

The problem of oral ulcerations in general practice with special reference to herpetic herpetiform lesions

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THE prevalence of oral ulcerations in the population is fairly high, and it is probably even higher than is generally realized as many of the more minor occurrences will not be reported by patients. There is no doubt, too, that a proportion of the less obvious lesions is missed in clinical or epidemiological examinations, as the diagnostician does not always have the necessary training and experience in oral pathology. Ship *et al*, (1961) dealing with only one facet of the problem, stated that recurrent herpes labialis, commonly referred to as 'fever blister' or 'cold sore', has been reported to occur in 38 per cent of the population.

No attempt is made in this paper to cover in detail the whole range of oral ulcerations either idiopathic or occurring as a manifestation of systemic disease. They are grouped and classified in the form of a table so that it can be used as an aid for reference and diagnosis. The four most common forms of oral ulcerations, and in particular herpetic and herpetiform lesions will be described in detail, whereas the other lesions will be dealt with briefly.

The four most common types of ulcerations found in the oral cavity.

- (a) Traumatic ulcers (denture sore—injury secondarily infected)
- (b) Aphthae (aphthous ulcers)—aphthous stomatitis
- (c) Acute ulcerative gingivitis (Vincent's infection—Fusospirochaetal gingivitis)
- (d) Herpetic—herpetiform gingivostomatitis

Ulcerations which can be found in the following groups of diseases

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|---|----------------------|
| VITAMIN DEFICIENCIES | Scurvy |
| BLOOD DYSCRASIAS | |
| Iron deficiency anaemia | Agranulocytosis |
| Pernicious anaemia | Leukaemias |
| Purpuras (Henoch-Schönlein and thrombocytopenic) | |
| INTOXICATION BY HEAVY METALS | |
| Bismuth stomatitis | Mercurial stomatitis |
| Lead stomatitis | Gold stomatitis |
| ALLERGIC MANIFESTATIONS | |
| Stomatitis venenata | |
| Stomatitis medicamentosa (due to certain drugs, for example thiouracil, barbiturates and many others) | |
| VIRAL DISEASES | |
| Herpetic—herpetiform gingivostomatitis | |
| Herpes zoster | Herpangina |
| Foot and mouth disease (stomatitis epizootica) | Glandular fever |
| EXANTHEMATOUS FEVERS | |
| Measles | |
| SPECIFIC INFECTIONS | |
| Tuberculosis | Syphilis |
| | Gonorrhoea |

FUNGAL DISEASES

Candidosis

SKIN DISEASES

Lichen planus erosivus

Behçet's triple syndrome

Benign mucous membrane pemphigus

Lupus erythematosus disseminatus

Erythema exudativum multiforme

Epidermolysis bullosa

Pemphigus vulgaris

ORAL MALIGNANCY

Squamous cell carcinoma

This list is by no means complete and has been compiled to stimulate interest and further reading. It gives an idea of the wealth of material and the scope of the subject. It shows that the mouth contains much more than people think. It gives evidence of the interrelationship of oral and systemic disease. It is a field where the physician, dermatologist, ENT surgeon and the dental surgeon find common ground and their close co-operation will be to their and the patient's benefit. Certain controversial views are expressed which in the author's opinion have proved helpful in the diagnosis and treatment of these complaints.

Next, short notes on the various headings other than the four most common types of oral ulcerations are provided.

Scurvy. Scurvy is not as rare as people would believe. A fair number of cases of C-vitamin subdeficiency is seen in children from poor homes with inadequate diet and even more so in elderly people living by themselves whose diet is lacking the essential nutrients. Some authors have described the condition in elderly men as 'bachelor's gingivitis'. Response to proper diet and C-vitamin therapy is good.

Blood dyscrasias. People suffering from iron deficiency and pernicious anaemia often have recurrent oral ulcers which in the first instant appear to be aphthous in nature but disappear for good as soon as the anaemias are successfully treated. The ulcerations in agranulocytosis, leukaemias and purpuras affect chiefly the gingivae and often have the appearance of a Vincent's infection. It is nearly always possible to isolate fusospirochaetal organisms from these lesions. These ulcerations appear almost invariably when the periodontal tissues have been affected prior to the onset of these diseases.

