CHAPTER 35 - LACTOBACILLUS ACIDOPHILUS PREPARATIONS:

In 1959 the Journal of the American Medical Association \textsuperscript{434} stated that a recently introduced preparation derived from Lactobacillus acidophilus and L. bulgaricus had been reported to give excellent results in relieving the pain and shortening the duration of aphthous ulcers. The preparation is dissolved in milk and used as a mouthwash.

Scott, in 1963, described the rationale of the treatment. It had been observed in 1958 that aphthous and herpetic lesions "of non-viral origin" healed rapidly in patients being treated with a lactobacillus preparation for diarrhoea arising from the use of broad-spectrum antibiotics. The preparation was found to be successful also when used for oral lesions not associated with antibiotic therapy. Lactobacillus acidophilus is the predominant organism in the normal bacterial flora of the bowel, \textsuperscript{196, 498} and by symbiosis and competition reduces the population of possible pathogens, preventing and correcting gastrointestinal symptoms. \textsuperscript{498} Its replacement from an exogenous source in cases of depletion such as following antibiotic therapy seems sound. However, the extension of this treatment for oral lesions where a bacterial aetiology has not been established, does not appear to be justified. Nevertheless, Scott claimed successful results in 84% of oral lesions.

Rapoport and Levine (1965) claimed that by the use of "Lactinex" (a standardized viable culture of L. acidophilus and L. bulgaricus) the soreness of aphthous lesions was relieved within 48 hours in an extremely high percentage of cases. However this study, like the previous, was uncontrolled.
In Rapoport and Levine's study no double-blind techniques were used, the patients returning to the office or merely reporting their subjective experiences per telephone. Patients were told that a preparation was being used "in the hope that it would clear up or at least lessen the discomfort caused by their oral lesions", and no attempt was made to check the accuracy of the patients' findings.

Subsequent reports have been largely unfavourable, the two which attribute some value to the treatment citing the findings of Rapoport and Levine. Graykowski et al. (1966) found no significant improvement with the use of Lactinex. Both McCarthy and Shklar (1964) and Brightman and Ship (1966) mention the uncontrolled nature of the trials of this preparation.

McCarthy and Shklar cite lactobacillus preparations among "an endless list of useless or semi-useless medicaments". They continue: "Any reports of success with such procedures are uncontrolled and probably portray the author's enthusiasm projected to his patients." Bhaskar (1965) describes lactobacillus tablets as of questionable value.

In 1970 Gertenrich and Hart (1970) employed a lactobacillus acidophilus preparation ("Bacid") in a double-blind study on the healing time of oral lesions in institutionalized retardates. Pain was not considered, as the subjects of the trial were largely unable to communicate with any precision. Approximately 90% of the lesions were diagnosed as aphthous ulcers, the remainder herpes simplex infections. Bacid did not affect the duration of healing of oral lesions.
The treatment was originally introduced in 1958 by Weekes who advised dissolving two lactobacillus suspension tablets in the mouth with milk four times daily for several days. Lactobacilli could conceivably inhibit other flora by competitive inhibition or by their acidogenic activity. The only justification for this form of therapy in the mouth, apart from any subjective comfort that might be experienced by the patient, lies in the possibility of bacteria being concerned in the pathogenesis of oral aphthae and those bacteria being controlled by the medication. This seems unlikely. Although Queries and Minor Notes suggests that secondary invasion by microorganisms generally found in the mouth may play a role in the continuation of the disease process, the most likely implication of bacteria is that the L forms of Barile and others are involved in a delayed hypersensitive phenomenon.

The use of yogurt, as mentioned by Brightman and Ship (1966) would appear to have a similar rationale, and one equally unsound.
CHAPTER 36 - MISCELLANEOUS MODES OF TREATMENT:

Aniline dyes:

Lehner (1967c) mentions the use of 1% aqueous gentian violet, but regards it as of doubtful value. Cooke (1961) says that secondary infection of an established ulcer is best controlled by two applications of 1% gentian violet per day. Farmer (1958) reported little success with these preparations, but 1% gentian violet, if applied early, was considered to bring about more rapid healing on the first few occasions. In 1963 Ryan stated that 4% methylene blue was once strongly advocated for mouth ulcerations in the hope that the dye would unite with the organisms responsible and so fix them.

Topical analgesic agents:

Lehner (1967c) states that the local anaesthetic effect of benzocaine troches containing 100 mg. of benzocaine, 50 mg. borax and 3 mg. menthol is occasionally helpful in cases of large pharyngeal ulcers with slow healing and dysphagia. This form of treatment in the same situation was also recommended by Kay (1969).

