet coined the name allergy, while the foreign substance provoking the reaction was disignated allergen. Von Pirquet and Schick emphasized that the reaction was due to a meeting between allergens and specific antibodies against these allergens, present in the organism.

Dale and Laidlaw (1919) observed a strong resemblance between the anaphylactic state, as observed by Richet, and acute histamin poisoning.

Prausnitz and Küstner (1921) were able to demonstrate the passive transfer of hypersensitivity from one person to the other.

A more exact definition of allergy was given by Bloch (1929) and reads as follows: "Allergy is that state which has as its basis the property of certain groups of cells (organs) of the living organism to react in a specific manner when brought in contact with a substance which is, as far as is known, foreign to the organ or cells; the characteristic of this specific pathologic process lies in the fact that it is caused by the reaction of this exogenous substance with its specific cellular fixed antibody. The basis and the essence of allergy is the ability of the living cell to react with the production of specific antibodies to the stimulus of foreign substances, which are therefore called antigens, as well as the fact that the contact of the antigen with its specific cellular fixed antibody causes a disturbance of cellular life which usually results in an inflammatory reaction".

The phenomenon of allergy bears a close relationship to many aspects of immunity. According to Fairbrother (1946) it differs, however, from the ordinary immunological reactions in that the reaction can only be demonstrated in the living tissues and, also, in that the resistance of susceptible individuals is not apparently increased by the injection of the foreign substance, but the tissues are rendered highly sensitive to subsequent inoculations of the same substance.

Payling Wright (1955) stated that anaphylaxis, both in its general form (Richet Phenomenon and its local form (Arthus Phenomenon) had become recognized as an immunological reaction to inoculation with allergens. The phenomenon had been observed - though elicited with different degrees of difficulty - in all the common species of laboratory mammal; while each possessed a distinctive clinical syndrome. The condition of anaphylactic hypersensitivity could sometimes be converted into one of raised resistance by further appropriately small inoculations of the antigen. The idea had thus emerged that hypersensitivity and resistance are intimately associated, and

that immunologically the latter may differ from the former mainly in the quantitative nature of the antibody response.

Antigens or allergens can be defined as substances which lead to the formation of antibodies, or substances, which can react with antibodies. They are mostly proteins and possess a high molecular weight (Van Vloten, 1950). That substances other than proteins may act as antigens was made possible by the work of Landsteiner (1946). Landsteiner found that if a substance such as sulphanilic acid is coupled to a protein by the process of diazotization the immunological specificity of the original protein is gradually lost and a new specificity to the attached substance is progressively acquired. In this way, an explanation can be afforded for the allergic manifestations encountered with drugs such as aspirin.

A variety of antibodies may be formed in response to the action of an antigen. Thus one finds for instance: antitoxins, lysins, opsonins, agglutinins, precipitins and virus neutralizing antibodies (Ruys, 1950).

Since many substances which may act as allergens are also known for their toxic effects on the organism, it is necessary to make a clear distinction between toxication and allergy. Attempts at differentiating allergic from toxic reactions of the skin were made by Darier and Tzanck (1930) and Miescher (1938). The findings of these authors were reviewed by Van Vloten (1950).

Darier and Tzanck (1930) listed the differences between allergy and toxication as follows:

	Toxication
Etiology	
Harmful substance is infra-toxic, or an antigen or a physical agent	Harmful substance is a poison
Harmful dose shows a marked individual variation	Harmful dose equal for all
Often increased action on increased dosage	Action proportionate to the dose
Intolerance sometimes appears paradoxical	Toxication appears logical
Pathological Anatomy	
Equal reactions to various substances, general and local	Specific lesions depends on the substance, the concentration, the duration of application
Transient lesions showing spontaneous regression	Destructive lesions after adequate dosage and time of action
Pathogenesis	
Active biological reaction Disturbance of physical balance (anaphylaxis, allergy, flocculation, colloidoclasia)	Passive course of the process Chemical process?

Clinical picture.	
Depends on individual	Depends on cause
Influenced by condition of body (Neurovegetative and endocrine system, local sensitivity)	Site affected has additional influence.
Development	
Critical	Progressive
If healing takes place, it is immediate, total and definite	Heals with after effects
Usually an incubation period	No incubation period
Humoral Phenomena	
Identical in the various conditions e. g. eosinophilia	Depends on organ affected
Method of Investigation	
Biological tests: Skin reaction, passive transfer	Search for toxic substance
Treatment	
Adaptation by means of vaccination, desensitisation. anti-shock etc.	Detoxication: antidote, part played by routes of excretion from body

According to Miescher (1938) the differentiation between allergic and toxic reactions of the skin are based on the following:

Allergy	Toxication
Clinical findings	
Characterized by formation of papules and vesicles on a reddened base. Not demarcated; reaction spreads to surrounding tissue.	Shallow appearance of lesions Lesions sharply demarcated from normal skin.
Histology	
Widening of basal layer. Spongiosis; in malpighian layer. Lymphocytes and polymorphonuclears present. No necrosis. Spongiosis, however, not pathognomonic for the allergic eczematous reaction. May find transitional forms, when differentiation from toxic reaction becomes impossible	No constant features. One finds a pure toxic and a mixed type. In pure toxic reaction: Necrosis with loss of staining properties. In the cutis a perivascular and perifollicular oedema. No spongiosis. Necrotic tissue sharply demarcated from healthy tissue. In mixed type spongiosis present
Functional	
Reaction with low concentrations of offending substance (In persons with slight sensitivity concentration necessary to provoke allergic reaction may approach concentration needed for toxic reaction).	Higher concentrations required to provoke reaction (Dependant on fluctuations within certain limits. Substances may be obligatory toxic or facultatively toxic).

Ramirez (1938) divided allergic phenomena in the oral cavity similarly as those of the skin, namely in endogenous and exogenous or contact allergy.

Burket (1957) made a distinction between true allergic manifestations and those due to hypersensitivity. According to him, the altered response of a sensitized individual to animal danders, certain foods, protein substances or plant pollens constitute examples of true allergy, whereas the altered response of certain individuals to drugs, contact with metals, actinic radiations, organic substances or even thermal changes are examples of hypersensitivity. Burket considers the oral mucosa to be frequently the side of both these manifestations.

Van Vloten (1950) stated that antibodies can be found in the circulation as a part of the gammaglobulin content of the serum proteins or may be fixed to tissue cells. He further emphasized that in the case of allergic skin manifestations it is assumed that the sessile antibodies are fixed to cells of the skin. This especially applies to sensitisation by means of external medication, where it is conceivable that the antibodies are fixed to the epidermis cells and that circulating antibodies may be completely absent. In this connection Van Vloten pointed out that a negative Prausnitz-Küstner reaction, where one works with blood serum, therefore does not necessarily rule out the allergic nature of a disease.

Various theories concerning the origin of antibodies have been made in the past. As was emphasized by Keuning and Van der Slikke (1950), the lymphocyte and plasma cell received special attention as possible producers. Ehrich and co-workers (1945), after a series of investigations, arrived at the conclusion that the lymphocyte was responsible for the formation of antibodies. The experiments of Fagraeus (1948), Keuning and Van der Slikke (1950) and Thorbecke (1954), however, have shown that this function must be attributed to the immature plasma cell. The experiments of Thorbecke (1954) also suggested the possibility that all gamma globulins are to be considered immune globulins.

Literature dealing mainly with chronic recurrent aphthae as a manifestation of allergy.

As early as 1866, Bohn stated that certain patients demonstrated aphthae which he related to their ingestion of fatty pastries. Interestingly enough, he considered the etiology of these aphthae to be similar to that of urticaria.

A patient, reported by Brubacher (1926), ascribed the cause of his aphthae to the use of Odol. After replacing this remedy by tincture of Ratannhae and tincture of Myrrh as a mouthwash, he was completely cured of aphthae. Brubacher, however, did not consider Odol to be the cause of the condition because the patient had suffered attacks before Odol appeared

on the market. Brubacher, as additional reason for rejecting Odol, recorded that another patient suffering from the same complaint had never applied this remedy. That Odol might have been a contributing factor is possible but, apart from the objections raised by Brubacher, one must of course consider two other factors: In the first place, a possibility exists that the tincture of Ratanhae and tincture of Myrrh may have had a beneficial influence; in the second place, the disappearance of lesions from the patient concerned coincided with the age when the disease tended to burn out in the case of males, according to Sircus et al. (1957).

After a series of observations made on patients suffering from chronic recurrent aphthae, Beecher (1928) concluded that CRA must be an allergic disease. He mentioned three cases where ommission of certain foodstuffs resulted in complete remission, only for the disease to reappear after these foodstuffs were added to the diet. One of his cases reacted to cocoa, another one to wheat and the third to cocoa, wheat and cabbage.

Basch (1928) considered aetherial oils often present in mouthwashes (peppermint, aniseed, eugenol and eucalyptol) to be important predisposing causes for the occurrence of lesions. Basch found that he could cure patients with CRA when these offending substances were ommitted, only to find a rapid reappearance of aphthae when they were used again.

Ochsenius (1931), Port (1932, 1933, 1934) and Haas (1936) supported the observations of Basch (1928). Ochsenius considered menthol pastiles an important cause. Port mentioned eucalyptus bonbons, menthol pastiles and certain toothpastes, but added one condition: that the sufferers usually are neutropathic individuals. He also observed aphthae after zinc oxide and eugenol were used and was convinced that these medicaments should be discarded from dental usage. Haas again, devoted attention to menthol and eucalyptol in the etiology of aphthae. According to him, these substances are often used in the treatment of colds and to combat halitosis.

Weinberger (1933b) described exogenous and endogenous forms of aphthae. Apart from mechanical, chemical and bacterial agents, Weinberger regarded allergy as the most important cause of chronic recurrent aphthae. He found that the exogenous formed of aphthae were due to the ingestion of certain foodstuffs.

Rattner (1936) observed the appearance of aphthae in the mouth as a result of sensitization caused by base plate material. According to him, allergic reactions in the oral cavity were of an inflammatory nature. The clinical picture varies from a diffuse catarrhal stomatitis to discrete erosive or ulcerative (aphthous) lesions.

Bottyan (1937) regards aphthae as of allergic origin. As support for this view, Bottyan referred to the histological picture of aphthae, according to him a fibrinous inflammation

Here he cited Rössle who stated that fibrinous inflammation is the histological expression of a hyperergic reaction. Bottyan also observed a disturbance of sodium chloride metabolism in cases of CRA. This consisted of sodium chloride retention and a diminished MacClure-Aldrich resorption time (in the method of Aldrich and MacClure, the time is measured in which an intracutanous wheal, caused by the injection of 0.2 - 0.8 cc of a 4% solution of sodium chloride, disappears). Bottyan regarded this disturbance in the sodium chloride balance of the body as a further proof of the allergic nature of the disease. In the final place, Bottyan referred to Haag (1935) who demonstrated a hypersensitivity to histamine in cases of aphthous stomatitis. Bottyan verified this finding in one patient, but owing to the severity of the reaction caused by the histamine injection, he decided not to repeat it.

Landgraf (1933), in a study of 10 patients suffering from CRA, found a diminished sodium chloride excretion in four. He concluded that, in a definite number of patients suffering from the disease, this was due to a transudative-exudative diathesis as the results of an extra-renal disturbance of sodium chloride metabolism.

Ramirez (1938) recorded that "among the more commonly encountered oral lesions generally accepted as being frequently of allergic origin I might mention stomatitis, glossitis, certain types of gingivitis, herpes labialis, angioneurotic oedema and persistent itching of the roof of the mouth. Under stomatitis there are, of course, a great many varieties from the stomatitis following the ingestion of drugs to the aphthous form with disseminated ulceration".

Prinz and Greenbaum (1939) were of the opinion that at least some cases of CRA are due to allergy.

Thoma (1944, 1954), who discussed CRA under the title of habitual aphthosis, considered the disease to be of allergic nature. Similar views were expressed by Harkavy (1948) and Cheney (1948).

No experimental evidence was given by Ramirez (1938), Prinz and Greenbaum (1939), Harkavy (1948), Cheney (1948) and Thoma (1944, 1954) to support their respective views.

Tomatoes were considered the cause of outbreaks in cases observed by Pusey (1930) and Weisshaar (1939).

One of the patients of Heinemann and Anderson (1945), a male 35 years of age, who suffered continuously from lesions for ten years, was found to be sensitive to eggs. Complete recovery followed when eggs were omitted from the patient's diet.

In a histological investigation of aphthae, Frech (1945) compared his findings to the changes observed in the artificially formed hyperergic inflammation as described by Gerlach (1923) and he concluded that common clinical and histological features exist.

Cheese seemed to be especially responsible in the cases observed by Pereira-D' Oliveira (1948). This author also observed good results in one patient after treatment with antistine.

Kranz (1949) mentions the case of a woman who for years suffered periodical outbreaks of aphthae in the upper buccal sulcus. After removal of Walkhoff' s iodoform root canal paste from the two upper central incisors and replacement by zinc chloride paste, the condition was completely cured.

Cahn (1950) believed that CRA was caused by the herpes simplex virus, which remains dormant in the body cells, only to be reactivated by certain stimuli from time to time - such as allergy following the ingestion of certain foods.

Chevallier and Moutier (1936) and Moutier and Cornet (1949; 1951), who observed oral aphthae in conjunction with aphthae in the stomach, considered the lesions to be of allergic origin because of the frequent association with allergic conditions on the skin (urticaria, prurigo, angioneurotic oedema) and the successful treatment of the lesions with antihistamines. Moutier and Cornet (1951) found that the diagnosis was often facilitated by a possitive history, obtained from the patients. Offending foodstuffs included strawberries, melons, peaches, chocolate, bread and game.

Aphthae after parenteral injections of penicillin were recorded by Bumiller (1952). He found that the lesions rapidly disappeared after treatment with vitamins. It is, however, difficult for us to evaluate this case of Bumiller. From his discription one can infer either a sensitivity to penicillin or a vitamin deficiency.

Kremer (1952) coincidentally found that some of his patients who suffered from asthma also had aphthae in the mouth. From this he inferred that aphthae were manifestations of allergy. Treatment with phenergan, theporine and other anti-histamines proved to be effective against the oral lesions. According to Kremer, the excellent results obtained in cases of CRA after repeated smallpox vaccinations (as mentioned by various authors) are based on the concept of hetero-allergy as postulated by Dujardin and Duprez. The latter found that tuberculosis and tuberculin reactions, syphilis, small-pox and small-pox vaccination, measles, scarlet fever etc. create a state within the body which more than before, causes either an increased or a diminished sensitivity against other substances. In his allergy practice, Kremer occasionally found that asthma disappeared after smallpox vaccination, while on other occasions the latter caused an aggravation of the condition.

Sugerman (1950) observed a patient who developed lesions in the mouth after eating mint chewing gum, while Archangeli (1954) recorded a case he considered to be due to metal and acrylic allergy. Patch tests were positive for both dental silver

alloy and acrylic resin. The partial acrylic denture and the silver alloy crowns present in the patient's mouth were replaced by other materials. This resulted in a complete remission of the lesions.

Benzuly (1956) wrote that "hypersensitive reactions to food are known to produce recurrent aphthae. Walnuts are especially incriminated although it has been found that other foodstuffs may also be associated with this trigger mechanism. Oatmeal and chocolate are frequent producers of these outbreaks".

Tuft and Ettelson (1956) recorded a case of CRA resulting from an allergy to weak organic acids, especially citric and acetic acid. Elimination from the diet of foodstuffs containing these substances resulted in the prompt disappearance of the lesions, only to return again when the patient ate these foods. The possibility that organic acids might be the cause of the condition gained further support when Moskowitz (1958) expressed the following: "In my experience most canker sores are allergic in origin. These patients are sensitive to acids in the diet, particularly ascorbic acid and acetic acid. The sores disappear and will not return if these patients will eliminate the following from their diets: vinegar, mayonnaise, sour pickles, ketchup, mustard, sauerkraut, lemons, oranges, tomatoes, pineapple, grape fruit, limes, sour grapes and all berries".

Stark et al. (1954) found that the histories of many of their clinic patients, suffering from CRA, indicated food allergy to be the cause of the lesions, but the use of elimination diets, skin tests, and antihistamines had no consistent effect on the frequency of recurrences and offered no support for their hypothesis.

In an attempt to prove or disprove the etiological relationship of organic acids – as suggested by Tuft and Ettelson (1956)- Kutscher and associates (1958) subjected 10 patients (3 males and 7 females), suffering from CRA, to tests incorporating acetic acid (in the form of vinegar), citric acid. sodium citrate and ascorbic acid. They concluded that allergy of a contact nature to citric acid, or any of the other related compounds tested, was not an etiological factor in the lesions under consideration.

In four female patients, observed by Rosenstein and Ziskin (1942), examination for hypersensitivity in the allergy clinic proved negative. No details were given by Rosenstein and Ziskin on the procedures adopted for this investigation.

Extensive intradermal food test studies on patients suffering from CRA were undertaken by Barbash and co-workers (1958). They found no evidence that the condition in their patients had any relationship to food allergy.

The good results reported (Pereira D' Oliveira 1948; Moutier and Cornet 1949; Daniel 1951; Kremer 1952) after treatment with antihistamines, could not be confirmed by Zegarelli, Silvers

and Kutscher (1953). The latter found that treatment with antihistamines (pyribenzamine, thenylene and di-paralene) relieved the pain while treatment was still in progress, but that no permanent cure could be effected.

Owen (1957) observed rapid healing of lesions with oral antihistamine traetment in the form of "Ambodryl" and concluded with the following words: "Perhaps the cure suggests the cause; it may at least point the way for further investigation."

Personal observations.

Nine of the 46 patients with CRA gave a positive history of allergy. Five suffered from eczema, three from bronchial asthma and one from hay fever. In two of the nine there were a family history of allergy. In case 21, who suffered from eczema as a child, there was a history of a brother and an aunt suffering from bronchial asthma, while case 27, who suffers from eczema, related that this condition was a common complaint in his family.

In 12 of our patients without personal histories of allergy, there were, however, positive histories in close relatives.

Skin tests for allergy were done on six of our patients (cases 2, 3, 6, 11, 20 and 29) with CRA by Dr. K. de Vries at the Allergy Clinic, Dept. of Internal Medicine, Groningen. The allergens employed in these cutaneous and intra-cutaneous tests included those which are known to be common offenders, such as house dust, yeasts, bacteria, weeds, pollens, hairs, feathers, cheese, eggs, milk, fish etc. The results of the tests were negative.

Blood eosinophilia are often found in allergic conditions. According to Zegarelli and co-workers (1953) an increase above 4% constitutes eosinophilia. The percentage eosinophils was determined in 20 of our CRA patients (see table V). Eosinophilia was present in only one case (case 20 with 9.4%). We may therefore conclude that eosinophilia is not a feature of CRA.

It is known that γ-globulin in the serum contains antibodies formed in responce to certain infections (Keuning, 1952; Thorbecke, 1954). Van der Kwast (1957) suggested, that the presence of numerous plasma cells in the hyperplastic gingivae of epileptics treated with dilantin sodium and the accompanying hypergamma-globinaemia, may be the result of an allergic reaction to this medicament.

The gamma globulin content of the sera of 15 patients with CRA was determined by means of paper electrophoresis at the Central Laboratory (Dr. A. Groen). The same technique as employed in Van de Kwast's study (1957) was used. In a similar way the total protein content of the serum was determined with the method of Weichselbaum (1948). The control group of Van der Kwast (1957) was also used by us for the sake of comparison.

The percentage gamma globulin and the total protein values are given in the following tables:

CRA Cases

Patient no.	Sex	% Gamma globulin	Tot. Protein in gm%
41	♂	11.0	7.0
9	♂	12.5	7.0
39	♀	13.9	6.7
27	♂	14.1	7.0
11	♂	14.2	8.1
40	♀	15.0	5.9
16	♀	16.8	6.2
22	♀	17.9	7.1
26	♀	18.5	7.0
24	♀	18.7	8.2
17	♀	19.3	7.1
10	♀	21.3	7.4
6	♀	21.4	7.9
19	♀	22.0	8.5
43	♀	17.2	7.1

Control group

Name	Sex	% Gamma globulin	Tot. Protein in gm%
E	♂	14.0	7.9
Z	♂	15.4	7.4
Bu	♀	16.2	7.7
La	♂	17.1	7.2
Ro	♂	17.3	7.2
Lo	♀	17.6	7.9
J	♀	18.7	7.2
Bul.	♂	18.7	6.3
K	♂	18.9	7.7
T	♀	19.0	7.7
E	♂	19.8	6.5
Ti.	♀	20.4	7.7

The gamma globulin values in the two groups were statistically analysed*). For this purpose the Wilcoxon test was employed (a level of significance of 5% was considered). No significant difference was found to exist in the two groups. This limited investigation on CRA patients provided us with no evidence in favour of an allergic etiology. Further consideration to allergy is given in the chapter dealing with the histological picture of the disease.

Is chronic recurrent aphthae caused by a virus?

Review of the literature.

We have already pointed out, that acute aphthous stomatitis and chronic recurrent aphthae (CRA) were considered for many

*) I wish to thank Dr. H. J. Bronts of the Dept. of Social and Preventive Medicine, State University, Groningen for the statistical analysis.

years to be the same disease with different manifestations in adults and children.

With the establishment of the viral etiology of acute aphthous stomatitis (Zamorani, 1930; Kumer, 1932 and Dodd and co-workers, 1938), however, it was hoped that the etiological agent of CRA would be found. That the herpes simplex virus seemed to be responsible for the disorder was further made attractive by the theory of Burnet and Williams (1939). In our discussion on acute aphthous stomatitis, we have mentioned the fact that Burnet and Williams postulated that initial or primary infection with the herpes virus leads to a lifelong infection, the virus remaining dormant in the body cells only to be reactivated by external stimuli, thus causing recurrent outbreaks of labial herpes. As a result, a similar explanation was given by authors for the development of the recurrent lesions in CRA.

The negative results reported (Templeton, 1926; Kumer, 1932; Münsterer, 1942; Rosenstein and Ziskin, 1942) after material from patients suffering from CRA was inoculated on the corneae of rabbits, received little consideration from subsequent supporters of the herpes virus hypothesis.

Cahn and Bartels (1942), Cahn (1950), Gottlieb (1951), Robinson (1951) and Kerr (1952) stated that herpes simplex virus is the cause of CRA, without giving experimental evidence supporting this statement.

Kochs (1940) found that material from CRA cases rendered negative corneal tests, but pointed out that labial herpes frequently accompanied the lesions of CRA.

In the two cases considered to be due to herpes infection reported by Ziskin and Holden (1943) no proof was given for such an assumption.

Kilbourne and Horsfall (1951) presented evidence that herpes simplex virus might be the etiological agent of CRA. On three occasions they were able to isolate the virus from lesions present in an adult male who suffered from recurrent lip vesicles and aphthous ulcers of the mouth and gums since childhood. Their experiments were conducted on infant mice and chicken embryos. Kilbourne and Horsfall (1951) stated: "It is, therefore likely that herpes simplex virus infection may account for some instances of recurrent aphthous ulceration and cannot be flatly rejected as an etiological agent of this process."

Dodd and Ruchman (1950), after corneal inoculations and neutralization tests performed with material obtained from 11 patients with CRA, arrived at the conclusion that herpes simplex virus is not the cause of the disease. They also cite Buddingh and Ruchman, who over a period of years, were unsuccessful in their attempts to isolate the virus from sporadic cases.

The findings of Dodd and Ruchman (1950) were corroborated by the results of Blank and co-workers (1950). The latter

were unable to show by means of viral isolation, serologic studies or biopsies that the lesions present in 27 patients had been caused by the herpes simplex virus.

The uncertainty about the role of herpes simplex virus in the etiology of CRA led Stark et al. (1954) to state as follows: "The general acceptance of the term recurrent aphthous stomatitis as a synonym for recurrent aphthae has been interpreted by some as implying that an etiological relationship exists between this condition and aphthous or herpetic stomatitis. This implication has gained further support from the fact that herpetic infection is, indeed, frequently characterized by the appearance of recurrent lesions. In addition, recurrent aphthae may, at times during their course, superficially resemble the oral lesions of herpes or occur coincidentally with herpetic infection. It is, therefore, not surprising that a relationship between recurrent aphthae and herpes simplex is thought by many to exist."

After serological investigations and skin tests performed on 29 patients suffering from CRA, Stark et al. came to the conclusion that herpes simplex virus is not the etiological agent of the disease. Twenty of their patients gave negative histories for past herpetic infections, two questionable histories while seven related previous infection with herpes simplex virus. Thirteen of the twenty patients with negative histories had no demonstrable complement fixing antibodies against herpes virus. Stark et al. interpreted this as presumptive evidence that the disease is not due to infection with herpes simplex virus. Neutralization and skin tests supported these findings.

Allen (1954) stated that evidence was offered by Ruiter (1950) that the virus of herpes simplex is responsible for at least some cases of chronic recurrent aphthae. In our opinion, this statement is unfounded, for Ruiter (1950) clearly differentiated acute aphthous stomatitis from chronic recurrent aphthae, as far as etiology is concerned, in his patient.

In preliminary studies on eighteen patients with a history of CRA, Farmer (1956) was unable to isolate a virus after chorioallantoic membrane inoculations. In four patients Farmer found high antibody titres for herpes simplex virus, in spite of the fact that the patients did not suffer from labial herpes. Histological examination of early lesions from eighteen patients indicated a variety of lesions. In one case Farmer could demonstrate the presence of inclusion bodies. According to him, the history of recurrent aphthae following acute aphthous stomatitis seems to indicate that some cases of recurrent aphthae may be due to herpes infection.

Dudgeon (1956) was unable to isolate a virus at each successive recurrence in adults suffering from CRA. In three of his patients Dudgeon found no herpes-neutralizing antibodies at the end of a three-year period.

Orban and Wentz (1955) stated that "recurrent aphthous stomatitis is not a manifestation of the herpes simplex virus", whereas the U.S. Navy Color Atlas of Oral Pathology (1956) contained a statement to the effect that recurrent aphthous stomatitis results from the reactivation of the herpes simplex virus residual in the tissue following the primary infection, and that the lesions are limited in extent because of the antibodies produced in response to the primary infection. It should be noted that in this Atlas, periadenitis mucosa necrotica recurrens and recurrent aphthous stomatitis were differentiated from each other.

The conflicting views in literature with regard to the viral etiology of CRA obviously caused Strean (1957a; 1957b) to contradict himself. Strean (1957a), who called the disease secondary herpetic stomatitis, stated: "Secondary herpetic stomatitis is a disease which attacks the adolescent and persons of middle age. The lesions have received the designation of canker sores, fever blisters or recurrent aphthae. Herpes virus is the etiologic agent and it is believed to have remained fixed to tissue cells throughout life following the first infection in childhood". In the same year, however, Strean (1957b) made a completely different statement: "It is our belief that aphthous ulcers are not caused by herpes virus but by an unknown virus since patients suffering from these ulcers have a low antibody titre against herpes virus, while those suffering from herpetic stomatitis frequently have a high antibody titre against the homologous antigen".

The following year Strean et al. (1958) reported as follows: ".....the possibility exists that oral aphthae may be caused by an unknown virus simulating herpes simplex. In fact, the antibody titer for herpes simplex virus in the presence of either condition is usually high".

The idea of an unknown virus as expressed by Strean (1957b), conveyed nothing new, however, for the possibility that other as yet undetected viruses may be the cause of CRA was considered by Fisher and Leider (1951). Similar views were expressed by others (Queries and Minor Notes, 1956; Baur, 1957).

In complement fixation tests, using mouse brain antigen, Sircus and co-workers (1957) obtained negative results for herpes infection in cases of CRA. They also failed to cultivate a virus on chick egg membrane after inoculation with ulcer scrapings, saliva and faeces from five cases suffering from the disease.

Tissue cultures and mice were employed by Weichselbaum and Derbes (1957) in their attempts to isolate a virus from one case. All their results were negative.

On the other hand, Burnett and Scherp (1957) stated that the etiology of CRA and its relationship to herpes simplex had not been adequately defined, even though it seems likely that the cause of the disease is closely related to, or is, the herpes simplex virus.

The possibility that CRA is caused by a virus receive further support from a somewhat different quarter. In 1941, Touraine came with a new concept, which is discussed more fully under the heading "Aphthosis." It will suffice to mention here that in this concept, CRA and the syndrome of Behçet are considered the same disease, and that Touraine expressed the opinion that it is probably caused by a virus related to that of herpes simplex. Evidence in support of this view was given, among others, by Haensch (1953) and Sezer (1953). Heansch was able to demonstrate the presence of elementary bodies in smears made from lesions of patients suffering from what he called chronic recurrent aphthosis, while Sezer (1953) was able to isolate a virus from cases suffering from Behçet's syndrome.

The results of our own viral investigation are discussed in Chapter VII.

4. THE HISTOLOGICAL PICTURE OF CHRONIC RECURRENT APHTHAE.

Review of literature.

Very little value can be attached to descriptions dealing with the histological picture of aphthae in literature prior to 1930. The reason is that no proper distinction has been made between the lesions of chronic recurrent aphthae and acute aphthous stomatitis.

The descriptions of Worms (1864), Fraenkel (1888), Ziegler (1898), Siegmund and Weber (1926) and Aschoff (1936) were probably based on some cases of chronic recurrent aphthae, but it is extremely likely that the majority were cases of acute aphthous stomatitis. We have already mentioned that Fraenkel's cases in all probability suffered from acute aphthous stomatitis. Aschoff (1936) for instance, described the aphthae of adults and children under the heading Stomatitis exudativa fibrinosa maculosa. Microscopically, Aschoff found epithelial necrosis with exudation of fibrin under the affected epithelium.