Intoxication by heavy metals. Bismuth and mercurial compounds are not used as frequently these days as in the past and damage due to these drugs is not often seen nowadays. Bismuth not only can produce the well known bismuth line but also a severe ulcerative stomatitis which will heal only slowly due to the fact that some H₂S producing bacteria bring about a precipitation of insoluble bismuth sulphides and thrombosis of some of the terminal capillaries in the affected tissues. The tissues are much more prone to be affected when periodontal disease is present. It is advisable that the periodontal condition is treated prior to starting therapy with any of these compounds especially prior to gold injections.

Allergic manifestations. Certain drugs like thiouracil, barbiturates and many others can, when resorbed, produce allergic reactions. A stomatitis produced this way is called stomatitis medicamentosa. The mere contact of a drug with the soft oral tissues can bring about an allergic reaction; this is called stomatitis venenata.

Viral diseases. Herpetic-herpetiform gingivostomatitis will be discussed later on. In herpes zoster with oral lesions the fifth cranial nerve is involved. Clinically, the appearance is almost indistinguishable from herpes simplex but the important feature is the characteristically unilateral involvement. Herpangina is rare in this country. It affects chiefly the faucial areas and the group A type 2 Coxsackie virus is the causative agent. Foot and mouth disease in human beings is very rare and even more so oral involvement. The occupation (farmers, dairymen) and the combination of oral symp-

toms with lesions on the hands will help in the diagnosis. Glandular fever or infectious mononucleosis is of unknown aetiology but may be of viral origin. About half of the patients have oral symptoms which can simulate Vincent's gingivitis. In fact it is a Vincent's infection which has developed as a result of the lessened tissue resistance.

Exanthematous fevers. They are often associated with oral ulcerations of varying degree and Koplik's spots in measles are one of the most well known diagnostic features.

Fungal diseases. Only candidosis is listed, as the other mycotic diseases affecting the oral cavity are extremely rare in Europe. Lehner's work (1964a) and classification of acute and chronic candidosis and his review (1964b) of recent reports on fatal cases of candidal fungaemia following tooth extractions have focused much more attention on this well-known subject.

Skin diseases. As skin and oral mucosa have a common embryological origin lesions on both often occur in dermatoses. But occasionally when the oral lesion is the only and first manifestation of the disease the diagnosis can become difficult indeed. The clinical appearance of the oral lesion usually varies from that on the skin. The influence of the oral environment alters the appearance of the lesions. The greater vascularity of the tissues, the constant moisture and warmth of the oral cavity, trauma, secondary infection and lack of the keratin layer modifies the character of these lesions.

Lichen planus. The non-erosive, the atrophic and the bullous form are not considered here in detail. In the author's experience lichen planus seems to have the highest incidence of all skin diseases in producing oral lesions. The view, held until fairly recently, that lichen affects only certain strata of society is not borne out by the patients seen over the last 20 years. The aetiology of this complaint is still unknown and psychosomatic factors appear to play a great part in its causation. Often desquamative gingivitis is present at the same time and complicates assessment and treatment. The non-erosive lichen planus needs the most careful attention being potentially premalignant. In particular there is a form of it chiefly found in young women between 20 and 35 years of age with lesions usually situated on the side of the tongue and the floor of the mouth. It hardly responds to treatment, is very painful and several cases have been under observation where initial biopsies were negative and suddenly a squamous-cell carcinoma started in the lesion. These patients should be kept under closest observation and repeated biopsies should be performed. A treatment line which has shown some promise—if there is no response to medicaments—is early excision of the lesion and replacing it by a skin graft.

Erythema exudativum multiforme. This has proved to be second to lichen in the incidence of frequency. It is an acute inflammatory disease of unknown aetiology and

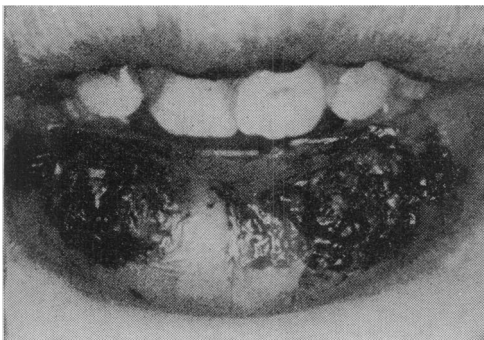


Figure 1
Bloodcrusts on the lower lip in erythema exudativum multiforme

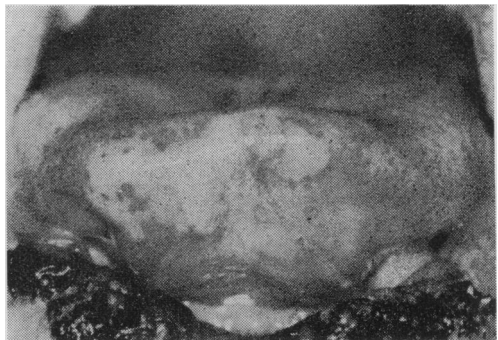


Figure 2
Shallow, irregular ulcers on the tongue in erythema exudativum multiforme