Kramer (1967) warns that although topical analgesics give temporary relief from pain, they may increase the trauma to the lesion in that it is not so well protected by the patient, and healing may be retarded. Brightman and Ship (1966) recommend the use of Xylocaine Jelly in appropriate cases but warn against possible sensitization from prolonged contact.
"Bonjela" is essentially a topical analgesic as it contains choline salicylate, but it is also claimed to expedite healing by virtue of its antiseptic component, cetyldimethylbenzyl ammonium chloride, a quaternary ammonium compound; but the latter effect appears unconfirmed (Kay, 1969). The other ingredients are alcohol (39%), menthol (0.057%) and glycerin (4.6%). "Teejel" is another proprietary compound of similar composition (Kay, 1969).

**Antiseptic agents and mouthwashes:**

Ryan (1963) mentions quinine sulphate and potassium chlorate tablets. Quinine sulphate (6%) may be used as both an application and a mouth wash. It is a powerful antiseptic against most forms of animal and vegetable life. Potassium chlorate tablets, Ryan says, are a relic of a bygone day, although they were once considered a panacea for all mouth ulcerations. These agents release oxygen in the presence of septic matter. Similar agents which Ryan mentions are sodium bicarbonate, "Bocasan" and "Ascocoxal".

Erich (1959) recommended a mild alkaline or diluted hydrogen peroxide mouthwash. Truelove and Morris-Owen (1958), however, stated that simple mouthwashes and paints have little influence on the course of the ulcers. Farmer (1958) used sodium thiosulphate, 10 mg. t.d.s., without significant success.

**Radiotherapy:**

Whereas Harrison (1953) reported highly successful results from the use of radiotherapy, a double-blind investigation carried out by Sircus et al. (1957) gave disappointing results.
"Attapulgite":
This is a hydrated magnesium silicate which, when heated, loses water and absorbs "viruses, bacteria, toxins and other irritants". Its use in aphthous ulceration was advocated by Engelman (1963) on the basis of the disease being caused by microorganisms or their products. Good results were claimed.

"Halidor":
Terner and Adler (1969) reports a favourable response of herpetiform lesions ("multiple small aphthous ulcers surrounded by a bright red, sharply defined halo, which occur repeatedly over several years") to Halidor. The authors speculate that the action of the drug is due to an anti-5-hydroxytryptamine effect, but admit that further elucidation and confirmation are required.

"Pyralvex Berna":
This product of the Swiss Serum and Vaccine Institute of Berne is claimed by Ryan (1963) to give rapid amelioration of symptoms after several applications, and was favourably regarded on the Continent. It comprises an alcoholic solution of anthraquinone glycosides with salicylic acid, and is said to be antiphlogistic, antibacterial and astringent, and to have the ability to reduce swelling, secretion and pain.

Physical protectants:
Stoy (1966) concluded, on the basis of 100 consecutive treatments of inflammatory conditions of the oral mucosa, that topical application of Orabase was an effective method of treatment.
He claimed that the response of the lesion was similar whether the base contained small quantities of corticosteroids or not, and that the factor inducing healing is probably mechanical protection. Orabase consists of gelatin, pectin and sodium carboxymethylcellulose (Orahesive) in an oleaginous ointment base (Stoy, 1966). Biobase is a material similar to Orabase in that it adheres to a wet mucosal surface and protects an underlying lesion (Kay, 1969).

Stoy's results were based upon the subjective experiences of his patients and a placebo effect may have been operating. In a later study, Browne et al. (1968) considered Orabase alone to be of no value, although one finds it difficult to dismiss entirely its value as a protectant.

Bioral is a preparation consisting of carbenoxolone in the vehicle Biobase. Carbenoxolone is a liquorice derivative used in the treatment of peptic ulcers and extended for use in aphthous lesions (Kay, 1969). Whether carbenoxolone confers an additional advantage over biobase alone is at present being investigated (Kay, 1969).

Bhaskar et al. (1966) reported favourably on the use of a new chemical adhesive, butyl cyanoacrylate, which is applied to tissue in the form of a thin spray. The material did not adhere well to movable tissues, on which aphthous lesions are typically situated, but while it could be peeled off easily from the epithelialised surface, it did adhere to the ulcerated area. Relief from pain and ability to eat were experienced while the material was in place, and this, on an average, was about two days.
**Polynoxylin:**

This preparation is given in the form of Anaflex lozenges, the active ingredient of which is polymethylene-dihydroxymethylurea, a synthetic product with bacteriostatic and antifungal activity (Kay, 1969). Kay states that the lozenges are useful in a number of oral disorders, and it has been claimed that the symptoms of aphthous ulceration abate within a day and lesions disappear by the fourth day. A more extensive clinical trial seems necessary.

**Idoxuridine (IDU):**

An antimetabolite, this drug blocks the metabolic pathways of virus synthesis, successfully competing with the virus for thymidine and thereby interfering with its powers of reproduction. It has been successfully used in the treatment of herpetic conditions by Hall-Smith (1963), Jaffe and Lehner (1968), Kay (1969), Najjar et al. (1969) and others, and its use has been extended to aphthous lesions (Ryan, 1963).

The rationale would suggest that the treatment would be effective in cases of herpetiform ulceration, but Kramer (1965) states that whereas lesions respond to tetracycline, they do not respond to IDU.