The description by Sutton (1911) is the only exception to the above. He found a superficial necrosis with decided inflammatory manifestations in the underlying structures. The connective tissue was infiltrated with cells of various types, predominantly plasma cells, fibroblasts and eosinophils. Accumulation of these cells was noted in and around the blood vessels and lymphatics. The endothelial lining of some of the vessels was swollen and in some places proliferating. Sutton also found that much fibrin was present in the tissues. The papillae were hypertrophied and the cells in the interpapillary plugs acanthotic, swollen, irregular in size, and poorly stained. A very prominent feature observed by Sutton was an intense inflammatory process in the periglandular tissues, with ensuing necrosis and separation of the central part of the affected area.

The condition, called periadenitis mucosa necrotica recurrens by Sutton, was considered a distinct entity and he never confused it with acute aphthous stomatitis.

Cahn (1936) gave a description of the histological picture of aphthae and although he stated that " it is quite likely that herpes simplex and aphthae are the same lesions in different stages of development ", we must consider the fact that his description dealt with chronic recurrent aphthae, for he also wrote " aphthae are painful circumscribed ulcers, usually recurrent, of the oral mucous membrane..... their cause is unknown, but they occur in certain individuals under the influence of the excessive use of tabacco, digestive irritants and among women, at the time of menstruation. In some specific foods, such as walnuts, will consistently incite the formation of aphthae". Histologically, Cahn found that the lesions begin as vesicles in the form of intra-epithelial oedema. In the vesicles he observed degenerating epithelial cells. The vesicles lead to ulcers surrounded by fairly normal epithelium. On the surface he observed cellular debris which formed a pseudo-membrane. Conspicuous to Cahn was the marked perineural and perivascular infiltration present in the corium and subcorium He ascribed the extreme discomfort caused by the lesions to the close proximity of the nerves to the ulcerated surface. In a later publication, Cahn (Cahn and Bartels, 1942) was inclined to consider chronic recurrent aphthae to be the same disease as acute aphthous stomatitis. In this paper he and Bartels obviously described the histological picture of herpetic lesions. We have already referred to this description in our discussion of acute aphthous stomatitis. It should be noted, however, that these authors distinguished aphthous ulcers (canker sores) from periadenitis mucosa necrotica recurrens. They gave no description of the histological picture of the latter except for a brief reference stating that the lesions in this condition resemble those of herpes zoster.

Fergusson (1939a; 1939b) described the histological findings of two lesions from a case he considered as periadenitis mucosa necrotica recurrens or ulcus neuroticum mucosae oris. He found a fairly normal epidermis and a dense subepidermal periglandular infiltrate. This consisted mainly of lymphocytes, polymorphs and numerous plasma cells. Slight necrosis of connective tissue was also present. Both the lesions showed the same changes and were considered to be of a non-specific granulomatous nature.

Davies (1939) reported two cases, considered to be suffering from PMNR and ulcus neuroticum respectively. In the former, a biopsy revealed oedematous but densely cellular granulation-tissue, a few giant-cells but no tuberculoid systems, while in the latter a non-specific granulation-tissue containing a fair number of mast-cells was encountered.

Kochs (1940) was unable to find an initial vesicular stage, although he considered it possible that the transparent glass-like appearance at the onset of some lesions might represent a vesicle. Even early microscopical examination, according to Kochs, showed a rapid developing necrosis in the epithelium. The necrotic foci are rapidly drenched by fibrin and an inflammatory exudate containing lymphocytes and granulocytes. The edges of the lesions were oedematous. He also remarked that the histological picture of chronic recurrent aphthae shows some resemblance to the initial stages present in mucosal defects of the stomach.

The only planned histological investigation of aphthae was undertaken by Frech (1945). His material was obtained from eleven patients, diagnosed as suffering from what he called solitary recurrent and solitary non-recurrent aphthae. He considered that there was no difference between the lesions of these two groups. Frech described the changes observed in the initial or alterative phase, and those observed in the subsequent regenerative phase.

In the initial stages of development, Frech observed a mixed leucocytic infiltration (polymorphs, lymphocytes and a few plasma cells) with the formation of a fine fibrin network in the connective tissue underlying the epithelial defect, while the structure of the papillary layer could not be distinguished any more. Marked intercellular oedema was present in the epithelium. In these oedematous spaces he found a round cell infiltration, while the epithelial cells showed fibrinoid degeneration (necrobiosis of the prickle cell layer). Many irregular forms of nuclei and nuclear fragments were found in the infiltrated fibrinous exudate and pointed to extensive karyorrhexis of the inflammatory cells. The vessels in the papillary and reticular layers were strongly dilated and revealed the presence of perivascular round cell infiltrates. The changes in the vessels of the papillary layer consisted of a thickening of the endothelium. This thickening could be traced back towards the deeper vessels. Frech observed that it was always the intima of the vessels, which showed the first signs of damage. According to him, the damage in the vessel walls resulted from a reversible stasis in the bloodcolumns which are transformed into glazed, homogenous compact masses of erythrocytes. Extravasation of erythrocytes, leucocytes and blood plasma occur before the bloodflow ceases completely. The connective tissue revealed a rapid oedematous change which could be followed to the vicinity of the serous glands situated deeper. The connective tissue fibres lost their wavy and fibrillous appearance, but no special fibrinoid changes were visible. As the process continued, more epithelial cells showed necrosis, while the sub-epithelial changes extended both in a vertical and a horizontal direction. The larger vessels in the stratum reticulare showed a thicken-

ing of the walls as the result of a loosening of the intimal and adventitial cell structures. Frech ascribed the latter changes to the passage of the cellular-fibrinous exudate. The alterative phase reached its peak when the lesions were approximately two days old. At this stage, extensive oedema was visible in the connective tissue. The changes in the walls of the papillary vessels became so extensive that it was difficult to distinguish the vessels from the surrounding tissue. Frech emphasized that the destructive phase took place so rapidly that within 12 to 24 hours a completely different picture emerged.

In the regenerative phase, Frech observed that the round cell infiltrate slowly retreated to the initial point of issue in the papillary layer. The oedematous changes in the connective tissue rapidly disappeared. In the superficial fibrinous mass, new connective tissue fibres appeared together with intact capillaries and fibroblasts. The edges of the epithelial defect still showed cellular infiltration but without oedematous changes. Growing epithelial pegs became visible in the depth of the lesion and would ultimately border on the future papillae. The regenerative phase begins on from the third to the fifth day. Another three to six days are required for complete healing.

On no occasion did Frech encounter ballooning or reticular degeneration, oxychromatic nuclear degeneration, nuclear inclusions, or changes in the nerve fibres. To him the defect represents a small ulcer and not an epithelial erosion only.

In a critical evaluation of his findings, Frech stated that the solitary aphtha is a local necrotic inflammation of the complete mucosa accompanied by cellular fibrinous exudation. Nothing indicates a specific infection. The rapid formation of an extensive round cell infiltration, vessel disturbances, massive erythrocyte expulsion and the formation of oedema were regarded by him as noteworthy. Compared with the artificially formed hyperergic inflammation of Gerlach (1923), he found common clinical and histological features. He therefore concluded that the solitary aphthae formed on an allergic basis definitely has the same reaction as that observed in hyperergic inflammation. The same probably applies to the remaining forms of solitary aphthae.

In contrast to Sutton (1911) and Fergusson (1939a; 1939b), various authors referred to cases as PMNR without being able to demonstrate any glandular involvement. Andrews (1946a), for instance, concluded that the histological picture of PMNR is non-specific ulceration with an extensive inflammatory reaction, mainly with various mononuclear cells. As stated, most observers regard this disorder as a severe form of aphthous stomatitis. Distelheim and Sulzberger (1949) naively stated that "a biopsy was taken which ruled out a papilloma, but a definite diagnosis was not made."

Miller (1954) observed a slightly acanthotic epidermis in

one case suffering from PMNR. In the corium he found an inflammatory reaction, while on both sides of the lesion he observed the formation of a new connective tissue matrix in which round cells, macrophages, leucocytes and occasional plasma cells were visible. Miller's diagnosis was "granulation tissue: no definite histo-pathologic picture".

Colby and co-workers (1956), however, still believed recurrent aphthous stomatitis to be a manifestation of herpes simplex virus and clinically distinguished it from PMNR. They described the histology of the latter as a necrosis and inflammation in the region of the ducts of the accessory salivary glands. Colby et al. (1956) gives no description of the histological picture of recurrent aphthous stomatitis.

Histological examination of early lesions from 18 patients with a history of chronic recurrent aphthae indicated to Farmer (1956) that more then one type of lesion existed. In one of his cases he found inclusion bodies resembling those of herpetic origin. He could not draw any conclusions from the histological findings, however.

Vest (1957) is of the opinion that the lesions arise as a result of thickening and turbidity of the epithelium with the formation of a fibrinous exudate in the mucosa. According to him the lesion extends as far as the vascular layer, while the epithelium is destroyed by necrosis.

Nasemann (1958) considers the histological picture of recurrent aphthae to be a fibrinous and granulocytic inflammation. According to him the epithelium shows superficial necrosis, but deeper ulcerations are by no means rare. Nuclear inclusions and multinuclear giant-cells as in herpetic aphthous stomatitis are absent.

Simons (1958) describes a strongly leucocytic occasionally lymphocytic, infiltration giving the impression of a lymphoblastoma, while Roggeveen (1958) considers the lesion as a fibrinous discharge in the mucosa together with ballooning degeneration and a necrosis of the epithelial cells, resulting in the formation of a small ulcer. According to Roggeveen, the surrounding area shows a lymphocytic infiltration.

Our histological findings of CRA are discussed with those of aphthosis in Chapter VIII.

B. Tropical aphthae.

(Synonyms: Tropical sprue, sprue, psilosis, Ceylon sore mouth, Indische spruw, chronic tropical diarrhoea, Tropendiarrhöe, white flux, diarrhoea alba, hill diarrhoea, white purging, diarrhè de Cochin-Chine, cachexie dysenterique, stomatitis intertropica, aphthoides indicae s. tropicae, aphthalo-gastroenteritis chronica, aphthosis tropicalis, aphthosis orientalis, seriawan).

This tropical disease, characterized by the formation of aphthae was first described by Van der Burg (1880) in Java as "Indische spruw" and shortly afterwards also by Sir Patrick Manson (1880) in Southern China as "sprue". (De Langen and Lichtenstein, 1933). Subsequently it was named "tropical aphthae" by various authors (Richartz, 1905; Kümmel 1922; Hiemcke, 1934; Carol, 1948; Rebel, 1948).

Manson-Bahr (1944) considered it a symptom-complex characterized by a glossitis, emaciation, megalocytic anaemia and steatorrhoea, of which the three cardinal symptoms are glossitis, meteorism and diarrhoea. The initial cause is still obscure.

The mouth and tongue lesions may be the only manifestations found in the patient, to be followed years later by the other symptoms (De Langen and Lichtenstein, 1933; Manson-Bahr, 1944).

The tongue is painful, smooth, glistening and red with erosions, hyperaemic spots and occasionally small vesicles along its border and on the tip. On both sides of the tongue frenulum-small erosions covered by a grayish membrane-are often visible. Localisation of the lesions on the cheek and lip mucosa is rare. The oral lesions are of a recurrent nature (De Langen and Lichtenstein, 1933).

Manson-Bahr (1944), however, speaks of the frequent occurrence of evanescent aphthae on the tip or undersurface of the tongue, the lower lip and the buccal mucosa.

Impaired fat absorption is considered the most important criterion for investigation in order to establish the diagnosis (De Langen and Lichtenstein, 1933). The faeces contains a highly increased amount of split fat, considered by these authors to be pathognomonic of the disease.

Two main theories have been advanced to explain the etiology of tropical aphthae, namely a deficiency theorie and an infection theory (Nieweg, 1958b).

In support of the deficiency theorie, Castle and co-workers (1935) reported good results after treatment with liver extract. Darby and co-workers (1947) provided evidence that folic acid has a beneficial effect on patients with tropical sprue, while similar results were obtained with vitamin B 12 by Suarez et al., (1949).

Infection was first considered in the etiology of the disease by Ashford (1915) and Sainz de Aja (1915). These authors considered monilia psilosis and spirochaetes respectively as the causative agent (Kümmel, 1922).

Leishman (1945) observed the disease in epidemic form among well-nourished troops in India, while Keele and Bound (1946) obtained excellent results in combating the diarrhoea by means of sulphonamides.

Chemotherapy was found very effective in seven cases trated by French and co-workers (1956).

Butterworth and Perez-Santiago (1957), cited by Abels (1959), considered a strain of streptococcus faecalis as a causative factor in a case they described.

We agree with Nieweg (1958b) and Abels (1959) that most likely it concerns a combination of both theories, for it is known that the intestinal flora is dependent on the nature of the food or on toxic products of bacteria, with a resultant diminished production of folic acid or vitamin B12. A lack of these vitamins may lead to atrophy of the mucosa with a subsequent diminished power of resorption.

C. NON-TROPICAL SPRUE.

(Synonyms: sprue, Gee's disease, Gee-Herter's disease, coeliac disease, idiopathic steatorrhoea, Einheimische sprue, Spruw, endemische spruw).

Gee (1888) published the first account of this disease he called it the "coeliac affection". It affected people of all ages but especially young children. He realised the similarity of this condition with tropical sprue; he was unable to distinguish between the two. The disease was rediscovered by Herter (1908) when he published his monograph, entitled "Infantilism and Chronic Intestinal Infection" (Bennett et al., 1932).

Important contributions to our knowledge of the disease were made by Hess Thaysen (1932), Bennett, Hunter and Vaughan (1832) and Hansen and Von Staa (1836).

In his monograph, Hess Thaysen (1932) attempted to show that non-tropical sprue, coeliac disease of infants and tropical sprue are the same disease. He was subsequently supported in this view by Hansen and Von Staa (1936), and Hurst (1942).

Recently, Nieweg (1958b) and Abels (1959) pointed out that non-tropical sprue forms part of the so-called "malabsorption syndrome" or "primary intestinal insufficiency", the other two members being coeliacie and tropical aphthae. These authors share the view held by Bennett and co-workers (1932), who stated: "We doubt whether there is justification for a separation of non-tropical sprue from coeliac disease, but on the other hand we feel that coeliac disease and tropical sprue are separate, though closely similar, entities".

Dicke (1950) and Dicke, Weyers and Van de Kamer (1953) showed that cases suffering from coeliac disease and non-tropical sprue could be cured after the exclusion of gluten from the diet. Similar results were reported by Nieweg (1953), Anderson et al. (1954), Haex and Lips (1955), French et al. (1957) and Abels (1959).

The exclusion of gluten from the diet in patients suffering from tropical sprue had no effect on the course of the disease (Frazer, 1955; Abels, 1959).

The main clinical features of non-tropical sprue include

fatty stools with or without diarrhoea, dilatation of the colon, tetany, osteomalacia, anaemia of various types, skin lesions and frequently infatilism (Bennett et al., 1932).

Oral symptoms were found in 90 of the 100 patients described by Cooke, Peeney and Hawkins (1953). Jolliffe (1950), cited by these authors, stated that "there were no diagnostic features by which the lesions could be differentiated from those occurring in other nutritionally deficient states."

Cooke et al. (1953) found that "in the most severe examples the whole tongue and the inside of the mouth were fiery red, usually with multiple areas of ulceration of the buccal mucous membranes and edges of the tongue. In the mild forms the tip and edges of the tongue presented a smooth, bright red, and sore surface. On other occasions aphthous ulcers, with little if any glossitis, were the chief feature."

Cooke (1953), in a personal communication to Sircus et al. (1957), observed aphthous ulcers in almost 100 per cent of cases suffering from steatorrhoea, while Dreizen, Stone and Spies (1958) consider aphthous ulcers a frequent manifestation in patients suffering from sprue.

D. SOLITARY APHTHAE.

(Synonyms: Localized solitary ulcers, trophic ulcers, neurotrophic ulcers, non-recurrent non-habitual solitary aphthae).

We reserve the name solitary aphthae for all those that usually appear singly in the mouth, never leading to recurrences, and whose etiology is still unknown.

In the past many cases of this nature were described under the names trophic ulcers or neurotrophic ulcers.

Thoma (1944; 1954) distinguishes a variety of lesions under the title "localized solitary ulcers", which, according to him, are generally caused by injury of the mucosa from where an infection spreads peripherally. Thoma (1954) therefore considers Bednar's aphthae (traumatic), decubital ulcers (traumatic), simple ulcers (traumatic?), trophic ulcers (disturbed nutrition of tissue after the use of local anaesthesia) and neurotrophic ulcers (disturbed nutrition because of a defective peripheral nerve) as belonging to this group.

The fact that in many cases no proof of any trauma can be found, forces us to draw a clear line of distinction between lesions of traumatic origin, and others (like trophic ulcers) which might as well be due to an allergic reaction as to a disturbance in the nutrition of tissues.

The following description was given by Johnston (1936) under the title "Neurotrophic Ulcer Following Mandibular Block Anaesthesia".

"Clinically the ulcer is in appearance like a circumscribed piece of pearly-white tissue superimposed on the epithelial

tissue of the mouth, and situated on the inner side of the corner of the lower lip. It appears the day after a mandibular injection, and is not painful. Later it penetrates some distance into the lip, and then becomes in appearance somewhat like a tubercular ulcer, with ragged undermined edges; it is then very tender".

Similar lesions were described by Baker (1937), cited by Thoma (1954). Baker (1937) found that the ulcers had clear-cut margins and no tendency to spread. Baker also considers the lesions to appear unilaterally and usually analgesic, but they may become painful. The photograph of Bloom's patient (in Thoma's textbook, 1954, revealing three neurotrophic ulcers on the lower lip, is not altogether convincing evidence of the unilateral distribution of the ulcers. No mention was made of a bilateral injection of local anaesthetic or of any possible exciting factor.

Jansma (1942) considers most cases of aphthae after local anaesthesia to be due to mechanical trauma. The trauma may be due to pressure or stretching of the anaesthetised lip by the dentist, or to biting on the lip. In the case reported by Jansma, however, he was able to exclude trauma as a cause. He therefore considered either a hypersensitiveness to cocaine or an abnormal reaction of the vasomotor and trophic sympathetic nerve fibres of the mandibular (?) and lingual nerves to the anaesthetic solution.

The following case history illustrates a case of solitary aphthae, according to our opinion:

J.I. (58/2905), Male, aged 30. Radiographer. Married. Two children.

Present History: The patient attended the Polyclinic of the Department of Oral Surgery, University of Groningen (Prof. M. Hut) on 30.10.'58 with a complaint of painful ulcers in the mouth. A week prior to this visit (23.10.'58) the patient was treated at the Department of Conservative Dentistry, University of Groningen (Prof. J. G. de Boer). Here he received a left tuberosity injection of 2 c.c. astracaine (2%) before removal of amalgam fillings from $\underline{|5}$ and $\underline{|6}$. Subsequently the two teeth were temporarily filled with the aid of gutta percha. During the operation cotton wool rolls were used in the mouth. After the anaesthesia had passed off he felt a slight burning sensation inside the mouth. This was located to the left side of the upperlip and right side of the lower lip. The day after treatment ulcers became visible on these spots, which caused pain with eating or when touched. After the ulcers had persisted for a week, the patient sought advice from the Department of Oral Surgery. At no time did he feel sick or feverish.
Previous History: The patient never had such lesions in the mouth before. From 1948 to 1950 he was on military service in Indonesia. In 1949 he contracted malaria which was completely cured after treatment. A year ago he received treatment for eczema around the anus, which according to the patient developed in conjunction with hemorrhoids. The patient gave a negative history of diarrhoea and of previous herpes infections.
Family History: Father suffered from TB, but otherwise negative.

Examination: General examination: NAD.
Intra-oral: Teeth in good condition. Many amalgam fillings present. The $\underline{|5}$ and $\underline{|6}$ revealed the presence of temporary fillings. The gingiva healthy with little calculus. On the inner aspect of the upper lip, opposite the left first premolar, a pea-sized round yellow ulcer on a slightly reddened area (Fig. 6). This lesion was painful when touched. On the inner aspect of the lower lip opposite the right lower canine, a similar, but smaller lesion was visible; this was only slightly painful when touched. No foetor ex oris was present. The regional lymph glands were not palpable.

Scrapings were made (as described on pages 140 and 160) from the lesion of the upper lip for viral and cytological investigation. Blood (15 c. c.) was obtained under sterile precautions for viral complement fixation tests and luetic reactions.

At the same time a biopsy was taken of the lip lesion under block anaesthesia of the right inferior alveolar nerve, and the specimen immediately fixed in a 5% formalin solution. No reaction or lesion resulted from the injection of 2 c. c. of a 2% astracaine solution.

Laboratory Results: Wa R: negative. V.D.R.L.-test: negative. No virus could be cultivated from the oral scrapings and the complement fixation test was negative for herpes simplex, adenovirus, ECHO Type 9, mumps, measles and L.C.M.-virus.

The pathological-anatomical report reads as follows: Result no. 124731. A slightly hypertrophic and acanthotic epithelial layer showed the presence of superficial intracellular oedema. Immediately beneath the epithelium a dense inflammatory infiltrate with numerous eosinophils was observed. In all probability we are dealing with a sub-acute inflammatory process. Below the dense inflammatory infiltrate the sub-epithelial connective tissue showed marked vascularity with a less dense round cell and leucocytic infiltration. Many eosinophils were encountered here. Two gland openings were visible. A sporadic mast cell was visible in the section stained with Giemsa'a stain. In our opinion the picture can fit in with that of sub-acute aphthous stomatitis.

DIAGNOSIS: Solitary aphthae or a first attack of chronic recurrent aphthae.

The patient was kept under observation for almost a year and he had no recurrence up to 5.10.'59.

We therefore feel justified to consider this a case of solitary aphthae.

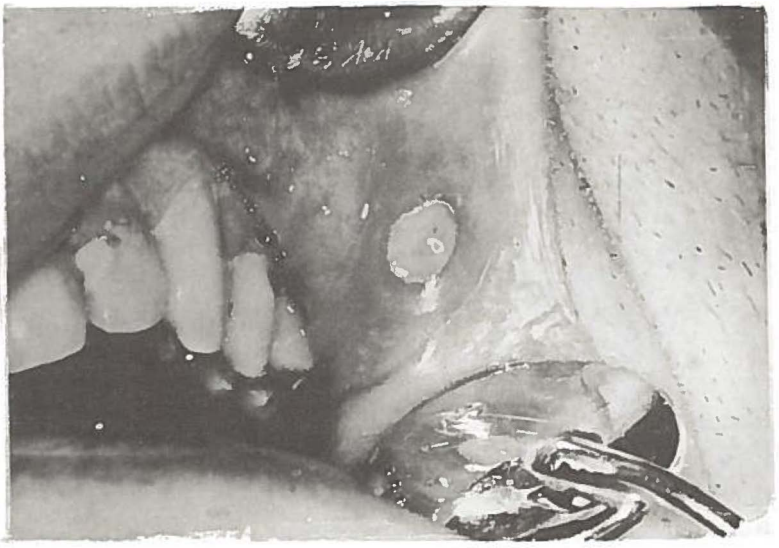

Fig. 6. Solitary aphtha on inside of upper lip which followed dental treatment. Pat.No. 2905/58 (Photo: Schults, Dept. of Oral Surgery, University Hospital, Groningen.)

CHAPTER VI

DISEASES WHICH HAVE BEEN NAMED APHTHAE, BUT WHICH ARE NOT CHARACTERIZED BY THE FORMATION OF TYPICAL APHTHAE.

A. Of known etiology.

1. Stomatitis aphthophyta.

(Synonyms : Thrush, moniliasis, candidiasis, sprue, Soor, muguet, Schwämmchen, stomatomykosis, Mehlmund, spruw, stomatitis oidica).

In Chapter I we have shown how for many years the lesions of this disease had been confused with that of aphthae, while both conditions were described by the same name. Towards the end of the eighteenth century, however, the two diseases were clearly differentiated from each other.

The etiological agent of thrush was shown by Vogel (1841), among others, to be a fungus and was known as Oidium albicans.

Today, it is hardly possible to confuse the lesions of thrush with that of aphthae in the mouth. Some authors (Blancke, 1934; Scales, 1952; Blank and Rake, 1955) still consider it in the differential diagnosis of acute aphthous stomatitis.

Clinically the mucosa is covered with numerous elevated white or grayish-white spots resembling pieces of curdled milk. The spots may coalesce to form large adherent plaques, and should then be differentiated from leukoplakia. When the plaques are removed, a red inflamed surface is exposed.

Thrush principally affects bottle-fed infants, but old and debilitated adults occasionally suffer from it (Burket, 1946).

Recently Lilienthal and co-workers (1957) reported cases of thrush in adults. These authors consider endocrine disturbances and the local and prolonged use of antibiotics important factors in these cases. It is well known that antibiotics interfere with the local bacterial flora, thereby creating favourable circumstances for the growth of fungi.

Letowska and Jaskiewicz (1957) who consider moniliasis a rare disease of the oral cavity, also employed aureomycin in treatment of the case they described. We agree with them as far as the use of vitamins and boraxglycerine are concerned, but share the view of Lilienthal and co-workers (1957) that antibiotics should be avoided. The following adult case we observed illustrates this point:

Case No.482/59. J.W.H. Male. Age 50. Occupation: carpenter. On the 25th of Febr.'59 the patient was referred to the Department of Oral Surgery by the Ear, Nose and Throat Department (Head: Prof.Dr. E. Huizenga). Previous History: A trans maxillofacial operation (Moure-Holmgren) was done on the patient on 30

January by Prof. Dr. Huizenga for an adeno-carcinoma on the right side of the nose which partly extended into the right maxillary antrum. The alveolar process remained intact. From 30.1.'59 until 10.2.'59 the patient received a daily dose of one million units of penicillin and one gram of streptomycin intramuscularly.
Subsequently the patient also received radium treatment on two occasions. On the 25th Febr.'59 the patient was found to have a perforation in the upper right buccal sulcus for which he was sent to the oral surgery department in the hope that the existing upper denture could be extended in order to cover this defect.

Examination of the patient on the 25th Febr '59 revealed the following:

Extraorally the patient seemed to be in good condition. A postoperative scar was visible on the upper lip and along the nose. Otherwise negative.

Intraorally: Edentulous patient with full upper and lower dentures. High up in the right upper buccal sulcus, opposite the canine, an eliptiform perforation of one centimetre diameter, at its utmost, was visible. On the mucosa of the left and right upper buccal sulcus confluent raised white patches were noticed. The patient was unaware of these (fig. 7).

A provisional diagnosis of moniliasis was made. Direct microscopical examination of smears from the lesions revealed the presence of branching hyphae and blastospores, characteristic of a fungal infection.

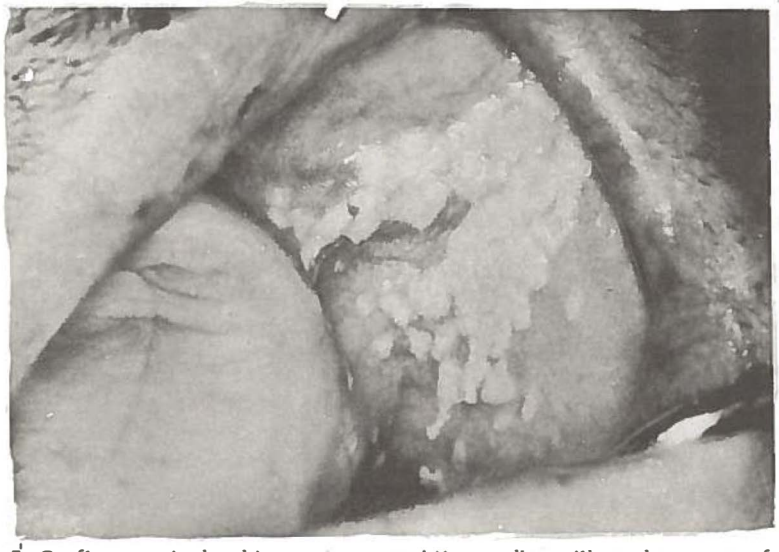

Fig. 7. Confluent, raised, white patches resembling curdled milk on the mucosa of the left upper buccal sulcus and cheek, due to monilia infection. (Photo: Schultz, Dept. of Oral Surgery, University Hospital, Groningen)

In order to determine the nature of the yeast, material was sent to the Bacteriological Serological Routine Laboratory at Groningen (Head:Prof. Dr. A. Pondman).

The results of the investigation done by Dr. R. K. Koopmans, were as follows:

Investigation No. 7084/5.

27. 2. '59: Microscopical examination of smears reveals a number of yeast cells. Subject to further cultural investigation.

2. 3. '59: Bacterial culture: Staphylococcus aureus (haemolytic and coagulase positive), fairly dense growth.

Yeast culture positive. Dense growth.

25. 3. '59: Determination of yeast: Candida albicans

Fleming (1958) and Schuermann (1958a) pointed out that Monilia albicans are often found in the mouths of normal people. Schuermann (1958) feels that a diagnosis of moniliasis can only be made where the clinical picture and laboratory evidence point in this direction. We therefore feel justified in diagnosing the case mentioned above as one of moniliasis or thrush.

In conclusion, we may mention that the lesions disappeared completely within 5 days after daily topical application of 1% Gentian Violet solution.

2. Malignant aphthae.

(Synonyms: Echtyma contagiosum ovinum, contagious echtyma, orf, chancre du mouton, der Lippengrind der Schafe, scabby mouth, sore mouth, infectious pustular dermatitis of sheep and goats, etc.).

This is a viral disease of sheep which has occasionally been observed in people who handled infected sheep or goats (Schoch 1939; Kingery and Dahl, 1945; Prakken, cited by Carol, 1948).

In sheep the lesions appear in the mouth and on the lips, but in man they are usually found on the hands.