as the name indicates of tremendously varying appearance. It is usually recurrent and may affect the oral mucosa only or also involve the skin, particularly the extremities, genitalia, arms and the conjunctiva. The severe form with high fever, eye involvement is known by the name of Steven-Johnson's syndrome and in the pre-steroid days sometimes ended in blindness or even had a fatal outcome. The diagnosis becomes especially difficult when the erythema multiforme is associated with a herpetic infection. Forman and Whitwell (1934) were the first to notice this association and this has also been confirmed in the author's experience. When skin lesions are present diagnosis is not so difficult, but without skin lesions the ever present extensive bloodcrusts on the lips are a great help in the diagnosis. (Figures 1 and 2).

Epidermolysis bullosa can appear in three forms:

1. Epidermolysis bullosa hereditaria simplex.
2. Epidermolysis bullosa dystrophica or letalis.
3. The acquired form starting in adult life.

The slightest trauma produces vesicles and bullae which generally undergo exfoliative and ulcerative changes which usually heal with formation of scar tissue. Bone atrophy of finger and toe phalanges sometimes occurs as a result of severe ulceration. The accompanying illustrations show the lesions in a brother and sister which the author (Fox 1955) has followed up for the last 12 years. (Figures 3 and 4).

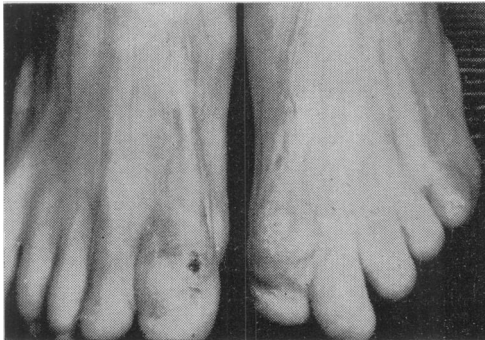


Figure 3
Scars and atrophy of toes in a boy suffering from epidermolysis bullosa



Figure 4
Tongue scars in his sister also suffering from epidermolysis bullosa

Behçet's triple syndrome, benign mucous membrane pemphigus, pemphigus vulgaris, lupus erythematosus are rarely seen by general practitioners and are therefore not discussed here.

Oral malignancy

It was not intended to deal with manifestations of oral malignancy as it is not within the scope of this report. But already in the discussion on erosive lichen planus attention was drawn to the potential premalignancy of this condition. Likewise the utmost care has to be taken in the assessment of any small ulceration on the gingiva or oral mucosa which does not yield to treatment quickly. Early biopsy or biopsy excision is definitely indicated. And that leads me conveniently to number one of the four most commonly seen ulcerations in the mouth. The denture sore normally responds to treatment quickly but, if there is anything suspicious in the appearance, biopsy should be carried out immediately. The accompanying illustration shows a squamous-cell carcinoma in a

man 58 years of age who had been a denture wearer for many years without any discomfort. Suddenly, without any apparent cause, he developed an ulcer on the labial aspect in the midline of his upper jaw. For a few weeks he tried to treat himself by hot mouthwashes and by leaving the denture out. As it did not improve he finally attended the hospital. The margins of this ulcer were slightly indurated but no glands could be palpated. Without delay a biopsy was carried out which proved to be positive. (Figure 5).