**Smoking:**

As pointed out in the chapter on the effects of smoking on the oral tissues, there is an inverse relation between smoking and aphthous ulcers in many reported cases. Thus it seems reasonable that, while being conscious of its health hazards, a mild cigarette consumption may be effective supportive therapy in certain cases of chronic recurrent aphthae.
Other treatments:

Various other miscellaneous treatments have been briefly mentioned. These include bone phosphate therapy (Grace, 1936), a barbiturate-hyoscine-belladonna mixture (Queries and Minor Notes 426), atropine-like drugs "to interrupt the neurogenic influence" (Queries and Minor Notes 424), proteolytic enzymes (Brightman and Ship, 1966), and arsenic and sulphonamides (Sircus, 1959).

Conclusion:

The fact that the range of advocated remedies is so wide suggests the lack of a truly acceptable one. No cure has ever been obtained. The fact that symptomatic relief has been achieved in so many cases of diverse therapy, even where an acceptable rationale is lacking, suggests the influence of a placebo effect in some cases and/or the value of protecting a sensitive lesion from further noxious influences.
CHAPTER 37 - SUPPORTIVE THERAPY:

It is obvious that aphthous ulceration can be severe and prolonged, and cause considerable nutritional and emotional problems. Birt and Mather (1968) described a severely undernourished sufferer from the disease, and Schaffer (1960) and Kingsley (1964) mentioned cases in which the patient was contemplating suicide. Nevertheless, this aspect of the disease has been given little detailed consideration.

An extreme view was taken by Erich (1959) who stated: "There is no known cause for aphthous stomatitis and there is no treatment which is of any value." Commenting on this, Spouge and Diamond (1963) claim the statement would have been more accurate had it read: "There are many potential causes for aphthous stomatitis, and consequently no single line of treatment is consistently of more than symptomatic value." Whichever version is accepted, the need for supportive care is obvious.

Ryan (1963) says that treatment should be directed first to removing any obvious cause such as food irritation or allergy which might be suspected, and trying to convince the patient that co-operation with the treatment plan will speedily bring about relief. However, with no form of therapy being able to affect a definite cure, it would be easy for a patient to become disillusioned if too much emphasis were to be placed on the necessity for his co-operation. Ryan is right, though, to draw attention to the need for emotional support. He goes on to state that with the obviously neurasthenic type, medical advice and treatment might be necessary and that the dentist's role is in the application of topical medicaments. The dentist can do more than this, however: he can adopt a prophylactic role.
To this end Cooke (1961) advises attention to the occlusion so that mastication is carried out with maximum efficiency and least trauma to the soft tissues. Rough cusps should be removed, edge-to-edge bites corrected, hard toothbrushes discarded, and the patient should be instructed to take care whilst eating. Cooke also states that remissions from ulceration can be expected when the cause of mental stress is removed. In the case of recent onset of ulceration, anaemia and diabetes should be excluded. The correction of a lowered resistance may materially help the patient.

Sutherland (1959) emphasizes the need for a careful history taking to exclude a possible allergic cause and to plan the appropriate treatment. He advocates oestrogen therapy where the ulceration is related to the menstrual cycle, antihistamines in the prodromal period, and psychic treatment where necessary.

Brightman and Ship (1966) state that when a severe episode of ulceration has been brought under control and pain and discomfort alleviated, the patient is then amenable to an investigation into his anxieties and problems, which, when recognized and faced, will diminish, with a consequent amelioration in any associated oral lesions. The dentist should remove sources of mechanical irritation and food allergy. He should be alert to the possibility of sensitization arising from the use of topical agents such as analgesics and antihistamines, and to antibiotic complications such as a resistant flora, thrush, or hypersensitivity. A proper check should be kept on the patient's diet so that adequate fluids, vitamins and protein are obtained. On rare occasions, the authors state, intravenous fluids and dietary supplements may be necessary.
The rendering of emotional support is also mentioned by Lehner (1967c) who advises the reassurance of the patient by the emphasis of the lack of serious consequences as compared to ulcers elsewhere in the gastrointestinal tract. Dietary advice, as to the avoidance of irritating foods with the preservation of a balanced diet with adequate caloric intake, is necessary. Finally, oral hygiene must be preserved (a soft toothbrush should be used) and conservative and periodontal care should not be neglected.

McCarthy and Shklar (1964) state that aphthous-like lesions occur in various systemic disturbances such as the blood dyscrasias, and this must be considered in diagnosis. This statement, taken in conjunction with that of Cooke in relation to anaemia and diabetes, plus the incidence of aphthous lesions in cyclical neutropenia (q.v.) would suggest that a full blood count, a differential white cell count, and a urine analysis (or even a glucose tolerance test) might prove useful diagnostic and therefore therapeutic procedures. However, positive evidence of disease from the above tests would be the exception rather than the rule as most sufferers from aphthous ulcers are not systemically ill.