The human infection begins as firm papules or vesicles which later change into pustules or haemorrhagic bullae. The lesions show a striking resemblance to the lesions of smallpox, with the typical central umbilication.

Kingery and Dahl (1945) described the histological picture of lesions in man. It consists of intra epithelial bullae filled with erythrocytes. In the corium a non-specific infiltrate and vasodilatation were observed. No inclusion bodies were present.

B. Of unknown etiology.

Aphtha cachectia.

(Synonyms: Sublingual fibroma, sublingual production of Fede. Riga's disease, Fede's disease, Riga-Fede's disease, Cardarelli's aphthae).

Fortunately the name aphtha cachectia is not in use any more, for the condition has in fact nothing to do with aphthae nor is cachexia an essential feature of it. Preference is given to the names sublingual fibroma or Riga-Fede's disease.

Clinically, the disease is characterized by the formation of a round or oval, elevated, pearl-like swelling or growth of approximately $1\frac{1}{2}$ cm. diameter, underneath the tongue and on its fraenum. The lesion has a grayish colour due to the deposit of fibrin on its surface. In an attempt to remove the fibrinous deposit, bleeding occurs. On palpation the lesion has the consistency of cartilage (Szücs, 1948).

It is a disease of infants, probably first described by Cardarelli in Italy (1857), and thought by most Italian authors to be a typical Italian disease. Cases, however, have subsequently been described in other countries. In Italy, cases have been reported by Riga (1881), Fede (1890 and 1897) and Callari and Philippson (1900). In the Netherlands, cases were described by Cornelia de Lange (1906), in Japan by Kasahara and Nagatani (1932) and in Hungary by Szücs (1948).

Fede (1897) considered friction of the central incisors against their alveoli during cutting of etiological importance. Szücs (1948) stated that the rough edge of these teeth in linguoversion seems to be a contributing factor.

Histologically one finds a chronic inflammatory reaction with fibrosis (Szücs, 1948).

CHAPTER VII

VIRAL INVESTIGATION OF CHRONIC RECURRENT APHTHAE AND APHTHOSIS

The observations of others (Kilbourne and Horsfall, 1951a; Farmer, 1956) that herpes simplex virus may be the etiological agent of chronic recurrent aphthae (CRA), provided us with a basis on which further experiments could be conducted in the hope to prove the viral nature of the disease. This was further made attractive by the views of Touraine (1941) who included CRA in his concept of aphthosis, and which he considered to be possibly due to a virus related to herpes simplex. If one adds the findings of Sezer (1953;1956) and Evans et al. (1957) who were able to isolate a virus from aphthosis cases, the line of our approach becomes clear.

With high hopes we therefore decided to follow the techniques commonly employed in the diagnosis of herpes simplex infections. This, according to Cath (1955), include the following:

1. Viral isolation.
2. Complement fixation test.
3. Neutralization test.
4. Skin reaction.
5. Cytology.

I. VIRAL ISOLATION

A great variety of experimental hosts have been employed in the laboratory for the isolation of viruses. The most common are rodents (rabbit, mouse, guinea pig, hamster) and the chicken embryo.

As far as the isolation of herpes simplex virus is concerned, we have already mentioned that Grüter (1920) first isolated the virus by means of inoculating material from patients with keratitis dendritica on the scarified corneae of rabbits. The virus could be passed from one rabbit to another, producing a purulent kerato-conjunctivitis.

Kilbourne and Horsfall (1951b) found that infant mice were especially suitable for the isolation of herpes simplex virus. Material is either injected intracerebrally or intraperitoneally. In infant mice, injected by means of the intraperitoneal route, the following signs and symptoms can be observed: For the first two days after the injection the animals appear normal. On the third day they become thin and irritable. After two more days cyanosis becomes evident, the abdomen is distended and respiration is retarded. In a few instances a haemorrhagic peritonitis is observed. If a higher dilution is used or in the case of older animals, signs appear at a later stage. The disease also runs a longer course. A spastic paralysis of the hind legs accompanied by a retention of urine is often encountered in these animals. Death follows within one or two

days after the first signs of paralysis (Cath, 1955).

The virus of herpes simplex was first isolated by Saddington (1932) on the chorio-allantoic membrane of chicken embryos. The virus multiplies itself on the membrane with the formation of pocks. Under the electron microscope (Bang, 1950), these pocks, visible to the naked eye, proved to be proliferative necrotic lesions. They seemed to increase in size with egg passage.

Techniques employing tissue cultures in work on viruses were greatly improved and simplified after the Second World War, and Enders, Weller and Robbins (1949) have shown that cultures made from various human tissues provided a rapid means of diagnosing and typing certain viruses.

Dulbecco and Vogt (1954) established a method by which monolayers can be obtained after trypsinization of tissue. Either continuous cultures or primary (fresh) cultures may be used.

Experimental data provides excellent evidence of the capacity of many viral agents to grow on different tissues derived from different hosts (Sanders and co-workers, 1953).

In tissue culture, herpes virus was first isolated by Parker and Nye (1925). They inoculated an emulsion of infected rabbit tissues (brain or testicle) on to hanging drop preparations of rabbit testicular tissue and plasma. Parker and Nye could demonstrate the presence of the virus up to the 10th subculture, after which no more virus could be demonstrated. The findings of these authors were later confirmed by Gildemeister et al. (1929) and Andrewes (1930). The latter also observed the presence of inclusion bodies in the tissue cultures.

Various tissues were subsequently employed for the isolation of herpes simplex virus, e.g. chick embryo lung-derived fibroblasts (Stulberg and Schapira, 1953), L-strain fibroblasts (Scherer, 1953), HeLa cells (Gray, Tokumaru and Scott, 1958), human and monkey kidney cells (Gray et al., 1958) and rabbit cornea cells (Scott and co-workers, 1953).

The cultivation of a virus in tissue culture is generally judged by the changes produced in the cells, and is named the cytopathogenic effect (CE). A cytopathogenic effect is not always due to the activity of a virus. Toxic substances present in the inoculum may lead to similar changes, which, in contrast to the CE caused by a virus, is not transferable to subsequent subcultures (Versteeg, 1959).

The CE produced by herpes simplex virus has been described by Scherer (1953) in the case of HeLa cells, and by Sosa-Martinez et al. (1955) in the case of rabbit kidney cells. These authors found that it mainly consisted of ballooning degeneration with rounding of the cells and granulation, together with the formation of multinucleate giant cells and lysis. Sosa-Martinez and co-workers (1955) concluded that similar chan-

ges were observed by other authors using different host cells. Gray and co-workers (1958) observed that three types of cytopathogenicity are produced in HeLa cells infected with herpes simplex virus. Firstly a proliferative type, secondly a non-proliferative type with rounding and thirdly a giant cell type with lysis.
Gray et al. (1958) found that all three types of cytopathogenicity are present in the same tissue culture, but that one type usually dominates.

Our investigations directed at the isolation of a virus from cases suffering from chronic recurrent aphthae (CRA) and aphthosis, were performed at the Virus Laboratory of the University of Amsterdam (Dr. F. Dekking).

A. In tissue culture.

Materials and methods.

1. Nature of specimens investigated.

Specimens investigated consisted out of scrapings obtained from the oral lesions of 20 patients with CRA and 2 patients with aphthosis. In addition, faeces and blood from 3 patients with CRA and one with aphthosis were obtained for investigation.

2. Collection of oral specimens.

Requirements: a. A wooden stick (length 12 cm, diameter 3mm.) carrying a piece of cotton wool on the one end was suspended in a test-tube of suitable length by means of a cotton wool stopper. The test-tube with the stick in place was sterilized in an autoclave prior to use.

b. Bijou* bottles with screw caps and containing a $\frac{1}{4}$ml. of skimmed milk were sterilized in an autoclave for 15 minutes at 118° C. After cooling, sodium penicillin (to give 100 units per ml.) and streptomycin sulphate (to give 50 μg per ml.) were added to each bottle. The bottles were then stored at -20° C until used.

Method: By means of the suspended stick, material for investigation was obtained by rubbing over the base of a lesion and then conveyed to one of the bijou bottles. This was accomplished by breaking off the end of the stick by means of leverage against the inside of the bottle. The bijou bottle was then corked, labeled and immediately dispatched by express train or car to the laboratory where it was kept at -20° C until used. It was found that herpes simplex remained stabile for six months or longer if stored in this way (Speck, et al. 1951; Dekking, unpubblished data).

* United Glass Bottle. Capacity 6 ml.

3. Materials used in the preparation of tissue cultures.

a. Glassware. This included:

(i) Record syringes of varying capacity (1ml., 2ml., 5ml., 10ml. and 20ml.) with long and short needles.

(ii) 100 ml. Erlenmeyer flasks (Pyrex glass).

(iii) 100 ml., 300 ml., and 500 ml. flasks of neutral glass.

(iv) Universal containers*.

(v) Square tissue culture bottles (Milk dilution bottles, Kimble) with screw caps. Capacity 250ml.

(vi) Tissue culture tubes (Kimble) with screw caps. Tubes measuring 16 x 125 mm.

(vii) Centrifuge tubes (Pyrex glass).

(viii) Glass pipettes of the type used in the determination of ESR, but with a different calibration (in ml.).

All glassware was previously sterilized by means of wet sterilization in an autoclave and subsequently dried in a hot air oven. Special care was taken to avoid cleaning with alcohol or other chemicals.

b. Solutions.

(i) Water.

Only glass-distilled water was used throughout.

(ii) Salts.

All salts used were pro analyse.

(iii) Phosphate-Buffered Saline (PBS).

This was prepared according to the formula of Dulbecco and Vogt (1954).

α	NaCl	8.0 gm.
	KCl	0.2 gm.
	$Na_2HPO_4.2H_2O$	1.15 gm.
	KH_2PO_4	0.2 gm.
	Aqua dest.	800 ml.
β	$CaCl_2$	0.1 gm.
	Aqua dest.	100 ml.
γ	$MgCl_2.6H_2O$	0.1 gm.
	Aqua dest.	100 ml.

Solutions α, β and γ were autoclaved separately and mixed after cooling.

(iv) Hanks Balanced Salt Solution (Hanks Solution).

This was prepared according to the formula of Hanks and Wallace (1949).

NaCl	8.0 gm.
KCl	0.4 gm.
$CaCl_2$	0.14 gm.
$MgSO_4.7H_2O$	0.2 gm.
$Na_2HPO_4.2H_2O$	0.06 gm.
KH_2PO_4	0.06 gm.
Glucose	1.0 gm.
$NaHCO_3$	0.35 gm.
Aqua dest.	1000 ml.
Phenol Red	0.002%

* United Glass Bottle. Capacity ± 25 ml.

Method: The sodium chloride, potassium chloride, sodium phosphate and glucose were weighed together and then dissolved in one litre of glass-distilled water. The other ingredients were then added from stock solutions as follows:

40% Magnesiumsulphate	0.5 ml.
12% Potassiumphosphate	0.5 ml.
14% Calcium chloride	1.0 ml.
0.5% Phenol Red	4.0 ml.
1.4% Sodium bicarbonate	25.0 ml.

All the stock solutions were made in glass-distilled water.

The Phenol Red solution was prepared by first dissolving 0.5 gm. Phenol Red in 15 ml. of a .1 N NaOH solution. To this 100 ml. aqua dest. was then added.

With the stock solutions at hand much time was saved in preparing the Hanks Solution. After each use the stock solutions were re-sterilized in the autoclave. Notwithstanding sterilization, the sodium chloride, potassium chloride, sodium phosphate and glucose became easily contaminated by yeasts when kept in stock solutions.

(v) Complete Medium (CM).

This was prepared by adding 5 gm. of Lactalbumine hydrolisate, 100,000 units of Sodium penicillin, 100,000 units of Streptomycin sulphate and 50 ml. of calf serum to 945 ml. of the Hanks Solution.

Method: 5 gm. of Lactalbumine hydrolisate were dissolved in the Hanks Solution. After it was completely dissolved 100,000 units of sodium penicillin were added. Twenty ml. of the solution were then used to dissolve 1 gm. of streptomycin sulphate (1,000,000 units). Two ml. of the streptomycin solution were then added to the bulk of the Hanks Solution containing the Lactalbumine hydrolisate. The remaining 18 ml. of streptomycin were stored in deep freeze at -20°C, for future use.

The bulk of the medium was then sterilized by filtration through a glass filter (G 5 manufactured by Schott and Gen, Mainz).

Calf serum: At the abattoir a few litres of blood were obtained from the carotid artery of a calf. This was collected in a closed sterile glass jar. After a few hours, 100 ml. of the supernatant serum were pipetted off and filtered through a Seitz "K" filter sheet in order to obtain a clear specimen. Sterilization of the serum was achieved by means of further filtration through a Seitz "EK" filter sheet. Fifty ml. of the sterile calf serum were then finally added to the Hanks solution containing the Lactalbumine hydrolisate and antibiotics.

(vi) Trypsin solution.

A 2% stock solution of Difco-trypsin was prepared in PBS. This was filtered through a glass filter (G. 5) and then divided

among sterilized bijou bottles in amounts of 2 ml. in order to minimize the risk of contamination. The bottles were stored in deep freeze at -20°C until used. Shortly before use, 1:8 dilutions of the trypsin were prepared in PBS to give solutions of 0.25%.

(vii) Host Cell.

Various host cells were employed in this investigation. These included:

1. A strain of epithelial-like cells derived from a culture of lung fibroblasts (Lofi cells) obtained from a human foetus and grown in continuous culture; its properties do not differ essentially from those of HeLa cells.
2. Primary cultures of monkey kidney cells.
3. Primary cultures of human amnion cells.

4. Tissue Culture Technique.

Lofi cells were grown in square culture flasks containing 10 ml. of CM., at 37°C. Subcultures for the investigation of material from patients were periodically made in tissue culture tubes.

Method: After a proper layer of cells became visible on the floor of the culture flask, the old CM was pipetted off and discarded. The cells were then covered with 8 ml. of a 0.25% solution of trypsin in PBS (preheated to 37°C), and left standing for 30 minutes at 37°C. After this period all cells were loosened from the glass. The cell suspension was then placed in a sterile centrifuge tube and centrifuged for 5 minutes at a speed of 800 r.p.m. The supernatant was pipetted off and the deposit resuspended in 5 ml. complete medium. The number of cells present in one ml. of this suspension were then counted by means of a Bürker counting chamber. The cell suspension was then distributed over a number of tissue culture tubes and diluted with CM so that approximately 20.000 cells per ml. were present. These tubes were placed at an angle of 5° in specially constructed wooden racks and incubated at 37° C. It is necessary to add here that the growth medium of all cell cultures not inoculated was renewed once or twice a week.

Inocculation of material:

By means of a sterilized 1 ml. syringe with needle, 0.2 ml. of skimmed milk, containing material to be investigated were removed from a bijou bottle. This material was then inoculated on the cells present in a culture tube after the CM. was pipetted off. The cells with the inoculum were left standing for 30 minutes. One ml. of CM containing 100 units of Mycostatin (Squibbs) were added to the tube which was then returned to the incubator.

Inoculated tubes and controls were examined twice a week under the microscope for any cytopathogenic effect (CE). The tubes were incubated for at least two weeks (as a rule from 3 to 4 weeks) before they were discarded. No blind passages were made.

Results in Tissue Cultures.

We observed no cytopathogenic effect in any of the tubes examined microscopically. Since the time lapse between obtaining the specimen for investigation until inoculation onto cell cultures may be considered detrimental to the growth of any possible virus, it was decided to perform tissue culture investigation on a small scale at Groningen*). For this purpose the same procedure was adopted as described above except that Lofi cells (obtained from Dr. F. Dekking, Amsterdam) in continuous culture only were used.

Material from five patients with CRA, collected as described, was immediately inoculated onto cell cultures and examined every two days for the presence of a cytopathogenic effect. The inoculated tubes were incubated for 3 weeks before they were discarded. No cytopathogenic effect was observed.

*) This investigation was conducted at the Histological Laboratory of the State University, Groningen (Prof. Dr. F. J. Keuning.)

Chorio-allantoic Membrane Studies

Materials and Methods.

1. Nature of specimens investigated.

Part of each specimen obtained from an oral lesion of 15 cases with CRA and 2 with aphthosis, as described under tissue culture experiments (page 140), was also employed for chorio-allantoic membrane (CAM) inoculation.

The ease with which Sezer (1956) was able to cultivate a virus from blood of patients with aphthosis on the chorio-allantoic membrane, compelled us to perform similar investigations. Samples of venous blood were therefore obtained from 4 patients with CRA and two with aphthosis. All these patients presented oral lesions of which the clinical age varied from 3 to 5 days.

2. Collection of Specimens.

Scrapings of oral lesions were obtained as described on page and kept at -20° C until used.

Blood (5 ml.) was collected from patients by means of venepuncture carried out under sterile precautions. Syringes and needles used for this procedure were sterilized in an autoclave and dried in a hot-air oven. Contact with alcohol or other chemicals were avoided throughout. The blood samples were collected in dry, sterilized tissue culture tubes or bijou bottles and immediately dispatched by express train or car to the labpratory; this involved a time-lapse of approximately four hours. On its arrival at the laboratory, the supernatant serum was pipetted off and stored at -20° C. The blood clot was chilled and grounded with 2 cc. of physiological saline in a Griffith tube. The resulting supernanant fluid was then aspirated by means of a sterile syringe and needle and 0.2 ml. used for the inoculation of each of three chorio-allantoic membranes, while the remainder was stored in bijou bottles at -20° C.

3. Technique of inoculating the chorio-allantoic membrane (CAM).

The same technique as described by Dekking (1950) and Cath (1955) was used.

Fertile White Leghorn eggs were incubated for 10 to 12 days at a temperature of 37° C. The eggs were then trans-illuminated by means of a Mercury lamp to see whether the embryos were alive, and to mark a spot (4 x 4mm.) where no blood vessels were visible in the CAM. The shell over the marked area was gently removed with the aid of a dentall drill, care being taken not to damage the underlying shell membrane. At the same time a slit was made into the air sac. With the aid of a pipe-cleaner of which the one end was formed into a small loop, a thin layer of melted paraffin wax was applied over the exposed shell membrane. On this membrane a small quantity of antibiotic solution (broth containing 500 units each of strepto-

mycin sulphate and sodium penicillin per ml.) was dropped. With a sterile needle and without injury to the underlying CAM, the shell membrane was gently pierced so that the antibiotic solution was sucked on to the chorioallantois. The latter frequenly dropped after this procedure to form an artificial air space. This was easily perceptible from the change of colour in the shell membrane from a darker to a lighter shade. In some instances dropping of the CAM was achieved by means of suction applied to the hole over the air sac. For this purpose a rubber teat was employed. After an artificial air space was established, the wax-covered shell membrane was carefully removed with sterilized dental cotton wool forceps. Through the opening obtained in this way, material to be inoculated was carefully dropped on to the CAM. The egg was then gently rocked to and fro in order to spread the inoculum evenly over the membrane. The opening was then closed off by means of cellotape and the egg returned to the incubator at 35°C.

With the exception of two blood specimens obtained from one patient with aphthosis (case A in our series), only material from oral lesions were inoculated on to the chorio-allantoic membrane in our first experiments. In all cases, the technique just described was employed. As proposed by Cath (1955), in the case of herpes simplex, the amount of material inoculated on to each membrane was 0.1 ml. Whenever possible, three eggs were used for each patient at a time.

Our later investigations were conducted on the lines suggested by Sezer (1956). This necessitated two slight changes in the technique employed by us up to then. Firstly, the antibiotic solution used was replaced by a small quantity of physiological saline, and secondly the amount of material inoculated onto each CAM was increased to 0.2 ml. Blood specimens from 4 patients with CRA and 2 with aphthosis were inoculated in this manner. Only one oral specimen (from case 8 in our series) was subjected to this technique. On this occasion the patient was able to present herself in person at the laboratory. Scrapings from an oral lesion was obtained in the same manner as before, but this time the material was collected in a sterile bijou bottle containing 0.5 ml. physiological saline, and at once inoculated onto eggs.

Harvesting of the Membranes.

After inoculation, all eggs were incubated for 48 to 72 hours, whereupon the chorio-allantoic membranes were harvested. With the aid of sterilized scissors the egg was cut open across the air sac. The embryo and yolk sac then easily dropped out, while the CAM remained fixed to the shell. With sterile dental cotton wool forceps the CAM, together with any remaining shell membrane attached to it, were gently stripped from the shell. After removal from the egg, the CAM was conveyed to a sterile Petri dish containing psysiological

saline in which it was washed and neatly trimmed with sterilized scissors. It was then transferred to a dry sterilized Petri dish, and gently stretched and examined with the aid of a hand lens for the presence of any pock formation.

Results of our chorio-allantoic membrane studies.

With the material obtained from oral lesions in 15 cases (patients no. 1, 2, 3, 5, 8, 9, 10, 15, 16, 19, 20, 22, 26, 27, and 34 of our series) suffering from CRA and two cases (Cases A and B) with aphthosis, no pock formation resulted after inoculation on to the chorio-allantoic membrane of hen's eggs. Blood specimens obtained on two occasions from one case suffering from aphthosis (case A) and inoculated in a similar way as the oral specimens, produced suspicious-looking vague, oedematous, white patches in the membrane. This was considered an atypical reaction. These negative findings confirmed the results of Blank and Rake (1955), Sezer (1956) and Nasemann (1958). It also provided further evidence that CRA is not caused by the herpes simplex virus.

Since Sezer (1956) was able to cultivate a virus with ease from the blood of patients suffering from aphthosis, we decided to perform identical experiments. In this respect it should be noted that our experiments with the blood specimens from Case A mentioned above, differed from those performed by Sezer in that he never added antibiotics to material inoculated by him. Blood from a patient (case 8) suffering from CRA was therefore inoculated on to the CAM, without previously making use of the drop of antibiotic solution to effect dropping of the membrane, a physiological saline being used instead. The result was remarkable, for large pock-like lesions, resembling those reported by Sezer (1956), developed on the membranes of three eggs. These membranes were grounded up with sterile physiological saline and the resulting supernanant fluid inoculated into a firther batch of eggs. The results of this first passage were, however, less satisfactory, for vague oedematous white patches, similar to those described above in the case of patient A, developed. A further passage again revived our hopes, for clearly discernable greyish-white pock-like lesions developed on the CAM. Subsequent passages produced similar changes (Fig. 8). In the meantime, blood from the two cases with aphthosis and from our cases 2, 3 and 41 suffering from CRA, was inoculated in a similar way. The results were identical to those observed with the material obtained from our case 8. A peculiar feature, however, was that the formation of these pock-like lesions was sometimes followed by the formation of vague, white, oedematous patches, again to be followed by the formation of clearly visible pock-like structures in subsequent passages. In some of the membranes these pock-like lesions were accompanied by much congestion of the blood-vessels in the CAM. The oral specimen obtained from our case 8 and col-

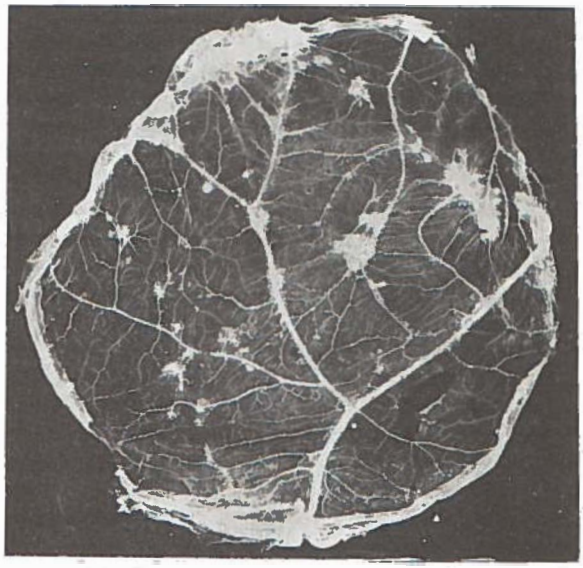

Fig. 8. Pock-like lesions produced on the CAM after the inoculation of blood from Case 8 with chronic recurrent aphthae.
(Photo: Virus Laboratory, University of Amsterdam).

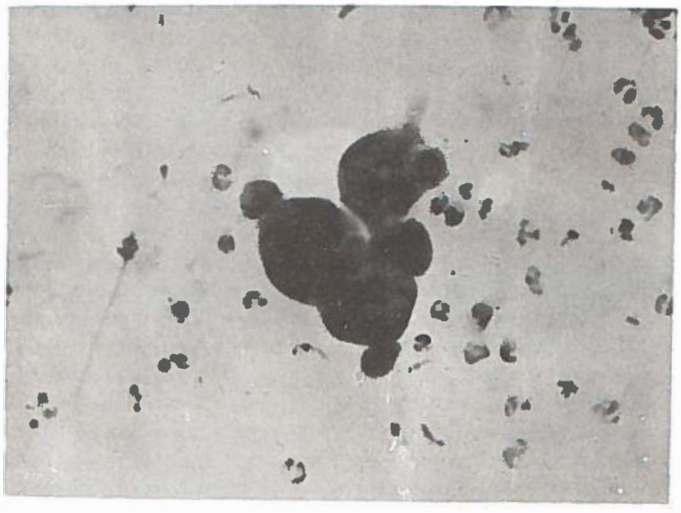

Fig. 9. Giant cells observed in smears made from a lesion of labial herpes. Weigert's haematoxylin. 450 x.
(Photo: D.C. Dijk, Dept. of Dermatology, University Hospital, Groningen)

lected in psysiological saline also produced vague oedematous lesions on the first passage. Subsequent passages produced pock-like lesions but always very few in number (five being the highest number counted).

Throughout our investigation death of the embryo seldom occurred. This was not in accordance with Sezer's findings. In the few instances where this happened, faulty technique must be considered responsible.

The fact that we were able to produce pock-like lesions in subsequent passages (as many as ten passages were undertaken in some instances) as well as the fact that as many as 40 of these lesions could be counted on occasions indeed gave rise to suspicion. Our hopes were, however, shattered when blood from normal individuals produced similar changes on the CAM.

Histological examination of the pocks performed by Dr. R. Korteweg of the Laboratory of Hygiene, Amsterdam, revealed ectodermal proliferation with oedema and numerous eosinophils in the mesoderm. No signs of a viral infection could be found, and these lesions are to be considered of traumatic origin (see below).

Sezer (1956) stated that he was readily able to produce a fatal encephalitis in mice after intracerebral injection of material from patients with aphthosis. He was also able to produce symptoms with the virus in young mice injected intraperitoneally. No details were given by Sezer, relating the nature and quantity of the material injected.

Experiments performed at the Laboratory of Hygiene, Amsterdam, in which newborn mice were injected intracerebrally and intraperitoneally, with material from patients with CRA and with aphthosis, produced no symptoms nor histologically detectable lesions. In these cases 0.03 ml., of the skimmed milk containing material from oral lesions, of the blood specimens and of the membranes showing pock-lesions, were injected intraperitoneally and intracerebrally.

Wyler and van Tongeren (1957) have clearly shown that non-specific lesions are frequently encountered on the chorioallantoic membrane. These authors could produce pock-like lesions on the CAM after inoculation of normal saline, destilled water, broth, skimmed milk, tissue suspensions and antibiotics. The pock-like lesions produced, varied more in degree than in kind, and ranged from small yellowish-white lesions to diffuse thickening and opacity of the membrane with whitish foci upon it. Histological examination of these non-specific pocks revealed similar changes to those found by Dr. Korteweg in the lesions observed by us. Wyler and van Tongeren (1957) stated that "from time to time membrane lesions are described as "specific" for some animal virus disease; when other workers fail to confirm such results it is probable that the lesions described may be non-specific".

Conclusions:

No virus could be isolated on the chorio-allantioc membrane of hen's eggs, after inoculation of material from 15 patients suffering from chronic recurrent aphthae and 2 patients with aphthosis. Our results suggest that the positive findings reported by Sezer (1956) and Evans et al. (1957) might have been of a non-specific nature.

II. COMPLEMENT FIXATION TEST.

In the course of a virus infection specific antibodies develop against the particular virus (Downie 1954). In the case of herpes simplex infections these antibodies persist throughout life and can be determined with the aid of the complement fixation test or with the virus neutralization test (Dekking, 1958).

The suggestion by various authors (Scott et al., 1941; Ziskin and Holden, 1943; Kilbourne and Horsfall, 1951) that herpes simplex virus might be the etiological agent of CRA led Stark et al. (1954) to determine the herpes complement fixing antibody titres in cases suffering from the disease. The results they appear in the following table:

	Number of patients	Number with C. F. Antibodies	Number without C. F. Antibodies
1. Cases suffering from CRA.	29	16(55%)	13
a. With a positive history of herpes	7	7	0
b. Questionable history of herpes	2	2	0
c. With a negative history of herpes	20	7	13
2. Controls not suffering from CRA	30	24(80%)	6
a. With a positive history of herpes	18	18	0
b. Questionable history of herpes	3	3	0
c. With a negative history of herpes	9	3	6

(A single antigen prepared on the chorio-allantois of hen's eggs was used by Stark et al.)

The fact that 13 of the 20 cases with CRA, having a negative history of herpes, had no demonstrable complement fixing antibodies was presumed evidence by Stark et al. that herpes simplex virus is not the etiological agent of CRA. These authors further observed that the median herpetic antibody titre of their subjects with histories of recurrent aphthae was approximately 1:2, whereas the median titre of the control group fell between 1:4 and 1:8. These authors regarded this finding as further evidence against the hypothesis that CRA is caused by the herpes simplex virus.