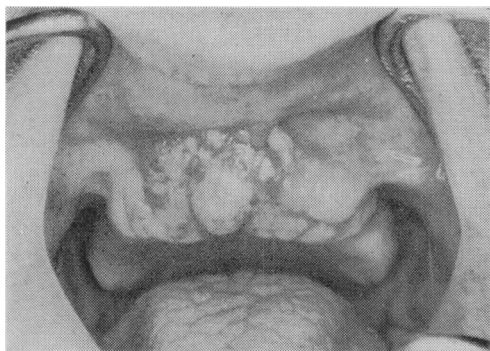


Figure 5
Squamous cell carcinoma in a man 58 years old,
midline upper jaw

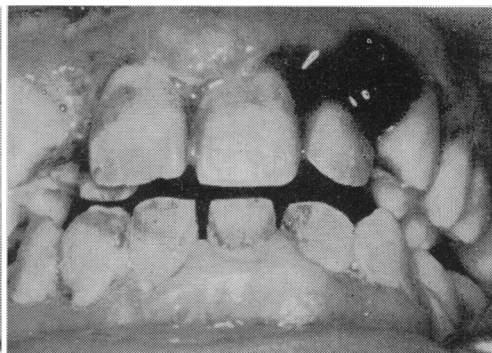


Figure 6
Acute ulcerative gingivitis, haemorrhagic type

Treatment

Simple traumatic lesions usually heal quickly unless they get secondarily infected. But even then they respond readily to treatment.

Apthous stomatitis, aphthae, apthous ulcers, canker sores, to use some of the most common synonyms, have puzzled the healing profession for ages. The most recent papers on the subject Lehner (1967), Browne, Fox and Anderson (1968), Macphee, Sircus, Farmer, Harkness and Cowley (1968) and a leading article 'Riddle of apthous ulceration' in the *British Medical Journal* (1968) establish the fact that the aetiology of apthous ulceration is still unknown although it is now certain that herpes simplex virus does not play any part in this complaint. And to quote from the *British Medical Journal* (1968): "Thus we still seem to be without an effective and harmless short-term treatment of this troublesome complaint".

The views on 'Acute ulcerative gingivitis' as we prefer to call it in this country have also undergone considerable changes during the last few years. The aetiology is still unknown but there has been some breakthrough in the approach to treatment. The use of antibiotics and of improved surgical procedures has brought this once dreaded condition under reasonable control. The drug of choice is no longer an antibiotic but metronidazole (Flagyl). This approach is supported by several recent publications, Duckworth *et al* (1966), Glenwright and Sidaway (1966), Stephen *et al* (1966), Emslie (1967). It is generally recognized that antibiotics should only be used if there is no other and better alternative. Metronidazole fulfils these requirements by controlling the pain within a few hours, by causing no tissue damage or allergic response and by accelerating healing. So far there have been practically no side effects. One variation of Vincent's infection which is not so well known is the so called haemorrhagic acute ulcerative gingivitis of which a typical picture is shown. (Figure 6).

Some of the features of this condition are produced by rapid sloughing deep down into the capillaries and by the effects of the toxins on vaso-constriction. Within a few hours patients can lose considerable amounts of blood. In these cases it is important to carry out immediate emergency treatment and then refer the patient without further delay for specialist attention. Emergency measures recommended are syringing and

swabbing the mouth to remove the blood and then let the patient bite on either a throat-pack or a lump of cottonwool to achieve some form of haemostasis before passing him or her on for the special treatment.

Herpetic and herpetiform gingivostomatitis.

Whilst herpetic lesions have been fully described in numerous publications the term herpetiform has only been mentioned fairly recently. Recurrent herpetiform eruption was first described by Cooke (1960). Recurrent crops of 20 or more ulcers can appear on any part of the oral mucosa and clinically resemble herpetic lesions. They are usually associated with swelling of the affected tissues and enlargement of the cervical lymph nodes. They differ, however, from herpes simplex in that the vesicular stage is rarely seen and multinucleated giant cells, typical intranuclear inclusion bodies