Specific diagnostic procedures have not yet been developed, although certain laboratory test results are suggestive:

(a) viral isolation studies will be negative
(b) *Str. sanguis* will usually be located in the deeper aspects of the lesions, as shown by Barile and his co-workers, although they are also present in other lesions and in healthy mouths.
(c) as demonstrated by Lehner (1969a and b), the patient will frequently have elevated levels of IgG and IgA, and fluctuating levels of humoral autologous antibodies.

(d) Francis (1970) states that the erythrocyte sedimentation rate and leukocyte count may be increased.

(e) Biopsy specimens show a non-specific ulcer; prior to ulceration the picture is one of a delayed hypersensitivity reaction.

These tests have little justification in clinical practice, however, the diagnosis being made on clinical findings.

As Francis (1970) remarks, the clinical management of a patient with aphthous ulceration is the most frustrating aspect of the disease. He presents an outline of the therapeutic regime followed in his clinic which is presented here as one method of approach and as a means of reiterating certain aspects of treatment:

1. Kenalog in Orabase - particularly useful topically on small infrequent lesions.

2. Ascorbic acid, 100 mg. twice daily, and ferrous gluconate, 300 mg. every day or twice daily - most useful in females and can be used in conjunction with other forms of therapy.

3. Achromycin for oral suspension (Lederle), 250 mg. suspension rinsed in mouth for one minute four times a day (following meals). Treatment is initiated when lesions first begin and continued 5 to 7 days.

4. Intermittent steroids, 20 mg. prednisone daily. Therapy is initiated when lesions first begin and continued 5 days. May be used in conjunction with No. 3. Most useful in mild and moderately severe forms of the disease.
5. Long-term steroid therapy - used to control the severe form of the disease. Appropriate dose must be established for each patient."

"In our study one patient with severe, destructive lesions was given long-term, low-dose immunosuppressive therapy (Cytoxan-cyclophosphamide - Mead Johnson & Company), 25 mg. per day for 9 months, which effected a long period of remission from the oral lesions and no observable side effects except a mild lymphopenia. Although this drug would be contraindicated in the mild form of the disease, it might prove to be the drug of choice in those severely involved patients whose disease is poorly controlled with steroids."

The main feature of this system of treatment is the inclusion of steroid and tetracycline therapy on the one hand (the acknowledged "big guns" of oral ulcer treatment) and preparations like vitamin C and iron tablets on the other, which bear a hint of placebo products. There is nothing in between, and nothing besides.

Steroid preparations are probably the clinician's best approach in cases of severe ulceration, administered topically, sub-lesionally or systemically depending on the severity and wide-spread involvement of the lesions. Tetracycline mouthwashes are the best palliative measures in lesions of viral cause.

Less severe ulceration is made more comfortable by the application of Bioral gel, which probably is most helpful as a physically protective agent.
This preparation is quite gelatinous and is well adapted to giving a thick adherent coating over an isolated lesion. Tannic acid and glycerin is advantageous where ulcers are mild and isolated. There is also a place for topical anaesthetic agents where painful lesions interfere with nutrition.

When lesions appear to be related to the menstrual cycle, oestrogen therapy may be appropriate. Keratinization may also be encouraged by a small daily cigarette quota where lesions are frequent.

Dietary investigations may reveal the presence of foods which seem to provoke lesions, or the absence of important nutritional constituents possibly because of lesional irritation. Blood and urine analyses may reveal signs of systemic disease predisposing to the development of oral ulcers.

A thorough review of the masticatory mechanism, natural and artificial, and chewing habits, may bring to light sources of trauma tending to initiate new lesions.

Emotional support and sympathetic reassurance are often required. The therapist must get to know his patient and the patient must get to know his total problem. Stressful situations at work or at home may be associated with new lesions and may require to be relieved. Sedation may be necessary during stormy periods.
In the absence of ascorbic acid and iron deficiencies, the prescription of vitamin C and ferrous gluconate tablets, as advised by Francis (1970), may appear to have no scientific basis in treatment, but that is not to say that they have no place. Vitamin C in particular has been advocated by clinicians for a variety of conditions despite the lack of an acceptable rationale. It is quite possible that the full extent of vitamin function has not been realised and one should not disregard entirely the value of placebo preparations.

The recurrent nature of aphthous disease, its apparent provocation by a number of different stimuli and the lack of a specific cure make it necessary for the clinician to involve himself as fully as possible in the therapeutic situation. Except in advanced cases of Behcet's syndrome the condition is benign, but can still present emotional and nutritional complications. There could hardly be a better illustration in dentistry of the need to treat the patient rather than the disease.
GENERAL SUMMARY
Possibly so named by Hippocrates, the term aphthous ulcer has been applied to a variety of oral lesions including thrush, herpetic conditions, and, most probably, diphtheria.