Sircus and associates (1957) compared the herpes complement fixing antibody titres of 42 cases with oral aphthous ulceration (of whom 23 had a positive history of herpes), 15 cases with recurrent herpes and 72 controls (of whom 34 had a positive history of herpes). In this study Sircus et al. made use of a single antigen. The number of cases in each group with a positive fixation, as observed by Sircus et al., is expressed in percentages as follows:

	Number of patients	Positive fixation	Negative fixation
1. Oral aphthous ulceration	42	59.5%	40.5%
a. With a positive history of herpes	23	60.9%	39.1%
b. With a negative history of herpes	19	52.7%	47.3%
2. Recurrent herpes	15	60.0%	40.0%
3. Controls without oral aphthous ulceration	72	34.7%	65.3%
a. With a positive history of herpes	34	44.2%	55.8%
b. With a negative history of herpes	38	26.0%	74.0%

The results suggest a marked similarity between cases of aphthous ulceration (59.5%) and recurrent herpes (60.0%). Different results were, however, obtained by Sircus et al. (1957), after making use of three different antigens prepared from mouse brain, allantoic membrane and rabbit kidney. These were as follows:

	Number of patients	Mouse brain neg.	Mouse brain pos.	Rabbit Kidney neg.	Rabbit Kidney pos.	Chorioallantoic neg.	Chorioallantoic pos.
1. Oral aphthous ulceration	10	4	6				
a. With positive history of herpes	4	0	4				
b. With negative history of herpes	6	4	2				
2. Recurrent herpes	14	0	14	7	7	6	8
3. Controls	22	6	16	13	9	15	7
a. With positive history of herpes	12	1	11	5	7	8	4
b. With negative history of herpes	10	5	5	8	2	7	3

From these results Sircus et al. (1957) inferred that in tests using mouse brain antigen, the evidence of herpes infection is clearly negative in cases of recurrent aphthous ulceration, but always positive in cases of recurrent herpes. This they considered strong evidence that aphthous ulceration is not caused by the herpes simplex virus.

Sera from 15 of our cases suffering from CRA were dispatched to the laboratory for an examination of the presence of complement fixing antibodies for herpes simplex, adenovirus, E. C. H. O. type 9, L. C. M., mumps and measles. Adeno-

virus (A.P.C.) seemed especially important, since Bataille (1958) suggested the possibility that one of this group of viruses might be the causative agent of chronic recurrent aphthae.

Material and Methods.

Blood (10 ml.) was obtained under aseptic precautions by means of a sterile syringe and needle from each of the 15 patients suffering from CRA and individually collected in dry, sterilized tissue culture tubes. Immediately after enough serum had formed in the tube, 2 ml. of it were aspirated under sterile precautions and dispatched in a dry, sterile tissue culture tube to the laboratory in Amsterdam.*) The specimen was not frozen or dispatched in a frozen state, since Lennette (1956) stated that "for the purposes of in vitro serology, there is no unequivocal evidence that shipment and storage of serum in the frozen state serves any special purpose".

All our patients on whom complement fixation tests were performed presented lesions (1-7 days old) in the mouth, at the time of obtaining the specimen, while all of them suffered from similar lesions 3 to 4 weeks prior to the examination.

At the laboratory, complement fixation tests were conducted by means of the micro-method described by Dekking (1950), in the case of ornithosis, and Cath (1955) in the case of herpes simplex.

Antigens of herpes, adenovirus, ECHO type 9, L.C.M., measles and mumps as used in the routine investigation of these diseases at the laboratory of Hygiene were employed in the tests.

In the case of herpes complement fixation tests, an egg antigen prepared from amniotic fluid, and from allantoic fluid from eggs inoculated into the yolk sac and allantoic cavity, were employed. In this respect, it should be noted that only eggs were used whose embryos did not die within two days after inoculation, nor were any eggs used whose embryos died later than five days after inoculation.

The results of the investigation were as follows:

Patient	Age	History of Herpes	C.F. Test for Herpes	A.P.C.	ECHO (type 9)	Mumps	Measles	L.C.M.
1	22	-	-	-	-	-	-	-
3	55	-	1:32	-	-	-	-	-
5	30	-	1:64	-	-	-	1:16	-
9	13	-	1:8	2 1:64 4 1:32	-	-	1:8	-
10	46	-	1:32		-	-	-	-
15	22	-	-	-	-	-	-	-
16	28	-	-	1:16	1:64	-	-	-
19	29	-	1.32	1:16	1:32	-	1:16	-
20	17	-	-	-	-	-	1:32	-
22	14	-	-	2 - 4 1:16	1:32	-	1:8	-
23	42	+	1:32	-	1:32	-	-	-
26	20	+	1:64	-	1:16	1:8	-	-
27	32	-	-	-	1:32	-	-	-
34	37	-	-	-	-	-	1:64	-
35	34	+	1:16	-	1:32	-	-	-

*) Complement fixation tests were done by Miss R. Braat of the Viral Laboratory of the University of Amsterdam (Dr. F. Dekking.)

Conclusion: Three of the examined patients had a positive history of herpes infection, confirmed by the complement fixation test for herpes. In addition, five of the twelve who gave a negative history showed the presence of herpes complement fixing antibodies. This finding must be considered the result of previous inapparent infection with the virus. A similar view was expressed by Stark and co-workers (1954). Subclinical infection with many viruses are known to occur (Downie, 1954). The fact that twelve of our patients with a negative history of herpes also showed a negative fixation for the virus, is further evidence that it is not the cause of CRA. This finding is in agreement with that of Stark et al. (1954) and Sircus et al. (1957). In this respect, it is also important to remember that these patients of us suffered from oral lesions 3 to 4 weeks prior to the time of examination for herpes antibodies. The results obtained with the complement fixation tests for adenovirus, ECHO type 9, mumps, measles and L. C. M. likewise form strong evidence against the possibility that any of these viruses play a part in the etiology of chronic recurrent aphthae.

Comparable results were obtained with complement fixation and neutralization tests in cases suffering from herpes infection (Cath, 1955).

With these two herpes tests, Stark et al. (1954) recorded almost identical results, in cases suffering from chronic recurrent aphthae.

No herpes neutralization tests were conducted in our study, since we did not expect to gain any more than was already known from the complement fixation test in these cases of possibly chronic infection.

III. SKIN REACTION.

In some viral diseases intradermal skin tests are often employed as an aid in diagnosis. Examples of such tests are the Frei-reaction used in cases of lymphogranuloma inguinale and the skin test proposed by Nagler (1944) in the case of herpes simplex infections. In both these instances use is made of antigens prepared from infected animal tissues or chicken embryos.

We could not find any reference in literature relating to a specific diagnostic skin reaction in the case of chronic recurrent aphthae. Claims, however, have been made of a specific skin reaction in the case of aphthosis.

Thiers, Colomb and Foyolle (1957) prepared an antigen from a cervical lymph gland of a patient suffering from hypopyon uveitis and recurrent oral aphthae. This was achieved by means of heating and formolization. Intradermal injection of the antigen provoked a positive reaction in one patient suffering from hypopyon uveitis without mucosal lesions, three patients with severe oral aphthae (of whom one also had skin

lesions) and one patient with iritis who suffered from oral lesions two years previously. A negative response was obtained in two patients with oral aphthae and in normal controls. A positive intradermal reaction consisted of a small, hard, elevated, slightly inflamed papule which lasted for a week. In two of the cases reported as positive by Thiers et al. (1957), the papule remained for three weeks, while a slight induration was still palpable after 30 days. Thiers and associates also employed their antigen as a vaccine and obtained excellent therapeutic results.

Jadassohn, Franceschetti and Golay (1957) adopted the technique used by Kornblith (1944), in the case of lymphogranuloma inguinale, to prepare an antigen from the skin lesions of a patient suffering from Behçet's syndrome. A biopsy was done of a non-ulcerating scrotal lesion of their patient (measuring approximately 1 x 0.5 cm.). The specimen was immediately frozen and cut into sections, which were collected in 1 ml. of normal saline and stored at $\pm$ 4° C. On four consecutive days the saline containing the lesion material was tyndallized for one hour at a time. Golay told us that this was done at 60° C.

After the last period of heating the material was filtered through filter paper. The clear filtrate was then used as antigen. 0.1 ml. of this so-called "Behçetine" was injected intradermally into the patient from whom the biopsy specimen was obtained, as well as in three controls who had never before suffered from aphthae. After 24 hours the patient showed a red infiltrated area of 10 mm. diameter at the site of injection. Forty-eight hours after injection, the injection area was surrounded by a red halo of 2.5 cm. diameter. After another 24 hours the reaction was still slightly positive but considerably diminished. In their three control cases the reaction was completely negative after 24 and 48 hours, the prick marks being almost invisible.

On the other hand, Vilanova and Pinol Aguadé (1958) prepared an antigen from saliva of patients suffering from aphthosis. Fresh saliva from a patient was diluted with a 7% sodium chloride solution in double-distilled water and filtered through thick gauze. The filtrate was then gently centrifuged and the supernatant divided over glass ampules so that each contained 0.5 ml. The ampules with their contents were then tyndallized at 60° C. for one hour on two consecutive days and then stored at 4° C. Intradermal injection of 0.2 ml. of this antigen in a patient suffering from aphthosis caused, within 2 hours, an erythema of 2 cm. diameter. The erythema disappeared completely after 72 hours. Twelve days later, however, an erythematous induration developed at the site of the injection. The papable nodule had the size of a hazelnut and was surrounded by by a red halo 3 cm. in diameter. This skin manifestation com-

pletely disappeared in three days. A similar response in this patient was obtained on four subsequent occasions. The delayed reaction then occurred at varying intervals of 13 to 19 days. Vilanova and Pinol Aguadé obtained similar results in three other patients suffering from aphthosis. In one of the patients recorded by them (case 6), who also suffered from recurrent skin lesions, a biopsy at the site of the delayed skin response to the antigen revealed the same histological picture as one of the patient' s skin lesions. The histological picture corresponded with that seen in Pfeiffer-Weber-Christian's panniculitis. This finding was considered by them an important prove of the value of their antigen. We must also add that Vilanova and Pinol Aguadé obtained spectacular therapeutic results after intravenous injection of their antigen into patients suffering from aphthosis. The third case recorded by them, where one eye had been enucleated and the other eye severely affected, almost completely regained vision after treatment with the antigen. Intradermal injection of the antigen in normal controls resulted in a transient erythematous reaction without delayed nodule formation.

The finding by the abovementioned authors of a specific skin reaction in cases suffering from aphthosis stimulated us to perform similar investigations. Confirmation of their results would not only give us some possible clue as to the etiology of the condition, but the finding of a common specific factor in cases of CRA and aphthosis would lend support to the view of Touraine (1941) that these conditions are actually the same disease. Our hopes were further strengthened by the positive skin reaction reported by Thiers et al. (1957) in cases who obviously suffered from oral lesions only.

Experience with Antigens prepared from Oral Lesions.

Having no cases suffering from aphthosis at our disposal at the beginning of our investigation we had to satisfy ourselves with an attempt to determine whether a specific skin reaction could be elicited in cases suffering from chronic recurrent aphthae. The method suggested by Thiers et al. (1957) was not deemed suitable, for none of our patients presenting oral lesions at the time revealed any palpable cervical lymph nodes. Since skin and scrotal lesions are not found in cases of CRA we were unable to use the method of Jadassohn et al. (1957). The only feasible method was that of Vilanova and Pinol Aguadé (1958). However, we decided to prepare an antigen from non-ulcerating oral lesions, thereby approximating a combination of the methods of Jadassohn et al. (1957) and Vilanova and Pinol Aguadé (1958).

Method.

Biopsies (approximately $\frac{1}{2} \times \frac{1}{2}$ cm.) were done on newly formed (one day old) oral lesions from two patients suffering

from CRA (cases 2 and 5). In both instances this was achieved under local block anaesthesia with the aid of a 2 per cent astracaine solution. The superficial epithelium covering the lesions appeared to be intact. Caution was taken to prevent unnecessary handling and contamination of the specimens. The latter were immediately frozen with the aid of carbon dioxide snow and cut into sections by means of a microtome. The sectioned material from each biopsy specimen was then transferred to sterile bijou bottles, each containing 1 ml. of sterile physiological saline and properly corked. The bottles were then stored at ± 4° C. On four consecutive days the bottles with their contents were subjected to tyndallization at 60° C. for one hour at a time. After the last hour of sterilization, the contents of the bijou bottles were separately filtered through sterile filter paper and the filtrates collected in sterile rubber capped ampules. In a similar way ampules containing physiological saline were prepared to serve as controls. All the ampules were kept at 4° C until used. In order to minimize the risk of infection, skin tests were performed with the antigens within two days after their preparation.

Results obtained with antigens prepared from oral lesions.

Four patients suffering from CRA (the two from which the antigens were prepared as well as cases 1 and 3) received 0.1. ml. of both antigens intradermally on the volar aspect of the arm. At the same time, 0.1 ml. of physiolocal saline was injected to serve as a control. In addition, three persons who have never had aphthae received similar injections.

Readings were taken after 20 minutes, 24 hours, 48 hours and 72 hours. Thereafter the patients as well as the control persons were kept under regular observation for three weeks.

In both patients and controls, an erythematous area became visible after 20 minutes on the side of the antigen injections. This erythematous area increased in size to reach its peak in 24 hours, when a slightly elevated papule was present. After another 24 hours only a small red area remained at the site of injection. Within 72 hours the reaction was completely gone. No reaction from the injection of physiological saline was encountered at any time. Subsequent follow-up of the patients and controls showed no recurrent reaction or nodule formation at the sites of antigen injections.

Conclusion: No specific skin reaction could be obtained in patients suffering from CRA after the intradermal injection of antigens prepared from oral aphthae.

Experience with Antigens prepared from saliva of patients with CRA and aphthosis.

Subsequently in our investigation, two patients suffering from aphthosis came to our notice. Therefore we decided to conduct further investigations in the hope of eliciting a specific skin reaction. Again we had to discard the method suggested

by Thiers et al. (1957) since none of the aphthosis patients revealed enlarged or palpable lymph glands. The method of Jadassohn et al. (1957) had to be rejected because the scrotal lesions present in the one case (Fig. 2)were already ulcerated at the time of examination. We therefore decided on the method of Vilanova and Pinol Aguadé (1958), employing saliva.

Method.

With the generous help of Prof. Dr. T. Huizinga, salivary antigens were prepared at the Dispensary of the University Hospital, Groningen. About 10 ml. of saliva were collected in neutral glass jars from each of three patients. Two of the patients (cases 2 and 3) suffered chronic recurrent aphthae and the other (case A) from aphthosis. At the time of collection of the specimens all three patients had lesions in the mouth. The same procedure was adopted in preparing the antigens as described by Vilanova and Pinol Aguadé (1958) (see page). In addition, another series of the same antigens was prepared likewise, but with the addition of 0. 5% phenol to act as preservative. A series of ampules containing a 7 per cent solution of sodium chloride, with and without the addition of 0. 5% phenol, was prepared to serve as controls. The ampules containing the antigens and control solutions were kept at $\pm 4^{\circ}$ C until used.

Results obtained with salivary antigens.

Intradermal injections of 0. 2 ml. of each antigen, as well as the same quantity of 7% sodium chloride solution, were given on the volar aspect of the arm in 13 patients and 3 normal controls. Eleven of the patients (cases 2, 3, 8, 10, 16, 19, 27, 31, 32, 35, and 37 of our series) suffered from chronic recurrent aphthae, while two (cases A and B of our series) suffered from aphthosis. The three controls never suffered from any lesions suggesting a diagnosis of either CRA or aphthosis.

Readings were taken after 20 minutes, 24 hours, 48 hours and 72 hours. Thereafter the patients and controls were kept under observation for three weeks.

Our results were rather disappointing. With the exception of one aphthosis patient (case A) all the other individuals gave an identical response, similar to that observed with antigens prepared from biopsy specimens of oral aphthae. No difference in reaction was observed between cases suffering from CRA, case B with aphthosis and normal controls. Case A developed a severe local reaction within a couple of hours after the injections. At all the injection sites (including those of the 7% sodium chloride solutions) postules developed surrounded by an intense erythema. After 24 hours a red line could be followed up the arm. On first sight it resembled a lymphangiitis, but closer scrutiny revealed inflammation along the course of a vein. This reaction subsided within about 7 days. No conclusions could be drawn from this reaction in case A, since many

cases of aphthosis, reported in literature, showed a sensitivity of the skin to all forms of injections and trauma (see page 54). All the other persons at all times showed a negative response to the 7% sodium chloride solutions, while after 20 minutes a local reaction to the different antigens occurred. Individually this reaction varied from a slight erythema to wheal formation. In the same way a varied response was observed after 24 and 48 hours. In some there were only slight erythema, while others showed a reddened, elevated papule. In all cases, except cases 3 and 10, the reactions were almost gone after 48 hours. All signs of a local reaction disappeared after 72 hours in cases 3 and 10. In none of the cases (including case A) a recurrent reaction or induration was found at the site of injection within three weeks following.

Conclusions: Our hope of substantiating the findings of Villanova and Pinol Aguadé (1958) met with failure. No specific skin reaction could be found in patients suffering from chronic recurrent aphthae or aphthosis after the use of salivary antigens.

IV. CYTOLOGY.

Tzanck (1948) proposed the use of cytologic smears as an aid in the diagnosis of certain skin and mucosal diseases such as pemphigus and herpes. Tzanck observed that multinucleated giant cells could be found in smears prepared from the vesicles of herpes simplex, herpes zoster and varicella. While no difference could be observed between the giant cells present in these three conditions, the method of Tzanck proved to be of value when a rapid differential diagnosis between smallpox and chicken-pox has to be made.

The diagnostic value of this method was considered by Blank and associates (1951). They concluded that it is a dependable, simple and rapid method of diagnosing herpes simplex, herpes zoster and varicella. The pathognomonic giant cells develope as a result of amitotic division in the nuclei of infected cells as we described in the histological picture of acute aphthous stomatitis. According to Blank and Rake (1955), each giant cell may contain as many as 15 nuclei, each of which may become as large as the original cell nucleus. The nuclei within the giant cells are filled with a homogenous, basophilic Feulgen-positive material.

The following technique was proposed by Blank et al. (1951): The youngest vesicle with clear contents that one can find is chosen and gently wiped off with alcohol. The top of the vesicle is then slit open with a small scalpel and the fluid contents gently absorbed with a piece of cotton wool. With the scalpel the base of the vesicle is curetted and the collected material spread on a glass slide. After the slide is airdried it is fixed in methyl alcohol and stained with Wright's Stain or Giesma's Stain. The dry, stained slide is mounted with a coverslip using

Canada balsam and then examined under the low power of the microscope.

Farmer (1956) was unsuccessful in his attempt to find multinucleated giant cells in smears, obtained from lesions in 10 patients with acute aphthous stomatitis, where as the diagnosis could be confirmed in histological preparations.

Dudgeon (1956) considered the method of Tzanck less satisfactory in the case of herpetic lesions of the mucosa than in the case of these on the skin. An investigation by Dudgeon into cases of chronic recurrent aphthae, in which this method was employed, revealed no evidence of any herpes simplex infection.

Cooke (1958) applied the method of Tzanck for the diagnosis of herpes simplex and herpes zoster affecting the oral mucosa. He made smears from lesions of ten patients dianosed clinically as suffering from primary herpetic gingivostomatitis, and from one patient with herpes zoster of the second division of the trigeminal nerve. Three slides were prepared from each patient in order to allow for the possibility that only a few cells are affected. The smears were stained with haematoxylin and eosin. In all the slides Cooke could demonstrate the presence of typical giant cells. In the discussion of his results, Cooke (1958) wrote: "Blank and Rake (1955) say that these microscopical changes are indistinguishable in the same tissue whether the lesion is primary or recurrent herpes simplex. Yet, smears taken from several cases clinically diagnosed as recurrent herpes simplex in the mouth in this department have not shown these changes. Apart from being recurrent these cases did not differ from the primary infections, except that they were less severe. If these clinical diagnoses were correct, perhaps this discrepancy arises from the difficulty of finding unbroken vesicles in the mouth; and it is not known for certain at which stage the affected cells may be found". This statement by Cooke (1958) lends further support to the viewa of Cath (1955), Blank and Rake (1955), Dekking (1958), Nasemann (1958), and our own findings up to now, namely that chronic recurrent aphthae is not caused by the virus of herpes simplex. The cases that were diagnosed in Cooke's department as suffering from "recurrent herpes simplex in the mouth" obviously suffered from chronic recurrent aphthae.

We decided to conduct a similar investigation on smears made from oral lesions of cases suffering from CRA and aphthosis. Such an investigation on smears, to confirm or exclude the presence of herpes simplex virus, would however be incomplete if no search is made at the same time for the presence of viral elementary bodies. The presence of such bodies in smears from oral lesions in cases of aphthosis were recorded by Behçet (1937), Melczer (1946), Haensch (1953) and Schuermann (1958a). Jensen (1941) and Curth (1946a), how-

ever, were unable to find such elementary bodies in smears from their cases of aphthosis. Behçet (1937) and Haensch (1953) employed the staining method of Herzberg (1934) for this purpose.

Cytological Investigation.

Smears prepared from the oral lesions of 20 patients with CRA and 2 with aphthosis were microscopically examined for the presence of multinucleated giant cells and viral elimentary bodies. The clinical age of the lesions of CRA varied from one to ten days, according to information vouchsafed by each patient. Again we must emphasize, that this information can be subject to error.

Preparation of Smears.

Since we did not encounter fluid-filled vesicles as observed in herpes infections in the cases of CRA and aphthosis, the method of obtaining material for the preparation of smears, as suggested by Blank et al. (1951), proved to be impractical. Attempts to slit open the grayish-with base of the lesions resulted in haemorrhage, making subsequent examination difficult. For this reason we contented ourselves with scrapings made of the base of each lesion with the aid of a sterilized scalpel. Material collected in this manner was thinly spread on sterile, dry glass slides. Six slides were prepared from each patient. Two of these were immediately placed in a closed jar containing equal parts of 95% alcohol and ether and kept until stained. This method was proposed by Boorsma (1956) for vaginal smears to be stained with the method of Papanicolaou and we found it equally suitable for oral smears to be stained with haematoxylin and eosin. Two other slides were air dried, fixed in methyl alcohol and subsequently stained with Giemsa's stain, as described by Blank et al. (1951). The remaining two slides were air dried and stained by the method of Herzberg (1934) for the purpose of eliciting the presence of viral elementary bodies, as described by Verlinde (1950). In a few instances additional air dried smears were also stained with Weigert's haematoxylin only, on account of it being very rapid and simple. This method was employed in the hope of showing the presence of viral type giant cells. An example of these cells, present in a lesion of labial herpes and stained with Weigert's haematoxylin, is given in Fig. 9.

Staining techniques.

1. Haematoxylin and eosin.

Fixed smears were stained with Weigert's haematoxylin (see below under 4) for 3 minutes, dipped in acid alcohol and rinsed in running water for 5 minutes. After this they were briefly immersed distilled water and stained with a 1% aqueous solution of eosin for 2 to 3 minutes.

Next the slides were passed successively through an alcohol

series (70%, 96% and absolute) cleared in xylol and finally mounted in Canada balsam.

2. May-Grünwald-Giemsa.

Air dried smears were fixed in methyl alcohol and covered by May-Grünwald fluid for 3 minutes. An equal amount of tap water was then dropped on to the slide. After one minute the May-Grünwald fluid and water were poured off and the smears covered with Giemsa's solution for 10 minutes. The smears were finally rinsed in running water, dried and mounted in Canada balsem.

3. Herzberg.

The air dried smears were placed in distilled water for 10 minutes after which they were dried at 37° C for one hour. Next the smears were stained for 10 minutes in Victoria blue. After this they were rinsed successively in two jars containing distilled water (30 seconds at a time). The stained smears were dried and examined for the presence of viral elementary bodies.

4. Weigert's haematoxylin.

Fixed smears were stained in Weigert's haematoxylin*) for 3 minutes and subsequently rinsed in running water. Next the smears were dipped in acid alcohol and then passed successively through 70%, 90% and absolute alcohol. The smears were finally cleared in xylol and mounted in Canada balsem.

Results.

In none of the smears from oral lesions of 20 cases of CRA and 2 of aphthosis did we observe any viral type giant cells after staining with haematoxylin and eosin or with Giemsa's stain. In our opinion, this finding must be considered further evidence against a herpetic etiology for these disorders.

With the method of Herzberg no viral elementary bodies were found in any of the smears of CRA and aphthosis cases. This result support the findings of Jensen (1941) and Curth (1946a) in the case of aphthosis. No explanation can be offered for the positive findings reported by Behçet (1937), Melczer (1946), Haensch (1953) and Schuermann (1958a).

* Weigert's haematoxylin is prepared shortly before use, by adding two parts of haematoxylin (1 Gm in 100 ml. 96% alcohol) to one part of ferrichloride solution (4 ml. Liq. ferri, 1 ml 25% HCl solut on and 95 ml. aq. dest.)

CHAPTER VIII

HISTOLOGICAL INVESTIGATION OF ORAL LESIONS OF CHRONIC RECURRENT APHTHAE AND APHTHOSIS.

Histological investigation was conducted at the Pathological Anatomical Laboratory, University of Groningen (Prof. Dr. H. N. Hadders).

Material and methods.

1. Biopsy Specimens.

Biopsy specimens consisted of oral lesions from 20 patients with CRA and 2 with aphthosis. The clinical age of the lesions varied individually from one to ten days. This age of the lesions was obtained from information vouchsafed by the patients and may therefore be subject to error in some instances.

2. Technique.

After local block anaesthesia with 2 to 4 ml. of a 2% astracaine solution, the lesions were excised by means of wedge-shaped incisions reaching as deep as the underlying connective tissue. The incisions were carried out in such a way that part of the surrounding normal mucosa was included with each specimen. The specimens were immediately fixed in 5% formalin or Bouin's solution. The biopsy wounds were primarily sutured with catgut.

At the Pathological Anatomical Laboratory the biopsy specimens were imbedded in paraffin wax, cut into serial sections of varying thickness (5-8 μ) and finally stained with haematoxylin and eosin, Weigert's fibrin stain, Giemsa stain periodic-acid-Schiff (PAS), toluidine blue. methyl-green-pyronin (Brachet) and Heidenhain's iron-haematoxylin.

Results of histological investigation.

Microscopical examination of day-old lesions of CRA revealed intact epithelium with slight parakeratosis (see fig. 10). In the epithelium, numerous large cells with pyknotic nuclei and pale vacuolated cytoplasma were visible (intracellular oedema). The prickle cell layer revealed locally the presence of intercellular oedema (spongiosis), while the intercellular bridges remained intact. No acantholysis was observed as in the case with pemphigus. In some areas the strongly vacuolated epithelial cells had formed an open meshed reticulum pointing to reticular degeneration with local intra-epithelial vesicle formation (fig. 11).Underneath the basal layer there was an accumulation of round cells invading the affected epilhelium and extending into the underlying tissue. The corium revealed the presence of numerous dilated blood vessels, surrounded by an infiltrate consisting of lymphocytes and an occasional polymorphonuclear (fig. 12). In these specimens of early lesions stained with haematoxylin and eosin and Weigert's fibrin stain no fibrin was present. The collagen fibres appeared normal.

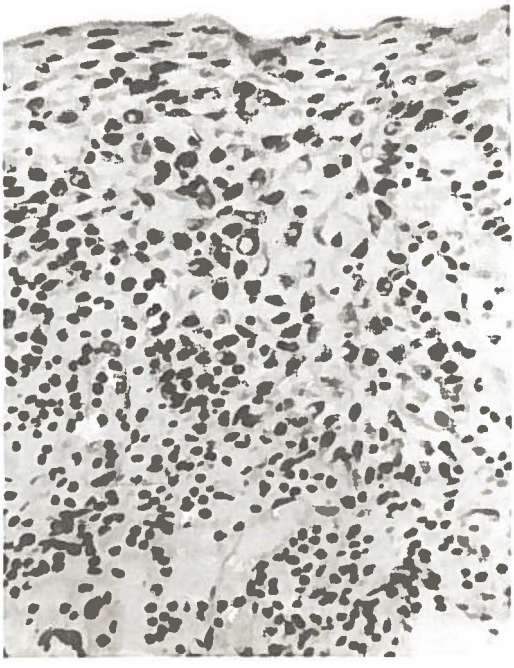

Fig. 10. Day-old lesion of CRA showing intact epithelium with slight parakeratosis and large cells with pyknotic nuclei and pale vacuolated cytoplasm.
(Haematoxylin and eosin, 300 x. Photo: D.C. Dijk, Dept. of Dermatology, University Hospital, Groningen)

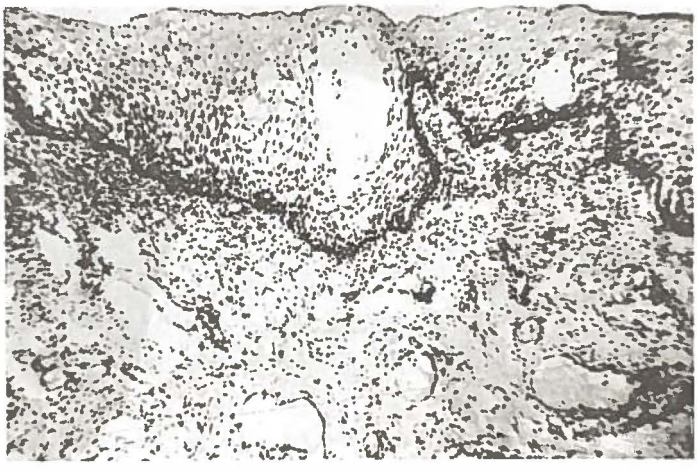

Fig 11. Day-old lesion of CRA revealing reticular degeneration with local intra-epithelial vesicle formation.
(Haematoxylin and eosin. 85 x. Photo: D.C. Dijk, Dept. of Dermatology, University Hospital, Groningen)

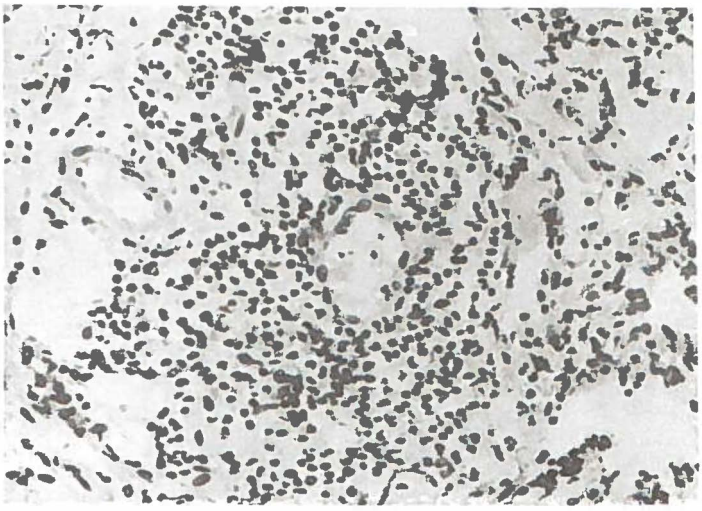

Fig. 12. Day-old lesion of CRA. Dilated bloodvessels in corium surrounded by a phocytic infiltrate.
(Haematoxylin and eosin. 280 x. Photo: D.C. Dijk, Dept. of Dermatology, versity Hospital, Groningen)

Fig. 13. Two-day old lesion of CRA revealing a defect of the epithelium covered with fibrin.
(Haematoxylin and eosin. 40 x. Photo: D.C. Dijk, Dept. of Dermatology, University Hospital, Groningen)

No fibrinoid changes were visible in the sections stained with haematoxylin and eosin, PAS (Hotchkiss-McManus) and Heidenhain's iron-haematoxylin. The endothelium of the dilated blood vessels showed oedematous swelling. In the sections stained with Giemsa and toluidine blue, a fair number of mast cells were visible. Ballooning degeneration or intranuclear inclusion bodies were not encountered in any of the sections. With the method of Hotchkiss and McManus no fungal spores or histoplasma bodies were found.