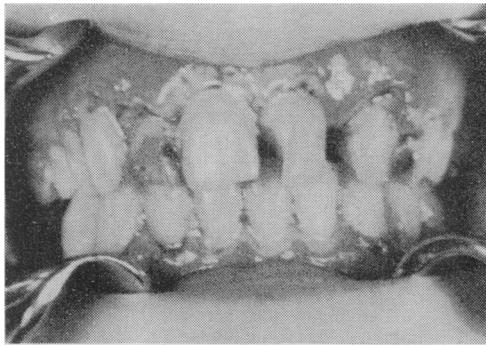


Figure 7
Acute ulcerative gingivitis in a very neglected mouth

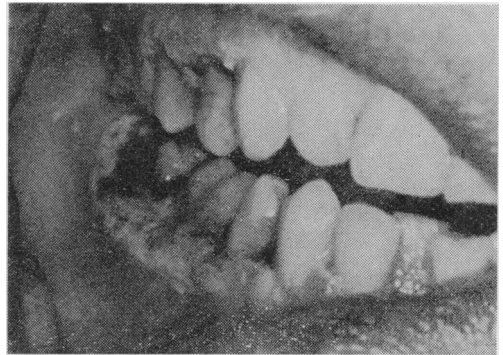


Figure 8
Acute ulcerative gingivitis affecting the premolar and molar region

and a rising antibody titre against herpes simplex virus have not been found. Lehner and Sagebiel (1966) in an investigation into the fine structural findings in recurrent oral ulcerations have by using the electron microscope failed to show recognizable mycoplasma or L-form organisms. But they have found intranuclear bodies in the epithelial cells of the herpetiform lesions consistently present. These intranuclear bodies in the herpetiform ulcers appear to have a virus like structure but do not resemble the herpes group of viruses.

Infection with the herpes simplex virus is extremely widespread and 75 to 80 per cent of the population have specific antibodies in their blood. Andrews and Carmichael (1930) and Hayward (1950) as quoted in Farmer (1956). The infection usually takes place at an early age before the children are six years old. Specific antibodies are developed in the patient's serum during the course of the first or primary infection, Burnet and Lush (1939). In spite of it the virus remains in the tissues probably for the rest of the patient's life as a latent source of infection which may be activated by a variety of stimuli, Burnet (1953). Oral herpetic lesions are common during the common cold, certain febrile diseases, during menstruation and may follow dental treatment. In most of the patients seen by the author the lesions originated in those areas of the mouth which Box (quoted in Coolidge and Hine 1951) called 'incubating zones', i.e. gumflaps over partly erupted, deeply carious, septic or malpositioned teeth. Poor oral hygiene was evident in most cases. It is most commonly seen in infants, adolescents and young adults. The incubating period is usually from 10 to 14 days. In the first instant the patients complain of soreness and pain in the mouth and throat, bleeding and swollen gums, enlarged and tender regional lymph glands and general malaise.

Temperature can go up to 103° to 104°F. Two to three days after the first symp-

toms small vesicles appear on the oral mucosa, lips, tongue but not so often on the gingiva proper. These vesicles break down and form shallow ulcers with an erythematous halo. Some coalesce and then form large irregular ulcers. (Figures 10 and 11). A diagnostic sign which has been found helpful is a milkish white film which covers the gingivae and can be wiped off. (Figure 9). It consists of food debris, desquamated epithelium and bacteria. The formation of this film is due to the fact that the gums are so painful that the patient is not able to clean the mouth properly and the tongue is not capable of its usual cleansing function. Occasionally facial lesions are also found. Without treatment healing usually starts on the sixth or eighth day and the diffuse