The term now signifies a mucosal ulcer which macroscopically resembles a minute infarct and which histologically shows the characteristics of a delayed hypersensitivity reaction. After frank ulceration has occurred, the microscopical picture is dominated by polymorphonuclear neutrophils when the lesion resembles a non-specific ulcer.

Clinically the ulcer is usually rounded with a yellowish or greyish-white necrotic centre surrounded by a narrow erythematous zone. Pain may be severe, but other signs and symptoms are normally absent. The lesion is usually less than 1 cm in diameter, although multiple ulcers may occur and there is a pronounced tendency to recurrence. Healing takes place within 10-14 days without scarring.

A major form of the condition is described in which the severity, size and duration of the lesions exceed the criteria mentioned above, and in which scarring is usually seen.

The disease may last for many years, appearing initially at any age, but most commonly affecting young adults. Women may be slightly more prone than men and show a somewhat more regular periodicity of attacks. The population incidence probably does not exceed the figure of 20% given by Sircus and his colleagues.
Aphthous ulcers may clinically resemble viral and traumatic lesions. The virus of herpes simplex is responsible for acute herpetic gingivostomatitis and for recurrent intra-oral ulcers which can be positively identified by fluorescent antibody techniques. Cooke described another type of oral lesion which he called herpetiform ulcers and which appear to be caused by another virus. Traumatic ulcers may show a clinical resemblance to aphthae, and aphthae may be provoked by trauma.

Oral aphthae may be the first sign of Behcet's syndrome which, in its extreme forms, may lead to blindness and death. A patient with a history of aphthous ulceration should be questioned and even examined for the presence of genital, eye and neurological involvement. Chronic involvement of the posterior part of the mouth may be an ominous sign of a forthcoming Behcet's syndrome.

Aphthous lesions appear most frequently on the non-keratinized mucosa and there is evidence that the degree of keratinization can be increased by agents such as oestrogen and tobacco smoke and the mucosa rendered more resistant.

Many aetiologies have been proposed and most are no doubt valid as contributory factors in selected cases, operating, perhaps, by a lowering of patient resistance. There is no worthwhile evidence, however, to support a theory of a frank invasion by microorganisms, although L form bacteria may be involved in a delayed hypersensitivity reaction.
Constitutional factors may very well be relevant and oral ulcers may appear in blood disorders and diabetes. Subjects prone to aphthous lesions should avoid emotional stress, undue fatigue, dietary inadequacies and oral irritation.

The basic pathological process, which works against the general and local resistance of the patient, appears to be either an autoimmune phenomenon or an antigenic cross-reactivity between a microorganism and some component of the oral mucosa, probably a cytoplasmic constituent of the prickle cell layer.

The mouth affords copious opportunities for immunological interactions because of the presence of a bacterial population and repeated inflammatory reactions. The specific situation pertaining in the mouth is expressed by Lehner 318 thus:

"The mouth is probably a unique site because bacterial stimulation of the local immune response is extremely frequent. Infection and tissue breakdown are associated with the eruption of deciduous teeth during the first three years of life and by dental caries and abscesses among children up to about 12 years old. Inflammatory and degenerative changes occur that are associated with shedding of the deciduous teeth and eruption of the permanent teeth. Recurrent tonsillitis is also common. Later, chronic dental granulomas and abscesses may occur. Gingivitis with subsequent periodontal disease exposes a large surface of tissue to bacterial attack, and bacteraemia occurs during chewing."
It is possible that recurrent tissue damage and bacterial assaults may heighten the local immunological response to a stage when an 'adjuvant' type of action may result. This may facilitate autoantibody formation against oral mucosa as a direct effect, or via some antigenically cross-reactive organism."

Agents employed in treatment have comprised topical applications designed either to cauterize or protect, palliative preparations, systemically administered agents often employed empirically and hydrocortisone derivatives. The last deserve special mention because of their sound rationale and clinical usefulness especially in severe cases.

Local palliation may be necessary in addition to more specific therapy, and may, on occasions, be all that is required. There is a marked placebo effect which should be recognized and even sometimes utilized by the clinician. The total patient situation should be explored by the clinician and emotional support, sedation and counselling made available as required.
BIBLIOGRAPHY
1. Adamantiades (1931) cited in Fraser-Moodie (1953), Theron (1959) and Nally (1968).


32. Basch (1928) cited in Theron (1959)

33. Bechgaard, P. (1940) cited in Sircus et al. (1957)


35. Bednar (1850) cited in Theron (1959)


46. Billard (1828) cited in Theron (1959)


56. Blanke (1934) cited in Theron (1959)


58. Bluthe (1908) cited in Nally (1968)

60. Bohn (1866, 1880) cited in Theron (1959)


63. Bottyan (1937) cited in Theron (1959)


71. Bruusgaard (1930) cited in Theron (1959)


73. Buddingh and Ruchman cited in Dodd and Ruchman (1950)


76. Bumiller (1952) cited in Theron (1959)


99. Case reports - Aphthous stomatitis

100. Cath (1955) cited in Theron (1959)


103. Cheney, G. Diagnosis and treatment of common forms of stomatitis.


106. Christensen, G. Oral ulcers.


123. Court (1899) cited in Sutton (1941)


129. Daniel (1951) cited in Theron (1959)

130. Danziger (1934) cited in Theron (1959)

131. Dascalopoulos (1932) cited in Theron (1959)


150. Dudgeon, J.A. in discussion with E.D. Farmer (1956)


178. Flusser (1930) cited in Theron (1959)


180. Fordyce (1920) cited in Ship et al. (1960b) and Sircus et al. (1957)


183. France et al. (1951) cited in Hills (1967) and Francis (1970)


Bristol: John Wright & Sons Ltd., 1970.