Examination of sections of two-day old lesions revealed a defect of the overlying epithelium covered with fibrin (fig. 13). The picture presented by lesions at this stage showed little difference from that at later stages of development. Under the defect, a massive infiltration of lymphocytes together with a variable number of neutrophil leucocytes, occasional eosinophils and plasma cells were found. Fibrin was observed between the cellular elements. In some cases a polymorphonuclear leucocytic infiltration dominated the picture. No fibrinoid changes were observed in the connective tissue or in the vessel walls in any of these older specimens. Plasma cells and eosinophils were always very few in number or completely absent. In all specimens, however, mast cells were present in fair numbers. No involvement of underlying glands was apparent in any of the sections we examined.

In the cases of aphthosis which we examined the earliest oral lesions were three days old (from case A). Those of Case B were already present in the mouth for five days. As far as the histological picture is concerned, we found no difference between the oral lesions of aphthosis and CRA.

Discussion of results.

Our histological investigation of sections of oral lesions in CRA and aphthosis cases revealed no distinct pattern. This finding seems to corroborate the view of Touraine (1941), namely that the histological picture of oral lesions is idential in the two conditions.

The reticular degeneration observed by us in the superficial epithelium of early lesions of CRA might be in favour of either a viral or an allergic etiology. According to Lever (1958), and Gans and Steigleder (1957), reticular degeneration is observed in viral infections and in contact dermatitis. Judgement should be reserved before a viral etiology can be assumed for CRA and aphthosis on histological grounds, since changes as described above were not pronounced in the sections examined by us. The absence of ballooning degeneration (considerable swelling of epithelial cells with a loss of their intercellular bridges) and intranuclear acidophilic inclusion bodies are evidence against a herpes virus etiology in our cases.

Frech (1945) considered the histological picture of chronic recurrent aphthae to be of an allergic nature. Similar views

were expressed by Talalov (1934) and Karani (1953) in the case of aphthosis. Frech (1945) arrived at his conclusion after comparing the histological picture of CRA with the so-called hyperergic inflammation (Gerlach) 1923). The hyperergic inflammation (extreme form is the Arthus Phenomenon) shows a great variety of manifestations, many of which are not specific for the condition. Its main characteristics are the occlusion of blood vessels in the area of reaction, oedema, swelling of connective tissue fibres, fibrinoid changes and a dense leucocytic infiltration.

It is generally conceded, however, that allergic inflammation shows no specific morphologic charateristics. According to Dijkstra (1958), fibrinoid necrosis of connective tissue, eosinophilia and the presence of epithelioid granulomata may focus attention on an allergic reaction. Businco (1958) stated: "Allergic conditions cause tissue changes of an oedematous and congestive nature accompanied by an infiltration of eosinophils and proliferation of perivascular histiocytes, together with the formation of cellular aggregates rich in lymphocytes and plasma cells of local origin."

Ruiter, of Groningen, in a series of publications (Ruiter and Brandsma 1948, Ruiter 1951, 1952a, 1952b, 1953, 1954, 1956) focussed attention on the vascular forms of allergy observed in the skin. On anatomical grounds he was able to distinguish two groups. In group A, called "arteriolitis allergica cutis", the pathological process is mainly confined to the small superficial bloodvessels in the connective tissue of the dermis, while in group B, referred to as the "cutaneous type of periarteritis nodosa", the process involves the medium-sized arteries of the muscular type at the cutaneous-subcutaneous junction or in the deeper fatty tissue. A detailed description of the clinical and morbid anatomical features of these conditions were again recently published by Ruiter and Hadders (1959). These authors found that the vessel changes in "arteriolitis allergica cutis" consist of an accumulation of fibrinoid material in and around the markedly thickened walls. They also observed perivascular infiltrates predominantly consisting of polymorphonuclear leucocytes together with lymphocytes and some eosinophils. A prominent feature was the nuclear disintegration of a considerable number of leucocytes. The infiltrates also invaded the vessel walls. A small number of reticulo-histiocytic cells were occasionally seen around the affected blood vessels.

Our hopes of finding similar changes in the oral lesions of CRA and aphthosis were not realised. In none of our sections stained with PAS, haematoxylin and eosin or Heidenhain's iron-haematoxylin any fibrinoid changes were observed in the walls of the blood vessels.

Van der Kwast (1957) found numerous plasma cells in histological sections of hyperplastic gingivae in epileptics treated with dilantin sodium. At the same time, he was able to demonstrate an increase in gamma globulin content of sera of such patients. Stimulated by the reports that immature plasma cells are responsible for the formation of antibodies, made by Fagraeus (1948), Keuning and Van der Slikke (1950) and Thorbecke (1954), Van der Kwast suggested the possibility of the proliferation of plasma cells together with hyper-gammaglobinaemia in his cases being the results of an allergic response to dilantin sodium. The reports, that numerous plasma cells were present in the lesions of their patients, made by Fergusson (1939a; 1939b) in the case of CRA, and Wien and Perlstein (1932) in that of aphthosis, therefore enticed us to conduct a special search for the presence of these cells in our cases.

Again we were disappointed, for none of the sections stained by the method of Brachet (methyl-green-pyronin) revealed the presence of any considerable number of plasma cells. On the contrary, most sections were completely devoid of any of these cells. To this we can add the fact, that no hyper-gammaglobinaemia was encountered in our patients (see page).

In this respect it should be noted that Frech (1945) and Miller (1954) found only occasional plasma cells in their patients with CRA, while similar reports were made by Talalov (1934) and Popoff (1938) in the case of aphthosis.

Our attention was also directed to a statement by Phillips and Scott (1955), who suggested that aphthosis was in all probability a disease of collagen. The so-called "collagen diseases" are supposed to be characterized by changes in the cementing ground substance of the collagen fibres. On the other hand the changes in the collagen fibres are possibly of a secondary nature (Van der Kwast, 1957). Lever (1958) speaks of fibrinoid degeneration of collagen in the case of acute erythematosus. This degeneration is characterized by changes in the interfibrillary mucoid ground substance as well as in the collagen fibres themselves. According to him the interfibrillary ground substance appears as homogenous, intense eosinophilic, refractile "fibrinoid" masses, while the collagen fibres are thickened and gell-like in appearance, while they stain deeply eosinophilic. According to Lever, fibrinoid material shows metachromatic staining with toluidine blue and gives a positive PAS reaction. Altshuler and Angevine (1949) found that fibrinoid is formed as a result of precipitation by alkaline proteins of acid mucopolysaccharides in the ground substance. The alkaline proteins are formed as a result of tissue necrosis or as a reaction to injurious substances by the tissue. They found that fibrinoid invariably gave a positive PAS reaction. Ehrich (1952) found numerous plasma cells and hyper-gammaglobinaemia in collagen diseases. As was pointed out by Van der Kwast (1957)

we have to infer that Ehrich considered an allergic etiology very attractive for such diseases.

In our investigation, none of the specimens stained with toluidine blue revealed evidence of metachromasia in connective tissue, while negative results were obtained with the PAS reaction. If we add to this the fact that no increase of gamma globulin was found in the sera of our CRA patients, we must conclude that it is not a disease of collagen.

In early lesions of CRA we found the primary changes in the epithelium. What value may be attached to this finding? Extensive investigations were carried out on the intradermal changes of eczema. If we want to apply these findings in eczema to CRA, we should have to accept the fact that the tissue changes in the latter are due to the milieu, which is still unproved.

Miescher(1952a;1952b) described the histological picture of acute allergic contact dermatitis. According to him, the initial stage in the development of the lesions (within 6 to 12 hours after contact with the allergen) is characterized by the formation of local spongiosis in the deeper layers of the epidermis, while the epithelial cells in the affected area showed no morphologic changes. This early stage of development was accompanied by lymphocytic infiltration into the affected area. Polymorphonuclear leucocytes or eosinophils were as a rule absent but may appear under certain conditions, especially when the process reach the epithelial surface. Miescher considered subsequent changes in the histological picture to be of a secondary nature. These changes which follow on the exudative primary change are often characterized by the presence of polymorphonuclear leucocytes. According to him, subcorneal pyknotic vesicle formation is in favour of a toxic origin of the lesions. Here one finds a local dissociation of epithelial cells which lose their staining abilities, while their nuclei become pyknotic. The affected area is infiltrated by lymphocytes and often also by polymorphonuclears.

On the other hand, Haber (1954) stated; "It should be emphasized that intercellular oedema, or spongiosis leading to the formation of vesicles is the main feature of an eczematous reaction but does not necessarily imply that it is of allergic origin."

In the sections of these early lesions of CRA, we found a distinct (primary) cell degeneration along with areas of typical lymphocytic spongiosis. From this finding one may infer the presence of both allergic and toxic factors. The clinical manifestations of CRA and eczematous reactions of the skin are so different that it seems to us unjustified to draw a definite conclusion from the histological picture.

Eosinophilia.

Tissue and blood eosinophilia are often encountered in al-

lergic conditions. The function and behaviour of these cells are not known. Their diagnostic value in atopic dermatitis and other members of the atopic syndrome (hay fever, vasomotor rhinitis and asthma) was described by Sulzberger and Witten (1954), Burbach (1957), Veening (1958), Voorhorst (1958) and Savelberg (1958).

Ramirez (1938) stated: "I do think that the presence of a local tissue eosinophilia is rather important corroborative evidence of local allergy".

The absence of eosinophils, however, does not rule out the possibility of allergy. In the case of contact dermatitis, for instance, lymphocytes predominate whereas eosinophils are only occasionally observed.

Veening (1958) extensively reviewed the factors bearing a relationship to the blood eosinophil count.

The fact that sections of oral lesions, from CRA and aphthosis cases examined by us, were practically devoid of eosinophils, therefore does not rule out the possibility of an allergic etiology.

Mast cells.

The presence of fairly large numbers of mast cells in the sections examined by us, naturally raised the question what importance to attach to them.

Jorpes, Holmgren and Wilander (1937), cited by Jorpes (1946), traced the heparin content of the body to the mast cells, while Riley and West (1953) showed the presence of histamine in these cells. Riley (1953) was able to demonstrate a correlation between the mast cell contents and the histamine value of a variety of normal and pathological tissues. Graham and co-workers (1952), cited by Riley (1955), gave evidence that much of the blood histamine also resides in the basophils. We can therefore infer that tissue mast cells and basophils have much in common.

Prakken and Woerdeman (1952) recorded that in all cases with a high tissue eosinophil count, examined by them, there were also a corresponding high number of mast cells present. On the other hand, these authors found that the presence of large numbers of mast cells was not always accompanied by tissue eosinophilia. They speculated on the possibility that mast cells may be an essential requirement for the development of tissue eosinophilia.

Cahn (1942) observed the presence of large numbers of mast cells in the normal oral mucosa. We are therefore unable to draw any conclusions from the fact that mast cells were present in considerable numbers in the lesions examined by us.

Cases of aphthosis.

Case A. J.W.H.J. (Hosp. no. 22778). Male, aged 41. Indonesian born in Java. Married. Occup: Motor mechanic.
Patient seen by us on 16-3-'59, 11-4-'59, 12-4-'59 and 21-4-'59.

Previous History: Patient suffers from oral lesions as long as he can remember. The lesions heal within two to three weeks without scarring, but tend to recur almost continuously. He was free from oral lesions for about two years while a prisoner of war in a Japanese prison camp in Timor. As a child he suffered from a discharge from the one ear. Since that time he also suffered repeatedly from skin lesions. According to the patient he also contracted malaria while in Java and at the same time suffered from attacks of diarrhoea. Since 1948 he lives in Holland. In 1955 his right eye began to ache. At he same time he noticed blurring of vision. He then received treatment at the Eye Clinic in Utrecht. He continued to have attacks of inflammation in this eye. In 1956 the other eye also became involved. This time he was admitted to the Eye Clinic, Wilhelmina Gasthuis, Amsterdam (Prof. Dr. A. Hagedoorn). In he meantime he experienced recurrent attacks of oral and skin lesions. From time to time he received treatment in hospital for his eye condition. On four occasions he also suffered from ulcerations on the penisand scrotum. On some occasions the eye exacerbations were accompanied by increased temperature and furunculosis.

The hospital record (Eye Clinic, Amsterdam) revealed the following facts: 16-6-'56: Vision: L.E. 1, R.E. 1; 17-7-'56: chorioretinitis in both eyes; 11-11-'57: patient admitted to hospital, vision: L.E. 3/60, R.E. 1/10; 13-11-'57: hypopyon left eye. ESR. 34 mm./first hour. Blood picture normal. Pirquet ±: X-rays of skull and thorax negative. 18-11-'57: Bang test negative. 20-11-'57: Vision L.E. 1½/60, after correction C + 1.00 axis 90°: 3/60; R.E. 1/10 after correction S + 0.50 = C + 1.00 axis 90°: 1/10. The conjunctivae slightly injected. Corneae show superficial maculae. Ant. chambers slightly clouded with a number of cells. Irides show no active process. Right iris reveals on temporal aspect a small posterior synychium. Pupils dilated. Lenses clear. Vitreous: On the right much opacities. On the left a similar picture.
Fundi: R.E.: in macular area a dark red spot surrounded by a brownish-gray halo. This gives the impression of a small defect. Papilla normal. In upper nasal quadrant an obliterated vessel, possibly an artery. L.E.: extensive exudative chorioditis with small haemorrhages, situated in the centre and below. Eye pressure normal. Fields of vision: bilateral central scotoma. 21-11-'57 Patient developed a high temperature with the typical picture of acute appendicitis. Transferred to the Department of Surgery where an appendicectomy was done. During the post-operative period a wound abscess developed. 6-12-'57 Patient returned to Department of Ophthalmology. Eye condition at rest. Following phenomena were recorded: 1. Patient reacts to all injections and venepunctures with the formation of local infiltrates and pustules. Cultures from material of the latter negative. 2. Patient complains of severe oral aphthae. At this stage a diagnosis of Behçet's syndrome was made. 10-12-'57: Tot. Serum Protein 7.7 gm%, Albumin 38.4%. Alpha ($\alpha_1 + \alpha_2$) globulin 7.2% Beta ($\beta_1 + \beta_2$) globulin 10.9%, Gamma globulin 20.5%. 10-2-'58: Tot. Prot. 6.7 gm%, Alb. 37% alpha ($\alpha_1 + \alpha_2$) globulin 6.0%, beta ($\beta_1 + \beta_2$) globulin 7.2%, gamma globulin 16.8% 15-10-'58: Viral cultures on material from leg ulcer negative (Dr. F. Dekking). 30-12-'58: Re-admitted in the Wilhelmina Gasthuis with a recurrent attack of uveitis. Vision L.E. 5/60. Anterior chamber slightly opalescent. Vitreous slightly clouded. Fundus no new foci. R E. Vision 3/60. Eye slightly injected. Many cells in ant. chamber. Vitreous cloudy. Fundus reveals on temporal side of macula a new focus with small haemorrhages 13-3-'59 Quantitative fat analysis of faeces after Schmidt's diet normal.

Family history: Mother and sister also suffer from recurrent oral lesions. Otherwise negative.

Examination on 16-3-'59: Six aphthae present in he mouth. Two on inside of upper lip. One on tongue and three on lower lip (one in right comer of mouth resembling the so-called "Faulecke"). The remainder of the oral mucosa fiery red and oedematous while a purpuraic lesion was present on the right side of the tongue. Teeth in a good condition. The right eye revealed the presence of a hypopyon. On the dorsum of both hands haemorrhagic spots in the skin. On the anterior aspects of the lower extremities haemorrhagic nodules the size of a pea. No genital lesions present. No lymph glands palpable. Scrapings of oral and skin lesions obtained for viral investigation. Saliva collected for the preparation of antigens. At the same time biopsies done of two oral lesions and fixed respectively in 5% formalin and Bouin's solution (both the biopsy lesions were approximately of three days duration). 11-4-'59. Three oral lesions present. One the size of a pinhead on inside of

upper lip and two the size of a match-end on the edge of the tongue. Entire mucosa appeared to be inflamed. No hypopyon present. Oral scrapings, blood and faeces collected for viral investigation. Skin tests performed on patient with salivary antigens. Within a couple of hours pustules developed at the sites of intradermal injeotion. On 12-4-'59 a phlebits was visible along the course of a vein on the injected arm. The patient never at any time revealed time nervous involvement, diarrhoea or joint manifestations.

Case B. H.P. Male, aged 35. Married. Four children. Office worker. Caucasion. Born in the Netherlands.
Seen by us on 15-4-'59, 16-4-'59, 17-4-'59 and 21-4-'59 at the Department of Internal Medicine, University Hospital, Groningen .

Previous History: On 31st July 1958, the patient developed a painful nodule below the right knee. This was followed three weeks later by a similar lesion below the left knee. Before this time he never suffered from such lesions. Since July 1958, he frequently suffered attacks of these skin lesions. They appear on the arms and legs (especially calves) where they can be felt as nodules in the skin. According to the patient these nodules appear more superficially on the legs than elsewhere. Since September 1958 he also suffered from recurrent oral ulcers. These heal within 7 to 10 days and recur at intervals of 3 weeks to a month. At the same time (Sept. 1958)) he developed ulcerson the scrotum which healed in a week's time. On a number of occasions he also suffered from swelling of the right knee for which he was admitted to the hospital in Emmen. He never suffered from diarrhoea or eye lesions. He was admitted to the wards of the Department of Internal Medicine, University Hospital, Groningen on 6-2-'59 with erythema nodosum. On 12-2-'59 the patient was referred to the Department of Oral Surgery where carious teeth and roots with granulomas removed. No history of previous herpes. After removal of the teeth the skin lesions rapidly disappeared and the patient was discharged from hospital on the 3rd of MarchOn 23-3-'59 the patient was readmitted with new attacks of skin and oral lesions

Examination: On 15-4-'59 oral examination revealed the presence of six aphthae which, according to the patient developed on 10-4-'59. On the right-hand side of the tip of the tongue was a pea-sized lesion presenting a grayish-white base and surrounded by a thin red halo (fig. 1). On the dorsum of the tongue two more slit-like lesions were present. On the inside of the lower lip a pea-sized lesion, showing the same characteristics as the one on the tip of the tongue. In both comers of the mouth similar lesions were found. On the right thigh the patient had a pustular lesion surrounded by a narrow red border. On the scrotum two ulcers were visible. Both showed a slightly depressed base covered with a grayish-white membrane (fig. 2) This was his second attack of lesions on the genitals. On the calf of the left leg an erythema nodosum-like lesion was visible. No lymph glands were palpable. A biopsy was done of the aphthae on the inside of the lower lip. Skin tests were also performed with salivary antigens, while scrapings of oral lesions together with blood were collected for viral investigation. General examination N.A.D. B.P. 135/80. Pulse: normal.

Laboratory data[1]) of the patient revealed the following: 23-3-'59: Diff. blood count: Eos 1%, Rod forms 1% Segm. polymorphs 69% Lymph. 25%, Monos 4%. 24-3-'59: Urinalysis: clear yellow colour. S.G. 1015, urobilin +, Bilirubin -, Albumin -, Reaction: Acid, Reduction -, Sediment: A few erythrocytes and Ca-ox late crystals. Tot. Proteins 6.90 gm% Albumin 46.7%, Alpha ($\alpha_1 + \alpha_2$) globulin 18.7%, Beta globulin ($\beta_1 + \beta_2$) 11.6% Gammaglobulin 23.0%. X-Rays of thorax revealed no pathology . E.C.G. normal. Report of the neurologist negative, Subsequent examination of the blood revealed the following Hb. 15 gm% Erys. 5,190,000, Leucos. 10,000 Diff. count Eos 2% Rods 1% Segm. Forms. 62% Lymphos. 26% Monos 9%. ESR 16/28 mm. Urine: Urobilin ++ L.E. cells negative. Sodium 139.3 m.aeq./L. Potassium 4.7 m.aeq./L. Chlorine 100.7 m.aeq/L. Wa R. neg. Liver function: Bilirubin (direct) -, Quantitatively 1.05 Units. Tot. Cholesterol 2.39% Esters 1.45% Calcium Formol Gel Reaction -. Alk. Phospathase 12.3 Units. AST 150 U/cc L. agglutination 1:160.0 agglutination neg. Rose test negative, Sternal puncture: normal marrow. Serum Proteins: Tot. 6.95 gm%. Albumin 50.0%. Alpha ($\alpha_1 + \alpha_2$) Globulin 17.2% Beta ($\beta_1 + \beta_2$) Globulin 11.1% Gamma Globulin 21.5%. Skin tests on allergy: negative. During his sojourn in hospital the rectal temperature was increased up to 38.4°C.

Biopsy report2) on skin lesion: Normal epidermis. Scattered perivascular infiltrates in subcutaneous tissue. One subcutaneous vessel reveals slight thickening of the vessel wall. Slight fibrosis with lymphocytic infiltration. No necrosis. No eosinophils. Vasculitis present but the picture does not correspond to that of other vascular disorders of the skin such as periarteritis nodosa.

1) These data are published with due acknowledgement to the Department of Internal Medicine, University Hospital, Groningen
2) Histological investigation was performed at the Department of Dermatology (Prof. Dr. M Ruiter)

CASES OF CHRONIC RECURRENT APHTHAE.

Case Reports.

Case 1. G.J.B. (58/1958), Female, aged 21. Single. Probationer nurse.
First visit 29-7-'58. (Referred by Dr. J J. Speelman, Institution "Dennenoord", Zuidlaren).
History: Recurrent ulcers in the mouth as long as she can remember. They first appeared singularly with intervals varying from 2 to 3 months. Since the previous three months never free from lesions which appear in greater numbers than before. The lesions are very painful and develop on any part of theoral mucosa, but especially on the inside of the lower lip. According to the patient, each lesion begins as a painful reddened area which can be felt as a slight elevation with the tongue. Within 24 hours, a tiny, whitish ulcer can be seen at the site of the elevation which gives rise to intense pain when eating and talking. The pain lasts for about 5 days after which the lesions heal gradually to disappear from within 10 to 14 days without scarring. The lesions were apt to occur more frequently if she made herself nervous. (This statement by the patient was in accordance with the observation made by Dr. Speelman, who found that the present stubborn attack of lesions coincided with the fact that she failed in her recent examination). The lesions bear no relationship to the menses, the eating of particular foodstuffs or climatic conditions. No history of allergy, previous herpes labialis, menstrual disorders, diarrhoea, genital skin or eye lesions. Her father and one sister suffered from similar lesion. Family history otherwise negative.

For the past two months she was treated by Dr. Speelman with succenyl cortisone lactate troches and Nivaquine without any benefit.

Examination: Nervous young woman of otherwise normal appearance and built. General examination: NAD. B. P. 130/90. Rectal temp. 37.9°C.

Intraorally: On the dorsum of the tongue near the left border two round aphthae were present. They were situated one behind the other at a distance of about two centimetres apart. Both measured approximately 4 mm in diameter. Their bases were slightly depressed and has a grayish-white appearance. The edges were not elevated or undermined. Around the lesions, a slightly reddened zone was visible. Both the lesions appeared at about the same time, seven days earlier. On the inside of the lower lip and on the mucosa of the left cheek five more lesions of similar appearance as those on the tongue could be found. All of them were the size of barley seeds. They appeared subsequent to the lesions on the tongue, but the patient could not recollect exactly when. Two of the lesions were situated opposite the left lower canine; one above the other at a distance of 5 mm apart; two were situated opposite the right and left lower incisors; while one was visible on the left interdental line. All of them had a yellowish-white appearance and were surrounded by a red halo of 1 mm. width. The remainder of the oral mucosa had a completely normal appearance.

All teeth were present except for the $\underline{8|}$ which according to the patient had not yet erupted. $\frac{6}{} \,|\, \frac{4\ 5\ 6}{}$ revealed amalgam fillings. All the teeth reacted normal to cold, heat and $7\ 6\,|\,5\ 6\ 7$ Faradic stimulation.

The gingivae around the upper and lower anterior teeth presented the picture of chronic gingivitis with a tendency to bleed. Around these teeth subgingival and supragingival calculus was present. No pockets could be detected. Slight salivation was present. Foetor ex oris was prominent, but not of the character of that found in Vincent's infection.

Röntgenograms of the teeth revealed no apical infection or loss of alveolar bone.

Results of Laboratory investigations:

Blood Morphology: Rbc. 4,400,000, Wbc. 7600 (Eos. 0.17%) Thrombos. 427,000, Hb. 83%.
Differential count: Segm. forms 86, Lymphos 10, Monos 4.
Bacterial and Serological Investigation: Microscopically few Gram + cocci mostly in duplo and few pseudodiphtheria-like Gram rods. No yeast forms present.
Bacterial cultures provided streptococcus viridans and pseudodiphtheria bacilli
Yeast cultures negative.
Guinea-pig test on Tb negative.
Wassermann negative. V.D.R.L. negative.
Cytological investigation revealed no viral type giant cells or inclusion bodies.

DIAGNOSIS: CHRONIC RECURRENT APHTHAE.

10-9-'58: Since the first visit the patient received aureomycin capsules per os (250 mg.

every 6 hours for 3 days) and injections of Vitamin B complex (2 c. c. three times a week intramuscularly) from Dr. Speelman. Initially improvement took place, but after the patient encountered difficulties with immigration plans new lesions appeared in the mouth.

Five lesions were now present, varying from the size of a pinhead to that of a lentil; two were on the dorsum, one on the tip and one underneath the tongue, while the fifth was situated in the lower labial sulcus. The lesions had the same characteristics as those observed during the first visit.

19-9-'58. All the lesions present at the second visit (10-9-'58) were completely healed except for the one on the tip of the tongue which was still visible, but almost healed.

Nine new lesions, however, could be found on the tongue and on the inside of the lower lip.

Biopsy was done on two lesions which, according to the patient, were present for about one day.

Pathological anatomical investigation (result no. 123333): Macroscopically: Biopsy material consisted out of two pale tissue fragments, the size of a match-end.
Microscopically: Two pieces of oral mucosa showing mucous glands, an epithelial defect and an inflammatory infiltrate. The picture can fit in with that of aphthous stomatitis. There are no signs of specificity.

26-9-'58. All the lesions observed on 19-9-'58 were completely healed. On the left side of the frenulum lingua an oval aphtha (1 cm x ½ cm) with a yellowish-white base and surrounded by a red halo of 1 mm. was present. The lesion started on 24-9-'58.

Viral investigation: No virus cultivated in tissue cultures.

Complement fixation test negative for A.P.C.-virus, Herpes, L.C.M., ECHO type 9. Mumps and Measles.

30-9-'59. Patient admitted to hospital for further investigation.

On the day of admission no lesions present in the mouth.

1-10-'59. A new lesion developed in the lower buccal sulcus opposite the left lower canine. It had the size of a match-end with a slightly depressed yellowish-white base. Around the lesion was a narrow red border of 2 mm. width. On the same day the patient began to menstruate; it lasted until 5-10-'58.

6-10-'58. Endocrinological investigation: No evidence of any hormonal disturbance. Menstruation normal. BMR 0. Slight muscular development. No abnormal fat deposit. Skin pigmentation slight. Hair distribution normal. Skeletal age determined röntgenologically 21 Length 171 cm. Weight 55 Kg . A 24 - hour urine specimen(1430 ml.)provided the following:

Neutral 17 - Ketosteroids	16.6 mg.
17 - Hydroxycorticosteroids	9.1 mg.
FSH	11 Mouse Units.
Oestrogenic substances	24-48 I.U.

Case 2. J.H.W B. (58/1760). Male, aged 32. Married. One child. Builder. First visit 7-7-'58 (Referred by Dr. F.J. Reneman, Groningen).