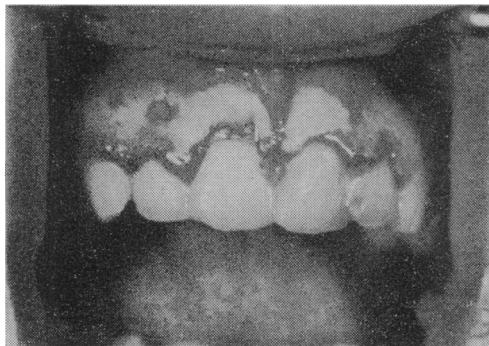


Figure 9
Film covering the gingiva in herpetic gingivostomatitis

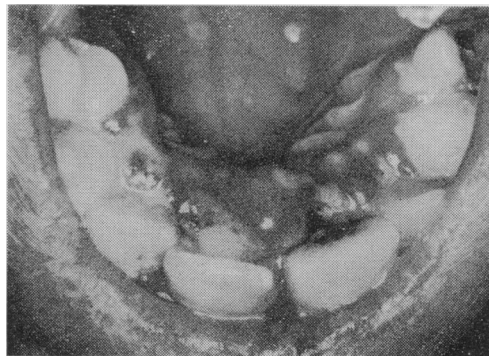


Figure 10
Herpetic ulcers chiefly affecting the palate

inflammation begins to subside. The condition is self-limiting and after a fortnight most of the lesions have healed. The above mentioned incubating zones, however, still remain and if not eliminated encourage recurrences. The presence of herpetic antibodies cannot prevent recurrences of the herpes simplex and so significant changes in the level of the neutralizing antibodies could be observed before, during and after attacks. As many as a third of patients with recurrent aphthous ulcerations lack herpes antibodies and although herpes simplex virus is readily isolated from herpetic lesions it has never been recovered from recurrent aphthae, Stark *et al* (1954). Antibodies from the mother are transferred during pregnancy and this passive immunity is maintained up to about six months. After that the antibody titre falls sharply and this is the reason that attacks of herpetic gingivostomatitis most frequently occur from the seventh month up to the sixth year. Brain (1956) in his Watson Smith lecture shows the tremendously wide range of herpetic infections which can affect the oesophagus, genitals, eye, skin and cases of trigeminal neuralgia which can be associated with herpes simplex. Of great practical importance are the contact lesions on the hands of nurses from patients with herpetic eczema or children with herpetic gingivostomatitis may suck their fingers and so produce a localized herpes as shown in figure 12. And even more so ocular herpes simplex. Herpetic infections of the outer eye can lead to serious and painful ocular disorders which can result in loss of sight. Herpes simplex virus is probably the chief cause of keratitis in this country. The majority of oral and other herpetic lesions are not of serious consequence. But they provide a reservoir of infection from which the virus can be constantly spread.

People with trivial cold sores or herpes carriers do not realize that kissing a baby might pass on herpetic infection and could cause blindness. It is therefore our duty to educate the public and so reduce these hazards to a minimum. All the more as our knowledge of the course and treatment of herpes simplex keratitis has not made great advances in recent years.

Treatment. Until fairly recently we have not had any specific and satisfactory treatment. There is no antibiotic which is effective against herpes simplex virus. Certain treatment methods which are still in vogue are, in the author's experience, undesirable and will now be discussed. There is no place for the time-honoured gentian violet which when painted on the painful and ulcerated oral mucosa acts as a caustic and often causes deterioration. Penicillin is badly tolerated in herpetic lesions. We do not know exactly why but it seems to upset the oral microbial balance in this condition. The antibiotic of choice to deal with the often present secondary infection is systemic tetracycline. The author always uses it in conjunction with Enpac, a lactobacillus preparation. More about it later. And another 'must not' are steroids. They mask the signs of inflammation and seem to favour spread of the virus. Another feature which is often over-looked

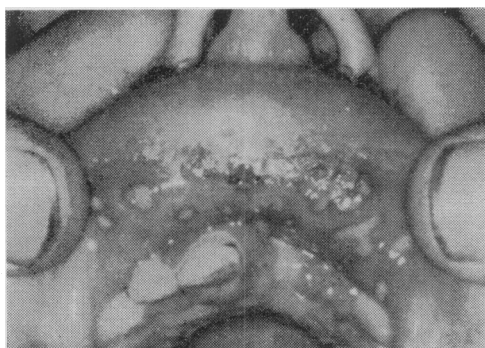


Figure 11
Herpetic ulcers chiefly affecting the upper lip



Figure 12
Herpetic lesion on the thumb of a child with herpetic gingivostomatitis, produced by sucking

is the possible danger of dehydration particularly in small children. A great effort has to be made to get as much liquid down as possible. Routinely tetracycline therapy in the author's hands is accompanied by the administration of a *Lactobacillus acidophilus* preparation to prevent the disturbance of the normal flora of the gut which otherwise happens so often. The *Lactobacillus acidophilus* in Enpac has been rendered resistant to most antibiotics. These lactobacilli replace the usual intestinal lactobacilli if damaged by tetracycline and so help to maintain the intestinal flora intact. As the response to this combined treatment seemed to be so much better than the previous one, the effects of this treatment were studied in more detail. This, as yet unpublished, work was done with G. H. G. Davis. After 75 patients with herpetic gingivostomatitis had been treated this way 35 others were used as controls. To these the base powder of Enpac containing no lactobacillus cells was administered and the healing of the ulcers and the response was markedly slower. To study the interaction of *Lactobacillus acidophilus* and herpes simplex virus *in vitro* suspensions of cells of the *Lactobacillus acidophilus* strain used in Enpac and a suspension of herpes simplex virus were prepared and tested in different concentrations. Some of the tests gave results indicating positive loss of virus viability. Weekes (1958 and 1963) and Abbott (1961) used a similar lactobacillus preparation in aphthous and herpetic gingivostomatitis and reported successful treatment without having been able to give a rational explanation of the mechanism of action. In our experience Enpac was found to have beneficial effect in herpetic gingivostomatitis, but not in aphthous stomatitis. So far we have not been able to explain the mode of action.