201. Goadby, (1925) cited in Strauss (1947) and Theron (1959)


207. Graham et al. cited in Riley (1953)


213. Griebel (1939) cited in Theron (1959)


217. Gruter (1920) cited in Theron (1959)


231. Hartmann, P., Schmitt, J., and Tridon, P. The 
significance of aspects of recurring and 
granulomatous phlebitis in the cerebral 
manifestations of Behcet's syndrome. 

232. Hashem, N., Hirschorn, K., Sedlis, E., and Holt, 
E.E. Jr. Infantile eczema. Evidence of 
autoimmunity to human skin. Lancet ii:269, 
1963.

Fatal herpes virus hominis (herpes simplex 
virus) infections in children. Clinical, 
pathologic, and virologic characteristics, 

234. Heinemann, M., and Anderson, B.G. Oral manifestations 
of certain systemic disorders. 
Yearbook of Dentistry, 1945.

235. Herbert, V., and Zalusky, R. (1961) cited in 
Mowat and Hothersall (1969)


240. Holzel, A., Feldman, G.V., Tobin, J.O'H., 
   and Harper, J. Herpes simplex: a study 
   of complement-fixing antibodies at different 
   ages. Acta Paediat. Stockh. 42:206, 
   1953.


243. Hunt, E. Recurrent ulceration of the mouth and 
   vulva associated with necrotic nodular lesions of the skin. 

244. Hurt, W.C. Periadenitis mucosa necrotica recurrens. 

245. Ingersoll, W.B., and Morgan, C.F. The values 
   and limitations of drugs in periodontal infections and inflammation. 
246. Jacobi (1894) cited in Sibley (1899) and Theron (1959)


248. Jadassohn, J. in discussion with Epstein (1930)


255. Jensen, J.S. (1944) cited in Ship et al. (1960b) and Sircus et al. (1957).
256. Jones, H.S. Local vs. systemic causes of aphthous stomatitis. 

257. Jordan (1933) cited in Theron (1959)


259. Jourdain-Berchillet (1778) cited in Sircus et al. (1957)


Bristol: John Wright & Sons, Ltd., 1969.

266. Keining (1933) cited in Theron (1959)

A.M.A. Arch. Otolaryngol. 54:505, 1951.


269. Kerlinger, F.N. Foundations of Behavioral Research,  

270. Kerr, D.A. Stomatitis and gingivitis - the adolescent and preadolescent.  

J.A.D.A. 44:674, 1952b


273: Kingsley, H.J. Rapid response of aphthous ulceration to steroid tablets.  


276. Kiryati, A.A. The present status of the adrenal
cortical hormones as therapeutic agents in
oral conditions.


278. Kleger, B., Prier, J.E., Rosato, D.J. et al. Herpes
    simplex infection of the female genital tract.
    I. Incidence of infection.

279. Klein (1934) cited in Theron (1959)

280. Knoedler, D., and Stanmeyer, W. Dental observations
    made while wintering in Antarctica.

    on the mucous membrane of the oral cavity.
    cited by Banoczy and Sallay (1969)


283. Kochs (1940) cited in Theron (1959)
Histologic and immunohistochemical features of the "Auercolitis" in rabbits.  


290. Kreibach cited in Theron (1959)


294. Kumer (1930) cited in Theron (1959), Sircus et al. (1957) and Ship et al. (1962).


296. Kutscher, A.H., Budowsky, J., and Chilton, N.W.

297. Kutscher, A.H., Lane, S.L. and Zegarelli, E.V.
Failure of smallpox vaccine in treatment of recurrent aphthous stomatitis.
A.M.A. Arch. Derm. 68:212, 1953c.