History: Suffer from ulcers in mouth as long as he can remember. Lesions very painful. The patient is of the opinion, that the outbreaks are more severe in summer, when the first fruit appear on the market. Grapes seemed to him especially liable to cause attacks. He is, however, also subject to attacks during the winter months. The lesions seem to appear periodically, but the patient cannot relate exactly with what intervals. Since April 1958 he was practically never free from lesions. Individual lesions heal from within 7 to 21 days. His baby daughter of 10 months recently had similar lesions in the mouth accompanied by salivation, for which she received treatment at the local children clinic (Acute aphthous stomatitis?). Family history otherwise negative.

According to the patient the lesions begin with a sensation of burning in the mouth to be followed the next day by the formation of a small white spot, the size of a pinhead The spot is situated on a localized area of redness. In the course of the next three days a typical yellowish or grayish-white ulcer is formed.

No history of diarrhoea, constipation, fever or malaise. Never had herpes labialis. No history of genital or skin lesions. Recently the patient suffered from a stye on the left lower eyelid, otherwise no history of eye lesions.

Examination: Adult male of normal appearance. Well nourished, of normal weight and build. General examination: NAD. Rectal temp. 36.9°C; B. P. 120/80.

Intraorally: On the inside of the lower lip, opposite the crown of the right lower canine was an irregular lesion (1 cm x 1 cm) of four days duration. The shape of the lesion resembled that of a triangle. The floor of the lesion was slightly depressed and had a grayish-white colour. Around the lesion an inflamed zone of 1 cm width was visble. The lesion had a

firm consistency. Lesion very painful when touched, The remainder of the oral mucosa was of normal appearance. No enlarged lymph glands palpated.

Upper jaw edentulous. Patient wearing a full upper acrylic denture. In the lower jaw

3 2 1 | 1 2 3 5 still present. No signs of parodontal disease or caries.

Diagnosis Chronic recurrent aphthae.

16-7-1958: Lesion present on 7-7-1958 almost completely healed. Since 15-7-'58 a new lesion present on the inside of the lower lip This lesion was almost round in shape and was the size of a match-end. The base of the lesion had a yellowish-white colour, while the edges had a punched-out appearance. Around the lesion was a red border of 1 cm.

Laboratory investigations:

Bacterial investigation (Bacteriological Serological Routine Laboratory: Prof. Dr. A. B.F.A. Pondman).

Microscopically a few epithelial cells. No bacteria.

Own cytological investigation: No intranuclear inclusion bodies or viral type giant cells.

Biopsy of lesion to prepare an antigen.

19-7-1958: No new lesions. Biopsy wound cleaned with a 3% hydrogen peroxide.

22-7-1958: Two tiny new aphthae visible alongside the biopsy wound.

Laboratory investigations:

Intradermal skin tests performed on patient with antigens prepared from one of his own lesions and that from of Case 5. No immediate reactions were observed. Control test with physiological saline: negative.

Blood Morphology (Central Laboratory: Dr. A. Groen):

Erythrocytes 4,970,000; leucocytes 5200 (Eosinophils 2.1%): Thrombocytes 220,000; Haemoglobin 93%: ESR 3/7.

Differential count: Rod froms 1, Segm. forms 56, Lymphocytes 45 Monocytes 4. Serological investigation (Bacteriological Serological Routine Laboratory: Prof. Dr. Pondman).

Wassermann -; V. D. R. L. -.

23-7-1958: No new lesions. No reaction from skin tests with antigens.

25-7-1958: No new lesions. Pirquet test negative,

4-9-1958: Patient still continuously troubled by the formation of new lesions. Six aphthae present in mouth. (Two on inside of upper lip, three on inside of lower lip and one on the floor of the mouth behind $\overline{3}$).

Aureomycin (250 mg.) prescribed. One per os, every six hours for five days, together with Vitamin B complex tablets (2 three times a day).

12-9-1958: Completely free from lesions. After three days treatment with the aureomycin rapid healing took place.

Investigation: Concentrated lactic acid solution applied by means of a cotton wool pledget for 15 seconds to an isolated area of the mucosa in the lower muco-buccal fold.

13-9-1958: A whitish ulcer of 1 cm. diameter, without a red border developed on the spot of the application with lactic acid. This lesion less painful than the lesions of chronic recurrent aphthae.

14-9-1958: New aphthae in upper left sulcus opposite the premolars. Ulcer produced by lactic acid application shows irregular outline and very narrow red halo.

16-9-1958: Another new aphtha on the floor of the mouth below the right side of the tongue.

Laboratory investigation:

Bacteriological investigation (Bacteriological Serological Routine Laboratory: Prof. Dr Pondman):

Result no. 31033: Microscopically a few epithelial cells. A few Gram + cocci in chains. No yeasts found.

Pathological Anatomical investigation (Pathological Anatomical Laboratory: Prof. Dr H. N. Hadders):

Result no. 123250:

Macroscopically: Of patient J.H.W.B. we received:

I. A split pea-sized tissue fragment.

II. A tissue fragment of similar size.

Microscopically: In I we found squamous epithelium with underlying submucosa. A round cell infiltrate was present in the submucosa directly underneath the epithelium, and in the deeper layers. The picture fits in with that of chronic recurrent aphthae.

20-9-1958: Small aphtha (pinhead size) present on the tip of the tongue. Submaxillary lymph glands palpable on the right side. Temp. 36.9°C.

Laboratory investigation: (Central Laboratory: Dr. A. Groen): Qualitative examination of urine Albumin -, Reduction -, Bilirubin -, Urobilin -, Sediment: no findings.
24-9-1958: Pinhead-sized painful new aphtha on the inside of the lower lip. Old lesions in the process of healing. When touched not painful any more. Lesion due to lactic acid application completely healed. No lymph glands palpable.
25-9-1958: Three new lesions appeared in the mouth. One in right upper sulcus, two on inside of lower lip. Old lesions still visible. One in left upper sulcus almost completely healed.
1-10-1958: Lesion which was present in left upper sulcus completely healed. Patient, however, feels a burning sensation in this area. Here a local ized reddening of the mucosa is visible. In the upper right buccal sulcus an almost healed lesion.

On the inside of the lower lip to the right of the median line two painless lesions. To the left of the median line two more lesions adjacent to each other.

Laboratory investigation:

Viral investigation (Virus Section of the Laboratory of Hygiene, University of Amsterdam: Dr. F. Dekking).

Result no 583: Attempts to cultivate a virus in tissue cultures from material obtained from two different lesions were unsuccessful.

Complement Fixation Test: Adenovirus negative, Herpes 1/8, L.C.M. negative, ECHO type 9 1/32, umps negative, measles negative.

22-10-1958: An almost healed lesion present in right lower sulcus. No new lesions developed during the past 14 days.

21-1-1959: Since the last visit (22-10-1958) the patient was continuously subject to outbreaks of new lesions. Now one of 7 days duration present on the mucosa of the lower lip and another of shorter duration on the inside of the upper lip, near the angle of the mouth. Saliva obtained from patient for the preparation of an antigen.

30-1-1959: Lesions almost healed. No new lesions.

Intradermal skin tests with salivary antigens: Results after 20 minutes:

I (Physiological saline) No reaction.
II (Physiological saline + 0.5% phenol) No reaction.
III (CRA Antigen without phenol) Erythema.
IV (III + 5% phenol) Erythema + slight wheal formation.
V (CRA Antigen 2 without phenol) Erythema + slight wheal formation.
VI (V + 0.5% phenol) Erythema.
VII (Aphthosis Antigen without phenol). Erythema.
VIII (VII + 0.5% phenol) Erythema + wheal formation.

2-2-1959 : Results skin tests after 24 hours:

I	No reaction.	V	Erythema.
II	No reaction.	VI	Erythema.
III	Erythema + slight elevation.	VII	Erythema.
IV	Erythema.	VIII	Erythema.

1-2-'59 No new lesions. Results skin tests after 48 hours:

I	No reaction.	V	Slight erythema.
II	No reaction.	VI	Slight erythema.
III	Slight erythema.	VII	Slight erythema.
IV	Slight erythema.	VIII	Slight erythema.

2-2-'59 Results skin tests after 72 hours:

I	No reaction.	V	No reaction.
II	No reaction.	VI	No reaction.
III	No reaction.	VII	No reaction.
IV	No reaction.	VIII	No reaction.

14-2-1959: Still no new lesions. Intradermal skin tests with salivary antigens gave no delayed reaction.
19-2-1959: Since 18-2-1959 three new aphthae in the mouth. Two on inside of lower lip. One in lower buccal sulcus adjoining medial muscle attachment of lip.
3-6-1959: Still continuously troubled by new attacks. Now four lesions present in mouth.
15-6-1959: Two lesions of 7 days duration present.

Laboratory investigation:

Viral investigation (Virus Section of the Laboratory of Hygiene, University of Amsterdam: Dr. F. Dekking):

All attempts to isolate a virus proved fruitless.

Laboratory Findings: (Central Laboratory: Dr. A. Groen) Blood chemistry: Diastase 4 units; Ca 10.1 mg%, P 3.6 mg%, Alk. phosphatase 5.6 units, Glucose 84 mg%, Serum iron 1973%, Vit.C. 0.2 mg%, K 4.3 mEq/L Na 141 mEq/L Cl 106.0 mEq/L Urea 300 mg%. Alk. reserve 32.7, Bilirubin (direct) -, bilirubin (indirect) 1.0 Units, Tot. Cholesterol

223.1 mg% (Cholesterol esters 55%). Thymol turbity test 3.2 CaFGR - Tot. Protein 7.4 gm%, Protein spectrum (paperelectrophoresis): Alb. 51.1%, Glob. α_1 7.1% α_2 8.2% $\beta_1 + \beta_2$ 14.4% γ19.2%.

Faeces (qualitatively): Few fat globules. No fatty acids. No amylum. No muscle fibres.

Vitamin determinations (State Institute for Public Health, Utrecht, Dr. A.H. Holtz) Result No. K 01900. Vit A (serum) 130 I.U./100 ml.
Vit E (serum) 0.75 mg%

Case 3. F.B.-E. (57/2725). Female, aged 55. Widow. Managing own household. No childeren. One miscarriage.
First visit: 22.3.'58 (Referred by Dr. W D. de Groot, Groningen)
History: Patient complains of troublesome recurrent lesions in the oral cavity since childhood. First the intervals between outbreaks were fairly long (sometimes months) and irregular. The past few years, however, the condition became more severe, so that she is now hardly ever without any lesions. Speech, eating and swallowing are difficult. She does not know how long it takes for the lesions to heal, because new lesions are continually recurring. They are found on any part of the oral mucosa, but mostly on the inside of the lower lip, the tongue, the floor of the mouth and in the bucco-gingival folds. As a child she had measles, scarlet fever, mumps and whooping cough. In 1928, at the age of 25, she received treatment for TB in a sanatorium for 7½ months. After discharge she had another relapse and was treated in various institutions. In 1932 she underwent a cholecystectomy. In 1934 she was again admitted in hospital, this time in the Wilhelmina Hospital at Assen. During this period in hospital she also received a number of X-ray treatments of the head at the Radiology Department of the University Hospital, Groningen. She does not known what the reason was for this treatment, but she remembers well that Dr. Koster and Dr. Heeres, who reated her at hat time in Assen, said that they intended publishing her case history in a medical journal.

On questioning the patient said hat she was now free from chest complaints. No cough. No haemoptysis. No pain on breathing.

As a child she had frequent attacks of eczema. No history of eye or genital lesions. In 1929 the menses ceased altogether, for a whole year. After that they were regular but very painful. Each period lasted from 7 to 8 days. At the age of 43 she married and had a miscarriage 3 months afterwards. The menses were for the last time observed a year ago. According to her doctor this is due to the menopause.

The statement by the patient that Dr. Koster and Dr. Heeres intended publishing the facts relating to her condition in a medical journal made us curious to know what the nature of her disease was at that time After a careful search through the literature, we found an article published by these two authors under the title "Hypophysaire Reactie by Tuberculose". (Tijdschrift voor Geneeskunde, 79 II page 2336, 1935). The first case, described by them (that of Miss A) fitted exactly in with the history related to us by the patient, except that no mention had been made of the fact that she also suffered from recurrent aphthae. The important features from the case history by Koster en Heeres (1935) can be listed as follows:

1. Miss A, 31 years of age, unmarried, never ill in her youth, developed 6 years ago. in 1928, complaints of fatigue and fever. During a sojourn of 7½ months in a sanatorium no definite lung tuberculosis could be established; the X-ray showed a single small focus in he right hilus. Her weight increased from 48.8 Kg to 60.5 Kg. Body length 1.55 meters. After discharge periods of rest at home alternated with periods of work.
2. In 1929 the menses caused suddenly for a whole year. In 1930 the periods re-apeared but henceforth were profuse and painful.
3. In 1931 she developed attacks of cholelithiasis. In 1932 cholecystectomy. Gall bladder was found to be filled with stones.
4. In winter of 1932-1933 she developed bronchitis accompanied by fatigue and fever, followed by haemoptysis. Again period of strict rest. Coughing and haemoptysis disappeared.
5. In 1934 patient complained of fatigue, backache, fleeting pains in the extremities, pain in the left side, while the temperature became elevated. Patient admitted to the Wilhelmina Hospital in Assen. Here no lung changes could be found. Examination revealed: a. definite adiposity. Weight 85 Kg with a length of 1.54 meters. Adiposity limited to face, neck, chest and abdomen. b. Face extremely red with pigmented areas on he right of the forehead. Hair of scalp thin. Patient revealed an obvious "facies lunata". c. Patient old for her age. Spine showed slight kyphosis in thoracic segment. Cutis marmorata and purplish-red striae present on upper half of arms and thigs. d. Thyroid gland palpable. e. Lungs revealed no changes. f. B.P. ranged between 180/110 and

195/110. Temperature varied between 37.3° and 37.8°C. Pirquet reaction strongly positive. g. Left kidney painful on pressure. Rectovaginal examination NAD. Aphthalmological and neurological examination: NAD. h. Blood examination: Rbc 5,200,000; Wbc 6.300 (slight shift to the left). Hb (Sahli) 92%. Tot. serum cholesterol 2.3 gm/L; Ca 12.3 mg%. Luetic reactions negative. ESR 19 mm. Blood sugar values after the ingestion of 50 gm of glucose were as follows:

Fasting value: 113 mg%
after ½ hour: 216 mg%
after 1 hour: 228 mg%
after 1½ hour: 228 mg%
after 2 hours: 199 mg%
after 2½ hours: 196 mg%

There existed a strong glycosuria, the reaction of the blood sugar value to adrenalin and insulin was completely normal. BMR ranged between -1% and + 6%. Kidney function normal. No tubercle bacilli, leucocytes, erythrocytes or albumin were found in the urine. i. In view of the preceding cholecystectomy the function of the pancreas was thoroughly investigated. Not a single disturbance was found. j. Röntgenological examination of heart, lungs, kidneys, skull and spine revealed no important findings. In the right lung hilus a single small focus of calcification was visible. No osteoporosis was present. The sella turcica, although slightly deep, was not abnormal. An initially observed shadow above the left kidney later proved to have disappeared. No abnormalities found at cystoscopy and on pyelograms.

Koster and Heeres (1935) concluded "we finally nursed the thought that we were dealing with changes of an adrenal or hypophysial nature, in all probability of the nature as first described by Harvey Cushing".

Examination: General examination reveals a well nourished middle-aged woman, She is a rather short, stout person, of fair complexion and does not appear old for her age. The hair shows no abnormal texture of distribution. No weakness or complaint of fatigue. The thyroid gland is not palpable. No abnormal pigmentation present. Striae visible on the abdomen, buttocks and thighs. No cutis marmorata. No signs of any kyphosis or abnormal fat distribution. Except for a systolic murmur over the mitral area no abnormal heart sounds audible. Auscultation reveals no changes in the lungs.

Abdomen: NAD. No lymph glands palpable.

B.P. 180/120; Pulse 78 p.m.

Intraorally: Two typical aphthae present. One on side of tongue, the other one in the lower buccal sulcus.

Teeth: $\frac{7\ 6\ 4\ 3\ 2\ 1 \mid 1\ 2\ 3\ 4\ 5\ 7}{4\ 3\ 2\ 1 \mid 1\ 2\ 3\ 4}$ Caries in 3, 2 very mobile while 4 is non-vital with a granuloma visible at the apex on X-ray. Pockets present around all the teeth. Parodontal disease is further confirmed by X-rays, which show considerable loss of alveolar bone.

Diagnosis: Chronic recurrent aphthae.

The patient was subsequently followed up for almost 18 months and we gained the impression that she is practically never free from oral lesions. During this perios the mobile and non-vital teeth were removed. This had no beneficial effect on the aphthae.

Laboratory investigation: Blood Morphology: Rbc 4.470,000/ Wbc 5500; Hb 73%; Diameter erythrocytes 7.1μ. Diff. count : Baso 1, Eos 3, Myeloc. O, Youth forms O, Rod forms O, Segm. Nuclears 62, Lymphoc. 31, Monoc, 3. Percentage eosinophils 0.5%. The patient was admitted to the wards of the Department of Gynaecology and Obstetrics (Head: Prof. Dr. B.S. ten Berge) on 14.7.'58 for further investigation.

Fractional test meal showed the presence of free hydrochloric acid in the stomach.

BMR 0%.

Blood sugar values after the ingestion of 100 gm. of glucose gave the following values.

Fasting value	89 mg%
After ½ hour	123 mg%
After 1 hour	123 mg%
After 1½ hour	131 mg%
After 2 hours	117 mg%
After 2½ hours	93 mg%

24 hour urine specimen:

17 Ketos	12.4 mg
17 Hydroxys	8.3 mg

Thorn test: Fasting eosinophil count 22 x 11 = 242
2 hours after I.V. drip of ACTH (25 units) 10 x 11 = 110

4 hours after I. V. drip of ACTH (25 units)	7 x 11 = 77
6 hours	4 x 11 = 44
24 hours urine specimen after ACTH	17 Ketos, 11.6 mg.
	17 Hydroxys, 20.9 mg.

Case 4. G.B. (58/2688) Male, aged 39. Married. Two children. Occupation: Blacksmith. First visit: 21-10-1958.
History: Troubled for two years by recurrent painful ulcers in mouth. Lesions appear periodically every 2 or 3 weeks. Individual lesions heal within 7 to 10 days. Lesions have a predelection for the inside of the lower lip and vary in number from one to three at a time. No other signs or symptoms accompany the outbreaks. Except for rickets as a child no history of allergy, labial herpes, diarrhoea or any other disease. Ulcers not influenced by foodstuffs, climate, nervousness or seasons of the year. No history of skin, genital or eye involvement. Family history negative for aphthae. Father suffers from bronchial asthma.

Examination: Healthy looking adult male. General examination N.A.D. Temperature normal.

Intra-orally: No typical aphthae present. Two hyperaemic spots on the alveolar process, buccally opposite 3| . Patient wears full upper and lower acrylic dentures for the past 10 years. No lymph glands palpable.
15-11-1958: Rectal temp. 36.8°C. B.P. 110/78. Pulse 68 p.m.
Intra-orally: Two round aphthae of yellow-white appearance present in the mouth. Both lesions surrounded by a thin red halo. One the size of a match-end on the inside of the lower lip, the other one 4 mm. in diameter on the floor of the mouth on the right hand side of the tongue. Lesions present for ± 3 days and painful when touched. No lymph glands palpable.

Diagnosis: Chronic recurrent aphthae.

Case 5. J.B -P. (58/1781) Female, aged 30, Married. Two children. Housewife. First visit: 9-7-1958.
History: Patient suffers from recurrent lesions in the mouth since her 16th birthday. Lesions are extremely painful, especially when she eats hot or spiced foods. They appear at completely irregular periods. Sometimes continual recurrences for months, at other times free from attacks for almost a year. Individual lesions heal within 10 to 14 days. She knows of nothing that bears any relationship to the attacks. Her youngest son (4 years old) occasionally has similar lesions on the inside of the lips. Family history otherwise negative. The patient never had lesions on the genitals, skin or eyes. No history of allergy, diarrhoea or menstrual disorder.

Examination: Well nourished healthy looking woman. General examination N.A.D.

Intra-orally: $\frac{5\ \ 3\ 2\ 1\ |\ 1\ 2\ 3\ 4\ 5\ 6\ 7\ 8}{6\ 5\ 4\ 3\ 2\ 1\ |\ 1\ 2\ 3\ 4\ 5\ 7}$ present with much calculus around them.

Many amalgam fillings and extensive caries visible. Oral hygiene badly neglected. Röntgenograms of the teeth reveal an apical infection at the mesial root of $\overline{6}|$, piece of root at $\underline{6}|$ area $\overline{6}|$ appears non-vital on examination. Three aphthae present. One on tongue, one on inside of lower lip and one in lower buccal sulcus opposite $\overline{4}|$.
14-7-1958: Four lesions present in mouth. Biopsy taken of a one-day old lesion on mucosa of right cheek.

Pathological Anatomical findings (Result no. 124187) by Dr. van de Poel: "On microscopical examination of biopsy specimen of patient we find squamous epithelium with slight intra- and intercellular oedema. We observe squamous cells with much cytoplasm and a small, dark nucleus surrounded by a "halo". Subepithelially we find a band of dense round cell infiltration. In the depth a more diffuse round cell infiltration and a number of polymorphonuclears. The submucosa is very vascular. In the specimen stained with Giemsa the large number of mast cells are very obvious. While the presence of mast cells has hither to not been considered typical for the diagnosis "recurrent aphthae", this eventually may prove to be the case. In the meantime we can only say that the picture fits in with that of recurrent aphthae".

Bacteriological investigation (Result no. 23833) by Dr. E.A. Beute:
Microscopically a number of epithelial cells. A number of Gram- rods and a number of Gram + diplococci. No yeast forms found. Part of the bacteria lies on the epithelial cells.
17-10-1958: Patient has two aphthae on the inside of the lower lip. No lymph glands palpable.

Qualitative Urine examination (Central Laboratory: Dr. A. Groen):
Albumin - Reduction -, Bilirubin -; Traces of urobilin present; Sediment: no findings.

Viral investigation (Result no. SM. 628) by Dr. F. Dekking: no virus cultured. Complement fixation test: Adenovirus -; Herpes 1/64; L.C.M. -; Mumps -; Measles 1/16.

Case 6. G.C. (58/1139). Female, aged 53. Unmarried. Occupation: House-keeper. First visit: 29-4-1958.
History: First noticed lesions in mouth at the age of about 15, while still at school. Lesions appear periodically at varying intervals. Sometimes every two weaks, at other times every three months. The lesions heal within 1 to 4 weeks. According to her, the lesions were more severe at the time of menstrual periods. The latter were regular, but ceased altogether two years perviously. At the age of 30, she received treatment in hospital for a nervous breakdown. She remembers being very strained at that time. She still complains of nervousness. She also suffered from hay fever, but for the past number of years entirely free from attacks. In 1939 she has an attack of diarrhoea, as well as anaemia. For the latter she received liver injections. After this treatment she felt much better but subsequently developed high blood pressure. The patient never had eye, genital or skin lesions. In her youth she occasionally suffered from labial herpes.

Examination: Pale appearance. BP 185/95. Rect. temp. 37.6°C.

Intra-orally: Two aphthae on inside of lower lip. No lymph glands palpable. Full upper and lower denture.

Blood: Rbc 3,640:000; Wbc 4,500; Hb 84%; Diff.count: Baso. 0, Eos, 0, Myeloc. 0, Youth forms 0, Rod forms 0, Segm. forms 65, Lymphoc. 0, Monoc. 1. No anisocytosis or poikilocytosis; ESR. 14/32.

Bacterial Investigation (Result no. 14548): Microscopically a few epithelial cells, few bacteria chiefly psuedo-diphteria bacilli, a few Gram + and Gram - diplococci, Gram- rods. The organisms lie predominantly on the epithelial cells. No yeasts. Luetic reactions (Result no. 57604): Wa -; V.D.R.L.-test.
12-5-1958: Referred to Dept. of Internal Medicine for further examination. Report of Dr. A.A. Idema read as follows: Patient examined by us in 1953 for a complaint of aphthous stomatitis. At that time histamine refractory achlorydria, hypertension and a fair kidney function were found by us. In 1939 she had diarrhoea and anaemia.

Examination: Well nourished. Full upper and lower denture. No aphthae present in mouth. Heart: Ictus one finger breadth outside the mid-clavicular line. Auscultation reveal a reduplication of the first heart sound over the apex. Abdomen: NAD. Extremities: Brachial artery feels hard. Urine: S.G. 1020, Albumin -; reduction -; sediment -; ESR 32 mm. Hb 11.8 gm%. Transillumination of thorax: left ventricle enlarged. ECG: normal. B.P. 195/100 almost the same as that found in 1953.
10-2-1959: Pinhead sized aphtha on tip of tongue.

Blood morphology: Rbc 3,540,000; Wbc 6,300; Hb 14.5 gm%; Thrombocytes 279,000; Diff. count: Baso 0, Eos 1, Myeloc. 0, Youth forms 0, Rod forms 2, Segm. forms 72, Lymphoc. 15, Monoc. 10; Bloodgroup: 0 Rh +; ESR: 14/33; Diameter erythrocytes: 7.2 .

Blood chemistry: Diastase 8 units; Ca 10.3; P 3.0; Alk. phosphatase 9.7 units; Glucose 85; Potassium 4.9; Sodium 139; Chlorine 104.0; Urea 270; Bilirubin (direct)-; Bilirubin (indirect) 0.9 units; Tot. cholesterol 266.7; cholesterol esters 195.6 (73% of total cholesterol). CaFGR: 2 +. Vitamin C. 0,48 mg%.

Serum Protein (Paper electrophoresis): Tot. Prot.. 7.99 mg.; Albumin 53.5%; Globulin 46.5% (α_1, 3.7%, α_2 10.1%, $\beta_1 + \beta_2$ 11.3%, γ 21.4%).
12-2-1959: No new lesions in mouth.

Urine (quantitatively): Diastase 8 units; Vit. C. 0.55 mg%.

Urine (qualitatively): Albumin , reduction -, bilirubin -, urobilin -, sediment: 1-2 leucocytes.

Faeces (qualitatively): Traces of fat. No fatty acid crystals. Amylum negative. Muscle fibres negative,

Case 7. P.D. (53/566) Male, aged 39. Married. Two children. Factory worker. First visit: 6-3-1953 with complaint of recurrent oral lesions. First seen by us: 24-9-1958.

History: Recurrent oral lesions began five to six years ago. Practically never free from lesions. Before one heals, another one appears in the mouth. Individual lesions heal within 14 days. He considers periods of stress important contributing factors. No history of genital, skin or eye lesions. Never more than five lesions present at one time. As a child he suffered from recurrent labial herpes. No history of diarrhoea. No family history of aphthae Mother and one sister had TB.

Examination: Five typical aphthae present in mouth. One of these appeared 9 days ago, the other followed subsequently. Patient wears full upper and lower dentures. No lymph glands palpable.
25-9-1958: No new lesions.

Bacterial examination (Result no. 32140): Microscopically a few epithelial cells and a number of Gram + cocci arranged in groups. Luetic reaction (Result no. 72504): Wa -, VDRL -

Blood morphology: Rbc 4,980,000; Wbc 6,300; Hb 89%; Colour Index 0.9, Diff. count: Baso 0, Eos 5, Myeloc 0. Youth forms 0, Rod forms 1, Segm. forms 68; Lymphoc. 22, Monoc. 4. (Percentage eosinophils: 3.8).

Blood group: ORh +, ESR 5/15. Urine (qualitatively): albumin -, reduction -, bilirubin -, urobilin + +, sediment -.

3-3-1959: One lesion present on inside of lower lip.

Urine (Qualitatively): Albumin -; reduction -; bilirubin -; urobilin: trace present; porphyrin -.

Vitamine C (quantitatively): 0.2 mg%.

Blood examination: Diastase 8. units; bilirubin (direct) - ; bilirubin (indirect) 0.9; tot. cholesterol 224 : cholesterol esters 149 (66% of tot.cholesterol): Thymol turbidity test 4.6; CaFGR -

Case 8. G.D. -H Female, aged 24. Married. One child. Housewife. First visit: 27-1-'59. (Referred by Dr. H. de Vries, Onstwedde).

History: First suffered from ulcers in the mouth at the age of 9. Progressively became worse. Lesions appear periodically in close relationship to the menses. Sometimes before, sometimes after the period. According to the patient the intervals between attacks vary from three weeks to two months. During pregnancy she had only one mild attack. After the birth of her child lesions re-appeared with greater frequency. Patient is of the opinion, that the lesions are most severe at times of nervousness. Except for frequent attacks of herpes labialis the patient never had skin, genital or eye lesions. Mother and one brother also suffered from recurrent oral ulcers. History of allergy negative. No diarrhoea. Menses normal and regular. Husband suffered from TB, but now cured.

Examination: Well nourished young woman of normal weight and build. General examination: NAD. Temp: (rectal) 36.8°C. Pulse 64 p.m. BP 110/78.

Intraorally: Behind left angle of mouth a grayish-white, oval aphtha, the size of a lentil, surrounded by a red halo of 2 mm. Lesion present for three days. On inside of upper lip, opposite the $\underline{1|3}$, a similar lesion present of the same size. On the upper lip opposite the $\underline{1|}$ an almost healed lesion. A small irregular lesion of 1-2 mm. diameter on right side of the dorsum of the tongue. No red halo. Lesion has a yellowish-gray appearance. Below the left edge of the tongue a grayish-white lesion, the size of a matchhead and surrounded by a red halo of ½ cm. width. The bases of the lesions slightly depressed. The lesions are extremely sensitive when touched. No foetor ex oris or salivation present. Dorsum of the tongue has a white coat. No regional lymph glands palpable. No genital lesions present. Full upper acrylic denture.

$\overline{3\ 2\ 1\ |\ 1\ 2\ 3\ 5\ 8}$ present. No signs of gingivitis. Extensive caries. Röntgenological examination shows carious teeth, but no foci of infection.