Doxuridine

During the last few years a new therapeutic approach has come to the fore—the chemotherapy of virus diseases. Various compounds have been developed which inhibit virus synthesis. One of these compounds Idoxuridine (5-iodo-2-deoxyuridine) has been shown to have antiviral activity against certain DNA viruses such as herpes simplex. When added to tissue cultures idoxuridine has been found to inhibit the replication of herpes simplex virus. Although it cured experimental herpetic keratitis in rabbits, Kaufman (1962 and 1965), in human beings its efficacy has not been established beyond doubt. In herpes labialis it has not been successful yet. Application of it in simple creams is ineffective. This is most likely due to the relative insolubility of the compound and the difficulty in getting the compound through the skin to the site of the virus. Juel-Jensen and MacCallum (1965) report on a double-blind controlled trial of intradermal jet injections of 0.1 per cent idoxuridine in aqueous solution using a modified airgun. The duration of the lesions (herpes of the face) was shortened by 37 per cent compared with the saline control. As idoxuridine is very insoluble in watery solution MacCallum and Juel-Jensen (1966) used dimethyl sulphoxide as a solvent and tested the effect of a 5 per cent idoxuridine solution in dimethyl sulphoxide in another double-blind controlled trial. They achieved an average shortening of the expected duration of the lesion of 63 per cent. Certain toxic effects, however, have been reported after larger amounts of this solvent were absorbed through the skin. Idoxuridine interferes with the formation of deoxyribonucleic acid in actively dividing cells and must therefore not be given to pregnant women. Various other combinations of solvents and idoxuridine have been tried, but so far no really successful one for application in the oral cavity has been found.

In conclusion a brief recapitulation of the routine treatment of herpetic lesions is given. Attention to oral hygiene is important. Frequent mouthwashes with a warm solution of sodium bicarbonate (one teaspoonful to a glass of water) and cleaning of the teeth and gingivae with cottonwool dipped in this solution. Sometimes tetracycline mouthwashes are employed using soluble tetracycline tablets to make them up. Enpac, one teaspoonful a day in milk is given four times a day and tetracycline 250 mg three times a day. This is usually administered in the form of tetracycline syrup which children find much easier to take. To alleviate the pain and to enable them to take food more easily the patients are given a small amount of 5 per cent lignocaine viscous which they are instructed to apply to the painful areas. Careful instructions about what food to take and about the importance of communicability are given. And as soon as the healing is sufficiently advanced incubating zones have to be eliminated. More or less the same line of treatment is followed in the management of herpetic gingivostomatitis.

The diagnoses and treatment of oral ulcerations may vary from easy to difficult and very difficult particularly when two or more conditions are combined which is not too rare. This presents a challenge and it is most satisfying when these problems can be solved successfully.

ADDENDUM

Since this article was written about ten months ago patients with herpetic and herpetic lesions received in addition to the aforementioned treatment topical applications of a 0.1 per cent aqueous solution of idoxuridine.

Jaffe and Lehner (1968) carried out a double-blind controlled trial to assess the efficacy of idoxuridine in primary herpetic stomatitis. They have also tried out the drug—made up as 0.5 mg tablets—in herpetic ulcerations where it failed to indicate any beneficial effect. In primary herpetic stomatitis, however, their trial showed that improvement was experienced in a significantly shorter time and the incidence of new

lesions and of residual marginal gingivitis was significantly lower in the patients receiving idoxuridine.

In recurrent herpes labialis they tried the idoxuridine solution in eight patients and the results suggest that the duration of symptoms and lesions were considerably decreased in six patients, and in two patients the vesicles were aborted by timely application of idoxuridine.

The author has not yet tested the drug under double-blind trial conditions and therefore results may not be entirely acceptable. The observations, however, in patients with herpes labialis and particularly in those who had the solution applied within 24 hours of onset of symptoms were more or less similar to the ones described by Jaffe and Lehner.

This type of treatment shows some promise and this is significant as herpes labialis is a common complaint and as our therapeutic measures to deal with this condition in the past have not been satisfactory.

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