298. Kutscher, A.H., Silvers, H., and Zegarelli, E.V.
Chloramphenicol and terramycin in the treatment of recurrent aphthous stomatitis.
J.A.D.A. 46:144, 1953b

299. Kutscher, A.H., Zegarelli, E.V., and Amphlett, J.


301. Kutscher, A.H., Zegarelli, E.V., and Hyman, G.A.


304. Lazar (1956) cited by Hall-Smith et al. (1962)


323. Lempke (1941) cited in Theron (1959)


325. Leslie (1945) cited in Marcus (1964)


330. Letter to the editor — Canker sores

331. Letter to the editor — recurrent aphthous ulcers

332. Levin, H.L. Bacteriostasis and virology of herpetic
    lesions of the face and oral mucous membranes.

333. Lewis, A.G. Effects of smoking on the oral mucosa.


335. Linenberg, W.B. Behcet’s syndrome: a new method
    of treatment.

336. Lipschutz (1912) cited in Theron (1959), Sircus
    et al. (1957) and Ship et al. (1962).

337. Lipschutz (1921) cited in Theron (1959)

338. Loblowitz (1910) cited in Sutton (1941), Sircus et
    al. (1957), Weichselbaum and Derbes (1957)
    Theron (1959), Francis (1970)


348. Marti (1940, 1941) cited in Theron (1959)

349. Matras, A. (1932) cited in Sircus et al. (1957); Theron (1959); Ship et al. (1962).

351. McCoy, C.T. Behcet's syndrome

352. McDermott, W. Microbial persistence

353. McDonagh, J.E.R. Acute ulceration of vulva.

354. McFall, W.T. Effect of fluandrenolone on oral

      changes in disease: quantitation on the
      basis of heavy polypeptide chains IgG, IgA
      and IgM, and of light polypeptide chains,
      type K(1) and type L (11).

      in Behcet's disease; report of necropsy findings

357. Mellers, N.W., and Herms, F.W. Investigation of
      neuropathological manifestations of oral tissues.
      l. Amer. J. Orthodont. 32:30, 1946.

358. Mellers, N.W. and Herms, F.W. Investigations of
      neuropathological manifestations of oral tissues.


363. Mikulicz and Michelson (1882) cited in Theron (1959)

364. Misch (1914) cited in Theron (1959)

365. Mishima et al. cited in Hills (1967)


371. Mortada & Imam (1964) cited in Lehner (1967a)


376. Moutier and Cornet (1951) cited in Theron (1959)


378. Muhlemann (1952) cited in Theron (1959)

379. Muller (1938) cited in Theron (1959)


409. Pike, R.M. Antibody heterogeneity and serological reactions.

    Copenhagen: Munksgaard, 1968.

    The effect of snuff in the oral epithelium.

412. Pindborg, J.J., Shrivastava, A.N., and Gupta, D.
    Studies in oral leukoplakias. Vlll. Epithelial changes in tobacco-induced leukoplakias in India.

413. Planner and Remenovsky (1922) cited in Phillips and Scott (1955)


415. Port (1932, 1933, 1934) cited in Theron (1959)

416. Port and Euler (1920) cited in Theron (1959)


418. Pospischill (1921) cited in Theron (1959) and Davies and Longson (1970)


422. Thomas, E.W. Prosser, So-called triple-symptom complex of Behcet.

423. Pusey (1930) cited in Theron (1959)

424. Queries and minor notes - Recurrent ulcers of the mouth.

425. Queries and minor notes - Ulceration of mouth

426. Queries and minor notes - Recurrent herpetiform lesions.
J.A.M.A. 141:299, 1949

427. Queries and minor notes - Aphthous stomatitis.
Canker sores and smallpox vaccinations.

428. Queries and minor notes - Canker sores.
429. Queries and minor notes - Oral aphthae.

430. Queries and minor notes - Recurrent ulcers of labia.

431. Queries and minor notes - Ulcers in mouth and throat.

432. Queries and minor notes - Behcet's syndrome

433. Queries and minor notes - Canker sores

434. Queries and minor notes - Aphthous stomatitis.

435. Queries and minor notes - Recurrent oral ulcers.

436. Questions and answers - Aphthous stomatitis.


449. Regan, F. cited in Rosenbaum (1960)


463. Roller (1939) cited in Theron (1959)


479. Samek, J., and Fischer, E. (1929) cited by Sircus et al. (1957) and Ship et al. (1962).


483. Savitt, L.E. Canker sores

484. Savitt, L.E., and Ayres, S. Jr. Persistent
       multiple herpes-like eruption.
       Response to repeated intradermal injections
       of smallpox vaccine.

485. Scales, J.L. Oral manifestations of infection
       with the virus of herpes simplex.

486. Schachter, M. and Schachter, R. The production of
       visceral lesions following attempted chronic
       irritation of the central nervous system.

487. Schaffer, J. Clinical pathology of the tongue (1)


489. Schlemmer, A. Aphthous ulcers

490. Schmidt (1940;1958) cited in Theron (1959)

491. Schmidt, J.H. Electrocautery for ulcers of aphthous
       stomatitis.
       D. Abs. 7:537, 1962.


   Acute infectious gingivostomatitis. 
   J.A.M.A. 117:999, 1941.