Bacteriological investigation (Result no. 3077): Microscopically a few squamous epithelial cells. Various Gram + cocci arranged in duplo. A few Gram - diplococci and a few Gram negative rods. No yeast forms.

Pathological anatomical investigation (Result no. 127283): Microscopical examination of biopsy specimen of the mouth reveals ulceration of epithelium and a sub-epithelial round cell and leucocytic infiltrate. After staining with Giemsa many mast cells were visible. The picture fits in with that of recurrent aphthae.

Blood morphology: Rbc 4.170,000, Wbc 5,000 (Eosinophils 1%): Hb 13,3 gm%; Thrombocytes 221,000. Diff. count: Eos 1; Segmented nuclears 58; Lymph. 38; Monos. 3; Haematocrit 46. Blood group: 0 Rh-. Diameter erythrocytes: 7.2 μ. ESR 16/36. Serum Protein (Paper Electrophoresis): Tot. protein 8.5 gm.%. Albumin 58.7%, Globulin 41.3% (α_1 4.1%, α_2 7.6%, $\beta_1 + \beta_2$ 10.5%, γ 19.1%).

Viral investigation (Result no. SM/46): Attemps to cultivate a virus unsuccessful.

Complement Fixation Test: Adenovirus -; Herpes 1/32; ECHO type 9, 1/32; Mumps -; Measles -.

30-1-1959: No new lesions. Skin tests performed with salivary antigens 9-2-1959: Since 2-2-1959 a very painful aphtha, the size of a bean, on the inside of the lower lip. Base slightly depressed with grayish-yellow cover. Red halo of 1 cm. around lesion. Behind the left angle of the mouth a similar lesion of shorter duration. On the hard palate a small lesion (the size of a barley seed) surrounded by a red halo. This lesion was noticed for the first time today. At sites of antigen injections no delayed reaction. Cytological examination of lesion shows no inclusion bodies or viral type giant cells.

Laboratory investigations:

Blood chemistry: Diastase 4 units; Calcium 9.9 mg%; Phosphorus 5.3 mg%; Alk. phosphatase 6.5 units; Glucose 93 mg%; Potassium 4.3 m.Eq/L; Sodium 140 m. Eq/L; Chlorine 107.6 m.Eq/L; Urea 495 mg. %; Vit.C. 0.43 mg%; Albumin 5.0 mg% Globulin 2.1 mg% Bilirubin (direct) -, Bilirubin (indirect) 1.1 units. Total cholesterol 2.1 mg%; Cholesterol esters 180.4 mg% (75% of total cholesterol); pH of blood 7.30. Haemotocrit 46; CaFGR -.

Vitamin determinations (State Institute for Public Heath, Utrecht Dr. A.H. Holtz: Result no. K 02206); Serum Vit. E 0.75 mg%. Result no. K 01893) Serum Vit. A. 120 I u/100cc.

Qualitative urine examination: Albumin - Reduction - Urobilin - Sediment: Leucocytes 1 - 2, a few epithelial cells.

28-5-1959: Two aphthae of 5 days duration present in mouth.

Viral investigation:

1. Oral scrapings, feaces and blood inoculated onto Lofi cells, monkey kidney cells and human amnion cells.
2. Oral scrapings, faeces and blood inoculated onto the chorio-allantoic membrane of hen's eggs.

Case 9. S.K.D. (58/2783). Male, aged 13 years. Scolar. Son of case 10. First visit: 29-10-1958.

History: The patient had his first lesion a year ago. Since then the had similar lesions on a number of occasions. The interval between attacks was approximately three months. On each occasion only one lesion developed. The lesions heal within 7 to 10 days and are extremely painful. Apart from his mother, a sister, maternal grandmother, maternal great grandmother, two maternal uncles and a maternal cousin suffered) from similar lesions. The patient never had skin, genital or eye lesions. No history of labial herpes, allergy or diarrhoea.

Examination: Healthy looking boy of normal size and build.

General examination: NAD. Intraorally: On the attached gingiva, between $\overline{1}$ and $\overline{2}$ a match-end sized aphtha of yellowish-gray colour and surrounded by a red halo 3 mm. in diameter. The lesion very painful when touched. According to the patient this lesion developed the day before. No lymph glands palpable. Excellent oral hygiene.

$\overline{7\ 6\ 5\ 4\ 3\ 2\ 1}\,|\,1\ 2\ 3\ 4\ 5\ 6\ 7$ present in the mouth and showing no caries.

$7\ 6\ 5\ 4\ 3\ 2\ 1\,|\,\overline{1\ 2\ 3\ 4\ 5\ 6\ 7}$

Pathological anatomical investigation (Result no. 124616): "Microscopical investigation reveals no hypertrophy or acanthosis of the superficial epithelium. In the superficial layers of the squamous epithelium we find some intracellular oedema. An inflammatory infiltrate is present in the basal layer. In the sub-epithelial area we find vascularisation and the presence of a diffuse perivascular roundcell infiltration. The specimen stained with Giemsa reveals the presence of numerous mast cells. The picture can fit in with that of recurrent aphthae.

Bacteriologicalexamination (Result no. 36621): Microscopically a few epithelial cells. No spirochaetes or other bacteria. No yeast forms observed.

Blood examination: Rbc 3,980,000; Wbc; 3,300 (Eosinophils 0,3%); Thrombocytes 255.000; Hb 12.9 gm%; Diff. count: Baso. 0, Eos 2, Myeloc. 0, Youth forms 0, Rod nuclears 4, Segm. nuclears 40, Lymph. 54, Monos 0. Bloodgroup: A Rh -.

Blood chemistry: Diastase 8 Units: Calcium 8,5 Phosphorus 5.8 mg%; Alk. phosph. 36, units Potassium 4.7 m.Eq/L; Sodium 137 m.Eq/L Chloride 115 m. Eq/L; Urea 285 mg%, Bilirubin (direct) -; Bilirubin (indirect) 1.0 units; Tot. Cholesterol 300.0 mg%; Cholesterol esters 187.5 mg% (62% of tot. cholesterol): Thymol turbidity test 11.8 CaFGR 14.

Serum Protein (Paper electrophoresis): Tot. protein 7.0 gm%; Albumin 62. 2%; Globulin 37.8% (α_1 5.1%, α_2 8.8%, $\beta_1 + \beta_2$ 11.4%, γ 12.5%).

Urine (quantitatively): Diastase 16 units.

Viral investigation: All attempts to cultivate a virus from oral scrapings and blood negative.

Case 10. M.D.-B. (58/1735) Female, aged 46. Married. Two children. Housewife. Mother of case 9. First visit: 2-7-1958. (Referred by dr. F. Stoker, Groningen).

History: Recurrent painful ulcers in mouth since childhood. Lesions continually present. While some are in the process of healing, others appear. Her maternal grandmother, mother, two brothers, a maternal niece and both her children (case 9 and a daughter of 17 years) suffer from aphthae. Patient considers the condition to be worse at the time of the menses. The latter is regular, but extremely painful.

Examination: Middle aged woman of normal weight and build. B. P. 100/70. Rectal temp. 37.1°C.

Now three aphthae present in mouth. No lymph glands palpable. Further visits: 1-10-1958; 23-10-1958; 29-10-1958; 30-12-1958; 20-21959; 20-3-1959; 170701959.

Case 11. H.V. (58/3188). Male, aged 42. Married. One child. Occupation: Director. First visit 12-12-1958 (Referred by the Department of Ear, Nose and Throat Diaseases: Prof. Dr E. Huizenga).

History: For the past 18 months troubled by recurrent painful lesions in mouth. These appear irregularly. Sometimes every two weeks, at other times every two months. Individual lesions heal within ten days. Often suffers from spells of nervous tension accompanied by abdominal complaints in the form of heartburn. Had a nervous breakdown while on militairy service in Indonesia. No history of diarrhoea, labial herpes, allergy, skin lesions or eye lesions. Family history negative.

Examination: Two aphthae on inside of lower lip. Only a small submental lymph gland palpable.

General examination: NAD. Temp. (Rectal) 37.4°C. BP. 120/80. Pulse 70 p.m. Further visits: 8-1-1959; 17-2-1959 andl 14-2-1959.

Case 12. T.F.-V. (58/1713). Female, aged 36. Married. Two children. Occupation: Housewife. First visit: 2-5-1958 (Referred by Dr. F.J. Reneman, Groningen).

History: Suffers from recurrent, painful oral lesions since childhood. Lesions appear every six weeks. Not related to menses. Individual lesions heal within three weeks. No history of diarrhoea, labial herpes, skin, genital or eye lesions. Menses regular. Patients suffers for the past 12 years from bronchial asthma and hay fever. Her mother and daugther (11 years old) also suffer from oral lesions. Family history otherwise negative

Examination: General examination: NAD. BP 130/85. Temp. 36.9°C.

Intraorally: An aphtha present on inside of lower lip

Diagnosis: Chronic recurrent aphthae.

Case 13 H.G -V. (54/2297). Female aged 32. Married. Two children. Occupation: Housewife. First visit: 21-9-1954. Seen by us 14-11-1958.

History: Since her 18th year, recurrent painful lesions in mouth. At that ageshe also suffered from anaemia. Lesions appear continually and heal in about 14 days time. Lesions not related to menses. The latter used to be very irregular, now regular every 21 days. Since 1951 she received liver injections for the anaemia. Niece (11 years old) also suffers from the lesions. Family history otherwise negative. History of labial herpes, allergy, skin, genital and eye lesions negative.

Examination: General examination: NAD. No signs of anaemia. BP. 110/80. Rect. temp. 37.5°C. Pulse 78 p.m. Lymph glands not palpable.

Intraorally: Painful aphthae present on tip of tongue.

Further visits: 20-11-1958.

History: Suffers from recurrent oral ulcers, since childhood. For the past few years attacks more severe than before. Patient observed lesions more frequently a few days before the onset of the menses. Dysmennorhoea, but periods regular. Now almost every two weeks a new lesion. They heal in about ten days. Twenty years ago the patient had an acute arthritis in the finger joints. After treatment with lemon juice the condition was completely cured. No history of skin, genital or eye lesions. Family history negative.

Examination: An aphtha present below tongue on floor of month, of four days duration. No lymph glands palpable.

Diagnosis: Chronic recurrent aphthae.

Further visits: 9-5-1958.

Case 14. A.G. (58/1180). Female, aged 47. (Referred by Dr. F. Stoker, Groningen).

Case 15. J.H. (59/2452). Male, aged 22, Single. Occupation: University Student. First visit: 23-9-1958 (Referred by Department of Dermatology: Prof. Dr. M. Ruiter).

History: Patient developed recurrent painful mouth lesions at the age of 13 years. For the past two years attacks more severe. Lesions appear irregularly. Sometimes continually for months, then perhaps a free interval of one month. Individual lesions heal from within seven days to three weeks. Nothing seems to have any influence on the lesions. The patient feels feverish when manv lesions are present. No history of allergy, labial herpes, skin, genital or eye lesions.

Family history: Fatner, mother and two sisters of the patient suffer from similar lesions. An aunt suffers from hay fever.

Examination: Two apthhae present in the mouth. One on inside of the lower lip on the left, of irregular outline and measuring about 2 cm x 2 cm. This lesion is surrounded by a

red halo of ½ cm width. The base of the lesion is slightly depressed and of yellow-gray appearance. The lip is slightly oedematous. On the right-hand side a smaller lesion present on lower lip. No lymph glands palpable.

Diagnosis: Chronic recurrent aphthae.

Further visits: 26-9-1958, 27-9-1958 and 8-10-1958.

Case 16. R.H.L. (58/1889), Female, aged 28. Married. No children. Housewife. First visit: 21-7-'58 (Referred by Dept. of Dermatology: Prof. Dr. M.Ruiter).

History: Lesions first appeared 8 years ago. They develop intermittenly at irregular intervals. The latter vary from 2 weeks to a couple of months. The lesions give rise to intense pain. They heal in about 14 days. No relationship to menstrual periods. No history of diarrhoea, skin, genital or eye lesions. Had nephritis at age of 10, and pneumonia in 1949. History of herpes negative. Received treatment with smallpox vaccine in 1953, without improvement in the condition. The past year often troubled by headaches. Menses irregular. A sister suffered from eczema. No family history of aphthae.

Examination: Thin, pale, nervous woman. Thyroid palpable. No other abnormality found.

Intraorally. Two typical aphthae in mouth. One on inside of lower lip, the other one underneath the tongue. Cervical lymph nodes palpable.

Diagnosis: Chronic recurrent aphthae.

Further visits: 4.10.'58, 23.10.'58 1.11.'58 and 16.12.'58. Admitted to hospital 2.2.'59 for further investigation.

Case 17. M.H.-K. (54/2086), Female, aged 35. Married for 14 days. No children. Housewife. First visit 30.8.'54. Seen by us for the first time on 12.12.'58.

History: Troubled with recurrent painful lesions in mouth since 1952. They appear irregularly. New lesions develop before existing ones are completely healed. Patient feels feverish when many lesions are present. In her opinion the attacks bear no relationship to the menses. On the other hand, lesions a e more severe at times of nervous stress. No history of allergy, labial herpes, diarrhoea, skin, genital or eye lesions. Maternal grandfather had asthma. A maternal uncle hay fever. Her mother (age 65) suffered from similar oral lesions years ago. Two sisters of the patient are also afflicted.

Examination: Healthy appearance. General examination N.A.D. B.P. 90/60. Rectal temp. 37°C. Pulse 64 p.m. Right cervical lymph glands palpable.

Intraorally: Bean-sized oval lesion in left lower buccal sulcus. Around the lesion a narrow red border. The lesion is now present for 7 days.

Diagnosis: Chronic recurrent aphthae.

Further visits: 9.2.'59 and 23.5'59. Admitted to hospital for further examination on 19.5.'59.

Case 18. G.H. (56/1838). Male, aged 26. Single: Dental student. First visit: 11.4.'58.

History: Patient suffers from recurrent painful oral lesions for the past 8 years. Intervals between outbreaks vary from one to three months. Lesions usually heal in about 1 week. No history of allergy, labial herpes, diarrhoea, genital or eye lesions. Years ago he suffered from acne of the face. Family history negative.

Examination: Adult male of normal appearance. B.P. 125/80. Temp. 36.8°C. Cervical lymph glands palpable.

Intraorally: Two typical aphthae present in mouth.

Diagnosis: Chronic recurrent aphthae.

7.5.'58 Patient referred to Dept. of Internal Medicine for further investigation. The results of this examination were: Healthy appearance. No anaemia, jaundice or cyanosis. Small pea sized lymph glands in the neck, mainly on the left side. Heart and lungs N.A.D.; ESR 2 mm; Hb 13.1 gm%; Rbc 3,880,000; Wbc 3,800; Diff.count: Eos 2; Segmented nuclears 65; lymphocytes 29; monocytes 4. ; WaR -; Urine : NAD ; X-ray thorax: NAD; Toxoplasma reactions negative; Paul Bunnel negative.

Case 19. G.H. (54/2931) Female, aged 29. Single. Occup.: Housemaid. First visit: 26.11.'54. First seen by us on 27.1.'59.

History: The patient developed painful oral ulcers for the first time fourteen years ago. Since that time frequent recurrences at irregular intervals. According to her, the lesions sometimes develop a few days before the onset of the menstrual period. They heal within 14 days. No history of menstrual disorde s, allergy, labial herpes, skin, genital or eye lesions. Her mother occasionally suffers from similar lesions. Family history otherwise negative.

Examination: Healthy appearance. NAD. B.P. 110/78. Rectal temp. 38°C.

Examination: Healthy appearance. NAD. B.P. 110/78. Rectal temp. 38°C.

Intraorally: A lesion of 7 days duration present on the inside of the lower lip. It reveals a slightly depressed yellow-white base surrounded by a narrow red border of 2 mm. width. The lesion was more painful for the first 4 days. No lymph glands palpable.

Diagnosis: Chronic recurrent aphthae.

Further visits: 30.1.'59, 1.2.'59, 9.2.'59, 19.2.'59, 21.2.'59, 9.3.'59, 28.3.'59, 31.3.'59, 1.4.'59 and 10.4.'59.

Case 20. F.J (1958/942) Female, aged 17. Single. Scholar. First visit: 9.4.'58 (referred by Dr. H. Picauly, Veendam). At this visit lesions were already healed.

History: Recurrent, painful lesions in mouth from her sixth year. They appear every three months and heal from within 14 days to one month. Lesions bear no relationship to particular foodstuffs, climate, nervousness, menses or to any other condition. No history of diarrhoea, labial herpes, genital, eye or skin lesions. Family history negative.

9.9.'58: Examination: Well nourished girl of normal build, but of a nervous disposition. Rectal temp. 36.8°C. B.P. 130/85. No lymph glands palpable.

Intraorally: Typical aphtha present on buccal alveolar mucosa between ⌈3 and ⌈4.

Diagnosis: Chronic recurrent aphthae.

Further visits: 20.9.'58, 25.9.'58, 22.10.'58, 29.10.'58, 8.12.'58, 17.12.'58, 9.1.'59 and 4.3.'59.

Case 21. G.J.K. (58/1940) Female, aged 31. Unmarried. Occup: secretary. First visit: 26.7.'58.

History: Developed painful mouth lesions for the first time 3 months ago. New lesions have since then appeared every 3 weeks. No history of diarrhoea, genital or eye lesions. Menses appeared for the first time at the age of 12. She developed acne on the face with each subsequent menstrual period. For the past number of years she was completely free of these facial lesions. In 1947 she developed palpitations for which she was treated in hospital. As a child she also suffered from eczema. Her brother and one aunt suffer from bronchial asthma.

Examination: Healthy appearance. No signs or symptoms of hyperthyroidism. B.P. 125/80. Rectal temp. 37.4°C. Lymph glands not enlarged.

Intraorally: Two lentil-sized aphthae present in mouth. When touched they give rise to much pain.

Diagnosis: Chronic recurrent aphthae.

Case 22. (59/249) Female. Aged 14. Scolar. First visit: 29.1.'59.

History: Past 2 years recurrent attacks of oral ulcers. These appear irregularly about every 2 months, and heal within ± 7 days. First menstrual period a year ago. The periods are regular and give rise to no complaint. Her father and two paternal aunts suffer from similar lesions. The patient occasionally develops eczema on the hands and feet. No history of labial herpes, diarrhoea, genital or eye lesions.

Examination: Healthy appearance, of normal weight and build. B.P.110/80. Pulse 68 p.m. Rectal temp. 37.1°C. Cervical lymph glands palpable.

Intraorally: Pinhead-sized, yellowish aphtha surrounded by a red halo of ½ cm in width.

Diagnosis: Chronic recurrent aphthae.

Further visits: 30.1.'59, 31.1.'59 and 17.2.'59.

Case 23. H.K.B. (2765/58) Female, aged 42. Married. Six children. Housewife. First visit: 3.11.'58.

History: Suffers from recurrent, painful oral lesions for 7 years. As a rule the patient is never without lesions, but occasionally a free interval of 14 days was experienced. Individual lesions heal from within 8 to 10 days. Outbreaks cause no malaise or fever. She cannot recollect any relationship to the menses. The latter are regular but very painful. In the course of three of her pregnancies the lesions completely disappeared, only to reappear after the confinements. She occasionally develops a herpetic lesion on the lips. Three of her children suffer from urticaria. Family history negative for aphthae.

Examination: NAD; Rectal temp. 37.2°C; B.P. 110/80; No lymph glands palpable.

Intraorally: Bean-sized lesion on junction of hard and soft palate. The lesion extremely painful when touched. The base of the lesion is slightly depressed and of a yellowish-gray colour. Around the lesion an area of redness, of 3-4 mm in width.

Diagnosis: Chronic recurrent aphthae.

Case 24. G.K.-O. (58/2246) Female aged 36. Married. Four children. Housewife. First visit: 3.9.'58. (Referred by Dr. Hoeksema, Groningen).

History: Lesions in mouth first appeared at the age of 15. They are very painful and take 10 to 14 days to heal. The lesions seem to appear a few days before menstrual periods. The latter are very irregular. Her mother (63 years old) suffered from similar lesions.for many years. For 3 years she is now entirely free from lesions. No other positive findings in the family history. The patient never suffered from diarrhoea, genital, skin or eye lesions.

Examination: Healthy looking woman of normal weight and build, but she appears to be very nervous.

Intraorally: Two aphthae in mouth as well as a chronic gingivitis. No pockets.

Diagnosis: Chronic recurrent aphthae.

Further visits 10.9.'58, 15.9.'58, 16.2.'59 and 17.2.'59.

Case 25. H.M-G. (56/1731). Female, aged 45. Married. Two children. Housewife. First visit: 4.7.'56. Seen by us for the first time on 3.11.'58.

History: Lesions first appeared 14 years ago. Since that time she was never free from them. Individual lesions heal within 7 days. Patient considers nervousness an important factor in the causation of lesions. They are prone to occur 2 or 3 days before the onset of the menstrual periods. The latter is accompanied by much pain and appear at irregular intervals. No relationship between lesions and specific foodstuffs, seasonal or climatic conditions. No history of diarrhoea, skin, genital or eye lesions. Family history negative.

Examination on 12.2.'59: Woman of normal build and weight. NAD. B.P. 95/65. Rectal temp. 37°C. No lymph nodes present.

Intraorally: Two small aphthae in mouth. One on the tip of the tongue, the other one on the floor of the mouth on the left side of the tongue.

Diagnosis: Chronic recurrent aphthae.

Case 26. T.M. (56/1732). Female, aged 20. Daughter of case 25. Unmarried. University student. First visit: 4.7.'56. Seen by us for the first time on 6.11.'58.

History: She noticed painful ulcers in the mouth for the first time 7 years ago. Her mother and sister suffer from similar lesions. The lesions give rise to intense pain and appear every 3-4 weaks. This coincides with the week prior to the onset of the next menstrual period. Lesions heal within 7 days. She suffers from labial herpes in conjunction with colds. No history of diarrhoea, skin, genital, or eye lesions. According to the patient, outbreaks are more severe at times of stress, (e.g. sitting for examinations). Her father and sister suffer from eczema.

Examination: Healthy appearance. Normal weight and build. General examination NAD. Rectal temp. 37.4°C. B.P. 110/80. No enlarged lymph glands.

Intraorally: Two lesions in mouth.

Diagnosis: Chronic recurrent aphthae.

Further visits: 25.2.'59.

Case 27. H.O. (65/3195) Male, aged 32. Married. One child. Teacher. First visit: 11.12.'56. First seen by us on 12.5.'58.

History: Patient developed painful oral lesions for the first time 5 years ago. They appear at irregular intervals of from 1 to 4 weeks. Occasionally they are completely absent for a number of months. No history of diarrhoea, labial herpes, genital or eye lesions. He suffers from seborrhoic eczema behind the ears and on elbows for many years. According to the patient, this skin condition is very prevalent among his relatives. One of his sisters suffers from similar oral lesions, but never had skin lesions. The patient noticed that outbreaks were more severe when he had to sit for examinations.

General examination: Healthy appearance. Behind ears and at back of elbow an eczematous eruption. Otherwise NAD. Rectal temp. 37°C. B.P. 120/75. One lymph gland palpable (submandibular).

Intraorally: Aphtha present in lower labial fold for 7 days.

Diagnosis: Chronic recurrent aphthae.

14.5.'58: Referred to Dept. of Internal Medicine for a control examination. Further visits: 14.7.'58 (2 lesions present), 30.10.'58 (New lesion on tip of tongue. Paronychia of 2nd and 3rd fingers of left hand); 31.10.'58.

Case 28. J.H.P. (58/1253). Male, aged 27. Married. No children. Occup: Roadbuilder. First visit: 17.5.'58. (Referred by Dr. van Dijk, Groningen).

History: Since 18 months painful oral lesions, which appear about every three months. Lesions heal within 10 to 14 days. Family history negative for aphthae. Father suffers from hay fever, mother from allergic dermatitis (caused by certain plants.) No personal history of allergy, diarrhoea, skin, genital or eye lesions.

Examination: General examination: NAD. B.P. 125/85. Rectal Temp. 37.2°C. Lymph glands palpable on right side of neck.

Intraorally: In right lower buccal sulcus opposite $\overline{6}$ an almost healed aphtha present.

Diagnosis: Chronic recurrent aphthae.

Case 29. J.R. (58/1664) Male, aged 33. Married. Four children. Occup: Welder. First visit: 24.6.'58.

History: Developed painful oral ulcers 7 years ago. Initially they appeared twice a year, but lately attacks are very frequent (every 6 weeks). Lesions heal from within 5 to 10 days. Patient suffers from hay fever for the past 10 years. He developed this on arrival in Australia as an immigrant. Back in the Netherlands now for 18 months but still suffers from hay fever. He also suffers from acne, and states that abrasions of the skin easily lead to blood poisoning. Worries seem to aggravate his mouth condition. No history of diarrhoea, genital or eye lesions. Family history negative.

Examination: General examination: NAD. B.P. 110/70. Temp. 36.4°C. No lymph glands palpable.

Intraorally: Five typical aphthae present.

Diagnosis: Chronic recurrent aphthae.

Case 30. N.R. (58/862) Female, aged 24. Unmarried. University student. First visit: 28.3.'58. (Referred by Dr. S.J. Rengers, Groningen).

History: Recurrent painful tongue lesions for 3 years. They appear at irregular intervals. As soon as a new lesion was noticed by the patient she took Vit. C tablets. The lesions then disappeared within 3 days. Fourteen days before she first observed the present large ulcer, but this time Vit. C had no effect. Three of her sisters develop similar lesions. One of them suffers from hay fever, another from urticaria. No history of diarrhoea, skin, genital or eye lesions.

Examination: General examination NAD. Healthy appearance.

Intraorally: In right lower buccal sulcus opposite $\overline{7}$ a slit-like lesion (1½ cm x 2 mm) is visible. The edges of the lesion are slightly undermined while the base has a yellowish-gray appearance. No red areola.

Diagnosis: Chronic recurrent aphthae.

Case 31. A.R. (58/851). Female, aged 23. Single. University student. First visit: 28.3.'58. (Referred by Dr. R.S. Snijder, Groningen).

History: Attacks of recurrent painful ulcers in mouth for 5 years. Lesions appear at irregular intervals. A free interval of 3 weeks to 4 months is sometimes observed. Lesions are painful for about 2 days only, and heal completely within 7 days. No history of herpes, diarrhoea, skin, genital or eye lesions. Family history negative for aphthae. Menses normal and not related to the lesions. Patient often troubled by headaches. Mother suffers from bronchial asthma.

Examination: Healthy young woman of normal weight and build. Rectal temp. 37.3°C B.P. 106/78. Pulse 92 p.m. Lymph glands not enlarged.

Intraorally: Two irregular, painful aphthae in upper sulcus. $\lfloor 1$ not present in mouth./ Röntgenograms of teeth reveal an unerupted $\lfloor 1$ (reason for headaches?).

Diagnosis: Chronic recurrent aphthae.

Further visits: 9.5.'58 (observed outbreaks of aphthae 2 days before the onset of the previous two menstrual periods. Now one aphtha visible near the opening of the left duct of Stenson. According to the patient it developed on 3.4.'58, 4.12.'58, 26.1.'59, 2.2.'59, 21.2.'59. (Patient now remarks that lesions always precede the menses by 2 to 4 days).

Case 32. M.S. (58/1171) Male, aged 41. Married. Two children. Occup. Welder. First visit: 2.5.'58 (Referred by Dr. Steenbeek, Hoogezand).

History: Recurrent painful ulcers in mouth for 8 years. They appear about once a year. Individual lesions heal within 3 weeks. The patient often suffers from bronchitis. Personal and family histories reveal no other important facts.

Examination: Normal outward appearance. General examination NAD. No lymph glands palpable.

Intraorally: Lentil-sized aphtha on alveolar mucosa opposite right lower canine.

Diagnosis: Chronic recurrent aphthae.

Further visits: 9.5.'58, 29.1.'59.

Case 33. C.S.-K. (59/2657) Female, aged 36. Married. One child. Housewife. First visit: 10.6.'58.

History: troubled by the appearance of painful recurrentulcers in the mouth since 1949. Lesions recur at intervals of one two weeks. Patient not sure of relationship of lesions to the menses. According to her, outbreaks are apt to be more severe when she is nervous. Menses irregular. Often sore throat and laryngitis. Year ago she had pneumonia. As a child she had vesicles on the hands and feet which, according to her doctor, was due to a fungal infection. No history of diarrhoea, herpes labialis, genital or eye lesions. Occasionally attacks of arthritis in the right shoulder joint. Family history negative.

Examination: General examination NAD. Rectal temp. 37.0°C. B.P. 150/90. Appearance normal. No lymph glands palpable.

Intraorally: A typical aphtha of 7 days duration present in left lower buccal sulcus.

Diagnosis: Chronic recurrent aphthae.

Further visits: 21.1.'59. Patient had only one outbreak since her last visit., this happened a month ago while she was on holiday. The attack appeared two days before the menstrual period.

Case 34. A.J.V. (58/2623). Female, aged 37. Single. Occup: State official.

First visit: 14.10.'58. (Referred by Dr. F. van der Veen, Leeuwarden).

History: Patient suffered attacks of recurrent painful lesions in the mouth from her eighteenth year. They used to appear periodically every month, but now practically never free from lesions. They usually appear two days before the menstrual period and heal within 7 to 11 days. According to her, she is always highly strung. On a few occasions she also had vesicles on the genitals(?). Twenty years ago she had inflammation in the eyes. In 1941, she received treatment in a sanatorium for TB. A year later after being cured, she was discharged. No history of diarrhoea or labial herpes. Menses regular, but profuse and painful. Family history negative for aphthae. Two of her sisters had eczema. One is still troubled by this condition.