504. Selling, B., and Kibrick, S. An outbreak of herpes 
   simplex among wrestlers (herpes gladiatorum) 

505. Sezer (1956) cited in Lehner (1967a)

506. Sezer, F.N. The isolation of a virus as the cause of 
   Behcet's disease. 

   of Oral Pathology, (Second edition), 

508. Shearer, M.L., and Finch, S.M. Periodic organic 
   psychosis associated with recurrent herpes 
   simplex. 


510. Shimizu, T., Kagami, T. Matsumoto, T., and Matsumura, 
   N. (1963) cited in Lehner (1967a)


Recurrent "fever blister" and "canker sore".
Arch. Oral Biol. 3:117, 1961c

521. Ship, I.I., Brightman, V.J. and Laster, L.L.
The patient with recurrent aphthous ulcers
and the patient with recurrent herpes
labialis: a study of two populations samples.

Recurrent aphthous ulcers.

530. Ship, I.I., Morris, A.L., Durocher, R.T., and Burket,
L.W.
Recurrent aphthous ulcerations and recurrent
herpes labialis in a professional school
student population. I. Experience.

531. Ship, I.I., Morris, A.L., Durocher, R.T. and Burket,
L.W. Recurrent aphthous ulcerations
and recurrent herpes labialis in a
professional school student population. II.
Medical history.

532. Ship, I.I., Morris, A.L., Durocher, R.T. and Burket,
L.W.
Recurrent aphthous ulcerations and recurrent
herpes labialis in a professional school
student population. III. Oral examinations.


537. Siegmund and Weber (1926) cited in Theron (1959)


543. Sizel (1965) cited in Nally (1968)


565. Stevens and Johnson (1922) cited in Theron (1959)


570. Strauss, K. Vitamin B₁ therapy in cyclic habitual aphthous stomatitis in women.

571. Strean, L.P. Possible role of cortisone in dental practice.


Dent. dig. 59:8, 1953.

574. Strean, L.P., Williams, B.H., and Pritchard, J.
Oral herpetiform lesions treated with gamma-globulin.


576. Sugarman, M.M. Contact allergy due to mint chewing gum.

577. Sulheim, O. Behcet's syndrome: report of a case with complete autopsy performed.


606. Tiscornia (1927) cited in Theron (1959)

607. Todd, I.P. An unusual case of ulcerative colitis. 

608. Tokumaru, T. A possible role of gamma A-immunoglobulin in herpes simplex virus infection in man. 

609. Tomasi, T.B. Jr. Human gamma globulin. 

610. Tomasi, T.B. Jr. The gamma A globulins: first line of defence. 


613. Touraine (1955) cited in Lehner (1968)

614. Trayanova, T., Sura, V.V., and Svet-Moldavsky, G.J. Destruction of human cells in tissue culture by lymphocytes from patients with systemic lupus erythematosus. 
615. Trousseau (1861) cited in Davies and Longson (1970)

616. Truelove, S.C. Treatment of ulcerative colitis
    with local hydrocortisone hemisuccinate
    sodium.

617. Truelove, S.C. Treatment of ulcerative colitis
    with local hydrocortisone.

618. Truelove, S.C., and Morris-Owen, R.M.
    Treatment of aphthous ulcerations of the
    mouth.

619. Truelove, S.C., and Morris-Owen, R.M.
    Aphthous ulcers.
    1960.

620. Truelove, S.C., and Morris-Owen, R.M.
    Aphthous ulcers.
    D. Abs. 5:662, 1960.

621. Tuft, L., and Ettleson, L.N. Canker sores from
    allergy to weak organic acis (citric and
    acetic).

622. Tuft, L., and Girsh, L. Buccal mucosal tests
    in patients with canker sores (aphthous


625. Tzank and Brunetiere (1949) cited in Cooke (1960)

626. Ullman (1927) cited in Theron (1959)


629. Vest (1957) cited in Theron (1959)


633. Weekers and Reginster (1939) cited in Fraser-Moodie (1953).


636. Weichselbaum, P.K., and Derbes, V.J.
   Chronic scarring aphthous ulcers of the mouth.


   Epidemic cutaneous herpes simplex in wrestlers (herpes gladiatorum)

642. White, S.J.
   in reply to Rosenbaum (1960)
   J.A.M.A.

643. Whitwell, G.P.B.
   Recurrent mouth ulcers.
644. Wien, M.S., and Perlstein, M.O.
        Ulcus vulvae acutum associated with lesions of the mouth.


646. Wise and Sulzberger (1939) cited in Zegarelli et al. (1953)

647. Wolff (1952) cited in Theron (1959)

        Arch. Dermat. & Syph. 43:543, 1941.

649. Worms (1864) cited in Theron (1959)

650. Yoshino, K., et al. (1962)
        cited in Smith et al. (1967) and Davies and Longson (1970).

651. Youmans (1932) cited in Theron (1959)


653. Zeavin, B.H.; King, M.J.; and Gohd, R.S.
        A case of Behcet's disease.


655. Zelman, S., and O'Neil, R.H.


661. Ziegler (1898) cited in Theron (1959)

Ziserman (1934) cited in Bishop et al. (1967)