Examination: Healthy complexion, but overweight. Length 1.65 m. Weight 67 Kg. General examination: NAD. Rectal temp. 37.1°C. B.P. 120/80. Pulse 60 p.m. No lymph glands palpable.

Intraorally: On the inside of the mandible opposite $\overline{8}$ a deep oval ulcer with a grayish-white base and surrounded by a red halo of ½ cm present on the alveolar mucosa. The lesion developed 16 days before.

Diagnosis: Chronic recurrent aphthae? Aphthosis?

Further visits: 4.11.'59.

Case 35. P.V. (58/2168) Male, aged 34. Married. One child. Occup: Dental mechanic. First visit: 25.8.'58.

History: Patient suffers from recurrent, painful lesions in mouth since the age of 12. Lesions appear at irregular intervals. Sometimes free from lesions for 2 months, at other times new lesions every 14 days. They become painless after 4 days, but patient can not tell exactly how long they take to heal. When lesions appear, he feels slightly feverish. No history of skin, genital or eye lesions. His mother, brother and daughter of 5 years had similar lesions in the mouth. Family and personal history negative for allergy or TB.

Examination: Adult male of normal weight and build. General examination NAD. Rectal temp. 37.1°C. B.P. 110/70. No lymph glands palpable.

Intraorally: Four aphthae present in mouth.

Diagnosis: Chronic recurrent aphthae.

Further visits: 26.9.'58 (no lesions present) 20.10.'58. Patient made the observation that the lesions frequently accompanied attacks of "flu". Two lesions present. 27.10.'58. Lesions present on inside of lower lip. With slight redness around it. It is situated in the same position as the lesion present on 20.10.'58 but slightly larger. 23.1.'59. One lesion present. 31.1.'59. No lesions present. 1.2.'59 No lesions. 10.2.'59. No lesions.

Case 36. G.W. (58/726) Female, aged 12. Scolar. First visit: 15.5.'58. (Referred by Dept. of Conservative Dentistry: Prof. Dr. de Boer).

History: Recurrent painful lesions for 18 months. After one lesion is gone another appears. Lesions heal within 14 days. No history of labial herpes, diarrhoea, skin, genital or eye lesions. Family history for aphthae negative. Patient suffers from asthma, but it is now months since she last had an attack.

Examination: Normal appearance. General examination NAD. Intraorally: No aphthae. In the buccal sulcus opposite. $\overline{E}$ a fistula present. $\overline{E}$ nonvital. This tooth was removed under local anaesthesia. 27.5.'58. Typical aphtha of + 14 days duration present in upper left buccal sulcus. Lesion very painful when touched. On muscle attachment in upper left sulcus a slightly smaller lesion of similar appearance. Remainder of mucosa normal. Gingiva not affected. Cervical lymph glands palpable.

Diagnosis: Chronic recurrent aphthae.

Further visits: 30.5.'58. Ulcers almost healed. No new lesions. 28.1.'59. No lesions since last visit. 3.2.'59. No new lesions. 10.2.'59. No new lesions. Herpetic lesion on lower lip. First time that patient develops a lesion of this nature.

Case 37. A.W-K. (58/649) Female, aged 40. Married. No children. Housewife. First visit: 11.3.'58. (referred by Dr. J. van Dijk, Groningen for removal of roots of 7 and 8. They were removed on the same day by Dr. G. Boering under local anaesthesia). Referred by Dr. van Dijk on 11.4.'58 with a buccal ulcer of 5 days duration.

History: Suffers from recurrent painful ulcers in the mouth since childhood. Lesions appear intermittently. Between attacks free intervals of irregular length. Four years ago she continually suffered from lesions, with the result that the diet consisted mainly of liquid foods. After much milk in the diet the condition improved considerably. The year before she only had two outbreaks. According to the patients attacks were always more severe after she paid a visit to the dentist. Not related to the menses, which are of a normal character. No history of allergy, diarrhoea, labial herpes, skin, genital or eye lesions. Her mother, a sister, two brothers and their children all suffer from similar oral lesions. (The patient is the aunt of case 22).

General examination: NAD.

Intraorally: Typical aphtha in upper right sulcus.

Diagnosis: Chronic recurrent aphthae.

Further visits: 28.1.'59.

Case 38. W.W. (59/2656) Male, aged 22. Unmarried. Dental Student. First visit: 31.3.'58.

History: Suffers from recurrent lesions in mouth since 12th year. Lesions appear once or twice a year, and heal within ten days. From 10 to 16 years of age the patient suffered from asthma. Maternal grandfather had aphthae up to his 60th year. After that time he was entirely free from lesions. His mother suffers from lesions which tend to appear a few days before the onset of the menses. No history of labial herpes, skin, genital or eye lesions.

Examination: Normal appearance. General examination NAD. No lymph glands palpable.

Intraorally: Typical aphtha with yellowish-white base and red border visible on right cheek mucosa.

Diagnosis: Chronic recurrent aphthae.

Further visits: 12.5.'58. Five small aphthae present in mouth.

Case 39. T.E.-Z. (59/459) Female, aged 34. Married. Two children. Housewife. First visit: 24.2.'59.

History: Twenty years ago, at the time of puberty, patient first experienced painful lesions in the mouth. Practically never without lesions, perhaps occasionally one week of freedom between attacks. Lesions heal in 10 days. They are more severe a few days before the menses. Patient suffered attacks of labial herpes since childhood, but never in conjunction with the painful ulcers in the mouth. Never had skin, genital or eye lesions. Menses appeared at age of 11. The latter are regular, but painful and profuse (7 days duration). No history of diarrhoea. Two children of her sister had similar lesions in the mouth.

Examination: General examination NAD. Patient overweight. Kg 84. Length 1.67 m. Rectal temp. 36.8°C. B.P. 110/80. No lymph glands palpable.

Intraorally: Aphtha present on inside of lower lip.

Diagnosis: Chronic recurrent aphthae. Patient admitted to hospital from 2.3.'59 to 5.3.'59 for further investigation. On admission no lesions. Menses appeared on 3.3.59. New aphtha developed on 5.3.'59.

Case 40. L.R-M. (59/612) Female, aged 28. Married. Two children. Housewife. First visit: 10.3.'59 (Referred by Dept. of Dermatology: Prof. Dr. M. Ruiter).

History: Lesions in mouth first appeared 10 years ago. Never without lesions, except perhaps for a few days. They heal within a week. In both her pregnancies lesions disappeared after the fifth month, only to return immediately after the confinements. No history of allergy, diarrhoea, skin, genital or eye lesions. Never had labial herpes. In 1953 she received treatment for her nerves. Family history: negative.

Examination: Normal appearance. General examination NAD. Rectal temp. 37.0°C. B.P. 122/80. No lymph glands palpable.

Intraorally: Three typical aphthae of less than 7 days duration. Behind the left corner

of the mouth an almost healed lesion visible. The latter appeared 7 days before.
Chronic gingivitis present.
Diagnosis: Chronic recurrent aphthae.
Further visits: 31.3.'59. New aphtha present for 5 days.

Case 41. J. W. (59/622) Male, aged 21. Single. University student. First visit: 11.3.'59.
History: Recurrent, painful oral ulcers since he was 12. Lesions appear about four times a year and heal within 14 days. Outbreaks not accompanied by malaise and fever. No history of allergy, diarrhoea, skin, genital or eye lesions. Mother suffers from similar lesions. Father from asthma.
Examination: Normal appearance. General examination: NAD. Rectal temp. 36.9°C. B.P. 110/75.
Intraorally: A typical aphtha the size of a lentil present on the mucosa of the left cheek. Lesion very painful. Of 4 days duration.
Diagnosis: Chronic recurrent aphthae.

Case 42. H.W.-B. (57/26) Female, aged 58. Married. Twelve children. First visit: 4.1.'57. Seen by us on 4.3.'59.
History: At the age of 25 patient developed painful oral lesions for the first time. They appear every month or two, and heal in about 10 days. The patient receives treatment from the Dept. of Dermatology for eczema behind the ears. The patient also suffers from arthritis in the knees, arms, back and shoulders for the past nine years. The onset of joint symptoms coincided with the onset of the menopause. The patient never had diarrhoea, labial herpes, genital or eye lesions. One of her sons was operated for gastric ulcer 2 years ago. From that time he also suffers from painful oral lesions.
Examination: Patient of normal weight and build, but looks worn. General examination: Patient advised to return for examination when new lesions develop.
Intraorally: Scar of almost healed aphtha on inside of lower lip.
Diagnosis: Chronic recurrent aphthae.

Case 43. G.D.-M. (59/644) Female, aged 46. Married. Two children. Housewife. First visit: 16.3.'59.
History: Periodic attacks of painful oral ulcers since the age of eighteen. Individual lesions heal in about 14 days. They appear regularly every month, 14 days prior to the menses. The menstrual periods were always very irregular and occasionally disappeared for months. Her doctor is of the opinion that she has now reached the menopause. She never had diarrhoea, labial herpes, skin, genital or eye lesions. The patient also suffers from rheumatic pains in the back and extremities. A few months ago the patient had attacks of nausea, which according to her doctor was due to cholecystitis.
Examination: General examination: NAD. No lymph glands palpable. Temp. 37.2°C. B.P. 180/100.
Intraorally: On the soft palate a round yellowish-gray ulcer surrounded by a narrow red border. The lesion measures 1½ x 1½ cm. Very painful when touched.
Diagnosis: Chronic recurrent aphthae.
Further visits: 25.3.'59. Lesion on soft palate almost healed. No new lesions.

Case 44. S.L.-S. (59/720) Female, aged 24. Married. One child. Housewife. First visit: 20.3.'59. (Referred by Dr. E. de Boer, Groningen).
History: Patient suffers from periodical painful lesions in mouth since the age of 14. Lesions appear very irregular. Initially they appeared with longer intervals of freedom between attacks, nowadays more severe. She is of the opinion that lesions appear 2 days before the onset of the menstrual period. However, this did not happen every month. Individual lesions usually heal within 10 days. Occasionally a new lesion develops on the mucosa to disappear completely after one day. Mother also suffered from similar lesions. No history of allergy, labial herpes, diarrhoea, skin, genital or eye lesions. Menses regular and of a normal character.
Examination: General examination NAD. Healthy appearance. Of normal build and weight. No lymph glands palpable.
Intraorally: On the mucosa of the lower lip two small round yellowish aphthae both the size of a match-end. Behind the left corner of the mouth an oval ulcer with a greenish-gray base. Lesions very painful when touched. They appeared three days before.
Diagnosis: Chronic recurrent aphthae.

Case 45. A.G.D. (59/1399). Male, aged 28. Married. One child. State official. First visit: 11.6.'59.

History: Suffers from recurrent painful ulcers in the mouth since the age of 16. The lesions appear at irregular intervals of one to three months. They are very painful. Never had labial herpes, diarrhoea, skin, genital or eye lesions. One of his brothers suffers from similar lesions. His mother and a maternal uncle suffered from allergic dermatitis(contact with certain plants).

Examination: Healthy appearance. General examination: NAD. Right supraclavicular lymph glands palpable.

Intraorally: Two typical aphthae of 7 days duration. One on the lower lip, the other on the inside of the upper lip.

Diagnosis: Chronic recurrent aphthae.

Case 46. E.N.-B. (51/3683). Female, aged 25. Single. Occup: Typist. First visit: 21.12.'51. First seen by us 11.6.'59.

History: Troubled by recurrent ulcers in mouth since the age of 18. They appear every month a few days prior to the menses. Individual lesions heal within 10 days. No history of diarrhoea, labial herpes, genital or eye lesions. Psoriasis present on both elbows and on the lower extremities. Family history negative.

Examination: Healthy appearance. Normal weight and build. General examination: NAD.

Intraorally: Scars of three healed aphthae present in mouth.

Diagnosis: Chronic recurrent aphthae.

Further visits: 28.12.'51, 7.1.'52, 0.2.'52, 23.2.'52, 12.4.'56, 24.4.'59, 27.4.'59, 29.5.'59, 2.6.'59.

SUMMARY

In Chapter I a historical account was given of aphthae. We defined aphthae as circumscribed, round or oval efflorescences of the mucosa, varying between the sizes of a pinhead and that of a bean, and which are superficially covered by an adherent fibrinous deposit (grayish-white or yellowish-white) surrounded by a red inflamed border of varying width.

The word aphthae first employed in the writings of Hippocrates of Cos (460-370 B. C.), was subsequently applied in the description of a variety of oral conditions. Billard (1828) and Bohn (1880) gave accurate descriptions of the lesions, but failed to distinguish between the acute variety, usually appearing in children, and the chronic recurrent variety which mainly affects adults. Mikulicz and Michelson (1892) must be credited for being the first to give a separate description of the two varieties. They called the recurrent variety of adults, chronic recurrent aphthae, and the acute variety of children, acute aphthous stomatitis.

In 1895 Neumann gave a description of oral aphthae in conjunction with lesions on the genitals and the skin. This condition became known as the aphthosis of Neumann.

In Chapter II we briefly discussed the various entities characterized by the formation of aphthae or to which at some time or other the name aphthae was applied. After considering various classifications of aphthae in the literature we decided upon a classification under the following headings: aphthous diseases of known etiology (e. g. acute aphthous stomatitis due to herpes simplex virus), aphthous disease of doubtful etiology, nl. aphthosis (considered by many to be due to a virus) and aphthous diseases of unknown etiology e. g. chronic recurrent aphthae of Mikulicz.

A description was given in Chapter III of the various aphthous diseases of known etiology. Here special attention was paid to acute aphthous stomatitis caused by the herpes simplex virus. At the same time a description was given of the other manifestations of infection by this virus, since oral aphthae were occasionally observed in conjunction with them.

No difference exists as far as the histological picture of these herpes manifestations are concerned. A description of the histological picture was given under the heading: acute aphthous stomatitis.

The other aphthous diseases of known etiology included herpangina, aphthae epizoötícae, vesicular stomatitis, false foot and mouth disease and traumatic lesions of the oral mucosa which may resemble aphthae such as decubital ulcers and Bednar's aphthae of infants.

Chapter IV was devoted to a description of aphthosis. In support of Touraine (1941) we included ulcus vulvae acutum

(Lipschütz),chronic recurrent aphthosis (Kumer), aphthosis of Neumann and the syndrome of Behcet under this heading. Touraine (1941) also considered chronic recurrent aphthae (Mikulicz) and the dermatostomatitis of Baader as aphthosis. On clinical grounds, however, we felt that these conditions should not be included under the heading of aphthosis.

Next we gave a description of the clinical manifestations of aphthosis. The theories concerning the etiology of the disease were then reviewed. In this respect we pointed out that a virus was considered the most likely etiological agent. In view of Touraine's concept that CRA and aphthosis were the same disease and the fact that a virus was cultured by Sezer (1956) and Evans et al. (1957) from cases with aphthosis, we decided to conduct further viral and histological investigations in this respect.

The findings obstained with these investigations are discussed in Chapters VII and VIII.

In Chapter V a description was given of the aphthous diseases of unknown etiology. This dealt mainly with chronic recurrent aphthae. An extensive investigation was conducted on 46 patients with CRA and the findings compared with those reported in the literature.

Clinically we found that an increased temperature and regional lymphadenopathy were not constant features of CRA. In our opinion the occasional presence of these changes may be ascribed to secondary infection. As far as the general incidence of the disorder is concerned we concluded that the prevalence is higher than generally supposed. Exactly twice as many females as males attended for treatment. No study of the prevalence in different races was conducted, but we gained the impression from previous experience in South Africa and Tanganyika that the disorder is less prevalent amongst the Bantu living in those parts. The geographical distribution is possibly world-wide. Cases were reported from all civilized countries. From regular observation of some of our patients we concluded that climatic or seasonal changes have little or no effect on the course of the disease. The age at attendance of our patients ranged from 11 to 55 years. The youngest age at onset was 6 years and the oldest 40. The majority of our patients (17 out of 44) suffered periodic attacks with intervals of from 2 to 8 weeks. Ten out of 44 showed no periodicity, the lesions appearing continuously, while 8 of the 44 had completely irregular intervals. Intervals longer than two months were observed in 9 of the 44 patients. The distribution of lesions in the mouth showed a predelection for the inside of the lower lip (31.48%)followed in descending order of frequency by the tongue the inside of the upper lip, the lower buccal sulcus, the cheek mucosa, the upper sulcus, the gingiva, the palate and the floor of the mouth.

The etiology of CRA was considered from the following aspects: 1. bacterial infection, 2. neurosis, 3. heredity, 4. vitamin deficiency, 5. gastro-intestinal disease, 6. disease of the blood or blood-forming organs, 7. endocrine disturbance. 8. allergy and 9. viral infection. Our own viral investigation in CRA was discussed with that of aphthosis in Chapter VII.

Our impression was that a neurotic factor plays a part in the development of lesions and that there exists a familial incidence in some cases. The latter may be of the nature of a sex-linked dominancy. Our patients revealed a slight deficiency of vitamin E and vitamin C. No therapeutic trials were conducted with vitamin E so that we are unable to ascribe the lesions to a deficiency of this vitamin. Deficiency of vitamin C may be ruled out as a causative factor, since healthy controls revealed a similar vit. C. deficiency in the blood. This was attributed to the fact that our investigations were carried out during the winter months when fresh fruit and vegetables are lacking in the diet. Blood examination revealed a hypochromic anaemia in some of the patients. This finding was not considered the cause of the lesions since anaemia was not a constant feature in cases of CRA.

A review was given of the literature dealing with the histological findings in CRA.

Finally in this chapter we gave a description of other aphthous diseases of unknown etiology. This included tropical aphthae, non-tropical sprue and solitary aphthae.

In Chapter VI we dealt with diseases to which the name aphthae was applied but which are not characterized by the formation of aphthae. This included stomatitis aphthophyta (moniliasis) and malignant aphthae (Orf) of known etiology, and aphtha cachectia (sublingual fibroma of Riga-Fede of unknown etiology.

Chapter VII was devoted to our own viral investigation in cases of CRA and aphthosis. Material from oral lesions, blood and faeces were inoculated onto tissue cultures, the CAM of hen's eggs and into infant mice (intracerebrally and intraperitoneally). No virus could be demonstrated. Complement fixation tests also gave no evidence in favour of infection with herpes simplex, adenovirus, ECHO type 9, mumps, measles and LCM viruses. The pocks observed by us, after inoculation of material onto the CAM, proved to be non-specific. It is very likely that the positive findings in their CAM studies in cases with aphthosis, reported by Sezer (1956) and Evans et al. (1957), were similarly of an unspecific nature.

Our viral investigation provides further evidence that herpes virus is not the etiological agent of CRA and aphthosis. No specific skin reaction was obtained with antigens prepared from oral lesions and saliva of CRA and aphthosis cases. We were therefore unable to confirm the findings of Jadassohn et al. (1957), and of Vilanova and Pinol-Aguadé (1958).

Cytological investigation of smears made from oral lesions in CRA and aphthosis gave negative results. No viral type giant cells, as observed with herpes infections or viral elimentary bodies, were found.

In Chapter VIII we compared the histological findings of CRA lesions with those of aphthosis. No distinct pattern was observed. The early lesions of CRA showed changes of the nature observed in contact dermatitis (eczema). Apart from the fact that the clinical manifestations of CRA and eczema are different from each other, there does not exist enough evidence to ascribe the lesions of CRA to allergens. No other changes relating a possible allergic etiology were found.

Our histological findings are further evidence against the possibility that the lesions of CRA and aphthosis are due to infection with herpes simplex virus.

SAMENVATTING.

In Hoofdstuk I werd een historisch overzicht over "aphthae" gegeven. Aphthae werden gedefinieerd als omschreven, ronde of ovale aandoeningen van het slijmvlies varierend van speldeknop- tot boongrootte, bedekt door een verklevend fibrineus beslag (grijs-wit of geel-wit) en omgeven door een rode ontstoken zoom van wisselende breedte.

Het woord aphthae, voor het eerst gebruikt in de geschriften van Hippocrates van Cos (460-370 v. C.), werd later gebruikt voor de beschrijving van een verscheidenheid van mondaandoeningen. Billard (1828) en Bohn (1880) gaven een nauwkeurige beschrijving van de laesies, maar lieten na een onderscheid te maken tussen de acute vorm, die gewoonlijk een kinderziekte is en de chronisch recidiverende vorm, die voornamelijk bij volwassenen voorkomt. Het is de verdienste van Mikulcz and Michelson (1892) het eerst een afzonderlijke beschrijving van de twee vormen gegeven te hebben. Zij noemden de terugkerende vorm bij volwassenen chronische recidiverende aphthae en de acute vorm bij kinderen acute aphtheuse stomatitis. In 1895 gaf Neumann een beschrijving van aphthae in de mond, samen voorkomend met laesies van de genitaliën en de huid. Deze aandoening werd bekend onder de naam aphthosis van Neumann.

In Hoofdstuk II werden de verschillende ziektebeelden, die gekenmerkt zijn door de vorming van aphthae, of waarvoor de naam aphthae ooit gebruikt werd, kort besproken.

Na een beschouwing over verschillende indelingen in de literatuur besloten wij tot een indeling in de volgende groepen: aphtheuse ziekten door bekende oorzaak (b. v. herpes simplex virus), aphtheuse ziekte met twijfelachtige aetiologie (n. l. aphthosis, volgens velen door een virus veroorzaakt) en aphtheuse ziekten door onbekende oorzaak (b. v. chronische recidiverende aphthae van Mikulicz).

In Hoofdstuk III werden de verschillende aphtheuse ziekten met bekende aetiologie besproken. Er werd voornamelijk aandacht geschonken aan de acute aphtheuse stomatitis, veroorzaakt door herpes simplex virus. Tegelijkertijd werd een beschrijving gegeven van de andere uitingen van infecties door dit virus, die soms met aphthae in de mond gepaard gingen. Alle verschillende uitingsvormen van herpesvirus-infectie vertonen hetzelfde histologische beeld. Een beschrijving werd gegeven van het histologische beeld van acute aphtheuse stomatitis. De overige aphtheuse ziekten met bekende aetiologie zijn: herpangina, aphthae epizoöticae (mond- en klauwzeer), stomatitis vesiculosa, pseudo-mond- en klauwzeer (Mollaret) en traumatische laesies van het mondslijmvlies, die op aphthae lijken, zoals drukulcera en de aphthae van Bednar bij zuigelingen.

Hoofdstuk IV werd gewijd aan een beschrijving van aphtho-

sis. In navolging van Touraine (1941) werd onder dit hoofd samengevat: ulcus vulvae acutum (Lipschütz), chronische recidiverende aphthosis (Kumer), aphthosis van Neumann en het syndroom van Behçet. Hoewel Touraine (1941) chronische recidiverende aphthae (Mikulicz) en de dermato-stomatitis (Baader) ook tot aphthosis rekent, menen wij op klinische gronden deze beide ziekten van aphthosis te moeten onderscheiden.

Vervolgens gaven we een beschrijving van het klinische beeld van aphthosis. Een overzicht werd gegeven van de theoriën over de aetiologie van deze ziekte. Hierbij bleek, dat een virus als de meest waarschijnlijke oorzaak wordt beschouwd.

Naar aanleiding van de opvatting van Touraine dat CRA en aphthosis dezelfde ziekten zijn en het feit, dat door Sezer (1956) en Evans e. a. (1957) bij gevallen van aphthosis een virus gekweekt werd, hebben we besloten in dit opzicht verdere onderzoekingen te doen.

De resultaten van deze onderzoekingen werden besproken in de Hoofdstukken VII en VIII.

In Hoofdstuk V werden de aphtheuse ziekten met onbekende aetiologie behandeld. Dit betreft voornamelijk chronische recidiverende aphthae. Een uitgebreid onderzoek werd gedaan bij 46 patienten met CRA en de bevindingen met die uit de literatuur vergeleken.

Temperatuursverhoging en regionale lymphklierzwelling werd niet constant waargenomen. Het soms voorkomen van deze verschijnselen moet volgens ons worden toegeschreven aan secundaire infectie. We kwamen tot de conclusie, dat de ziekte vaker voorkomt dan algemeen wordt aangenomen.

Precies tweemaal zoveel vrouwen als mannen meldden zich voor behandeling.

Het voorkomen bij verschillende rassen werd niet bestudeerd, maar uit vroegere ervaringen in Zuid-Afrika en Tanganjika hebben we de indruk, dat de afwijking minder vaak voorkomt bij de in deze streken levende Bantoes.

Daar uit alle beschaafde landen gevallen worden gemeld, is, geografisch gezien, een verspreiding over de hele wereld waarschijnlijk. Naar aanleiding van geregelde contrôle van enkele van onze patiënten zijn we tot de gevolgtrekking gekomen, dat klimaat- en seizoenveranderingen geen of weinig invloed hebben op de ziekte.

De ouderdom bij eerste onderzoek van onze patiënten varieerde van 11 tot 55 jaar.

De leeftijd, waarop de ziekte zich voor het eerst voordeed, wisselde van 6 tot 40 jaar. De meerderheid van onze patiënten (17 van de 44) leden aan periodieke aanvallen met constante tussenpozen van 2 tot 8 weken, terwijl 9 van de 44 tussenpozen van langer dan 8 weken hadden. Bij 10 van 44 patiënten had de afwijking geen recidiverend karakter, maar waren er constant laesies aanwezig, terwijl 8 van de 44 volkomen onregelmatige tussenpozen vertoonden.

De verspreiding van de laesies in de mond vertoonde een voorkeur voor de binnenkant van de onderlip (31.48%) in afnemende mate gevolgd door de tong, de binnenkant van de bovenlip, de onderste omslagplooi, het wangslijmvlies, de bovenste omslagplooi, de gingiva, het palatum en de mondbodem.

De aetiologie van CRA werd uit de volgende oogpunten benaderd: 1. bacteriële infectie, 2. neurose, 3. erfelijkheid, 4. vitaminetekort, 5. ziekten van de tractus digestivus, 6. ziekten van het bloed en de bloedvormende organen, 7. endocrinestoornissen, 8. allergie, 9. virusinfectie. Ons eigen virusonderzoek bij CRA werd samen met het virusonderzoek bij aphthosis in Hoofdstuk VII besproken.

Onze indruk was, dat bij het ontstaan van de laesies een neurotische factor een rol speelt en dat deze soms in families voorkomen. Dit laatste zou mogelijk duiden op een aan het geslacht gebonden dominante factor. Onze patiënten vertoonden een gering tekort aan vitamine E en vitamine C. Geen therapeutische proeven werden gedaan met vitamine E, zodat het niet mogelijk was het gevonden tekort als oorzaak van de laesies te beschouwen. Het lijkt ons onwaarschijnlijk om het gevonden tekort aan vitamine C als oorzaak van de afwijking te beschouwen, daar gezonde contrôlepersonen een even lage bloedspiegel vertoonden. Dit tekort moet worden toegeschreven aan het feit, dat ons onderzoek werd uitgevoerd gedurende de wintermaanden, wanneer vers fruit en groenten vaak in het dieet ontbreken.

Bij bloedonderzoek vertoonden sommige van de patiënten een hypochrome anaemie. Deze bevinding kan niet als de oorzaak van de laesies worden beschouwd, daar andere CRA-patiënten geen anaemie vertoonden. Verder werd een overzicht gegeven van de literatuur betreffende het histologische beeld bij CRA. Tenslotte werd in dit hoofdstuk een beschrijving gegeven van andere aphtheuse ziekten met onbekende aetiologie, n. l. tropische aphthae, inheemse spruw en solitaire aphthae.

Hoofdstuk VI handelt over ziekten, waarvoor de naam aphthae werd gebruikt, maar die niet gekenmerkt zijn door de karakteristieke laesies, n. l. stomatitis aphtophyta (moniliasis) en maligne aphthae (Orf) met bekende aetiologie en aphtha cachectia (sublinguaal fibroom van Riga-Fede) met onbekende aetiologie.

Hoofdstuk VII is gewijd aan een eigen virusonderzoek bij gevallen van CRA en aphthosis. Materiaal van mondlaesies, bloed en faeces werd geënt op weefselculturen, de CAM van bebroede kippeneieren en op zuigelingenmuisjes (intracerebraal en intraperitoneaal). Er kon geen virus worden aangetoond. Bovendien waren de complementbindingsreacties negatief voor herpes simplex, adenovirus, ECHO type 9, bof, mazelen en LCM-virus.

De pokken door ons waargenomen na enting op de CAM bleken van een niet specifieke aard te zijn.

Het is zeer waarschijnlijk, dat de positive bevindingen gemeld door Sezer (1956) en Evans e. a. (1957) bij gevallen van aphthosis, van soortgelijke niet-specifieke aard waren.

Ons virusonderzoek is mede een bewijs, dat het herpesvirus niet de oorzaak is van CRA en aphthosis.

Met antigenen bereid uit mondlaesies en uit speeksel van CRA- en aphthosis-patiënten, kon geen specifieke huidreactie worden verkregen. We waren daarom niet in staat de bevindingen van Jadassohn e. a. (1957) en van Vilanova en Pinol Aguadé (1958) te bevestigen.

Cytologische onderzoekingen van uitstrijkpraeparaten van mondlaesies bij CRA en aphthosis gaven negatieve bevindingen. Er werden geen reuscellen zoals bij herpesinfecties of elementaire lichaampjes gevonden.

In Hoofdstuk VIII hebben we de histologische bevindingen bij CRA-laesies vergeleken met die bij aphthosis; er werd geen typisch beeld gevonden. De vroege laesies bij CRA doen denken aan veranderingen, zoals gezien bij contactdermatitis. Echter, behalve dat het klinische beeld van de beide aandoeningen verschilt, bestaat er ook geen voldoende bewijs dat CRA veroorzaakt wordt door allergenen. Geen andere histologische veranderingen werden gevonden, die aangevoerd kunnen worden voor een allergische aetiologie. De histologische bevindingen pleitten verder tegen de mogelijkheid van een herpesinfectie.

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