bulla supra-basal in position following closely the outline of the epithelial ridges. The bulla is not under tension and its lateral margins are acute. Many acantholytic cells lie free in the space. In other fields there are micro-abscesses full of eosinophils and acantholytic epithelial cells. This is a striking feature of pemphigus vegetans, as is the marked acanthosis of the epithelium.

Epithelial smears are simple to obtain but can never replace the need for a biopsy. Many smears have to be taken and the real Tzank cells with round hyperchromatic nuclei and the peripheral condensation of a basophil cytoplasm are not easily found. A platinum loop is used to remove cells from the base of intact bullæ or recently ruptured bullæ or from the depth of fissures in the surface of granulations. In some smears the diagnosis is almost a low power one with isolated acantholytic basophilic cells. All gradations are seen between normal epithelial cells and Tzank cells. Perhaps the most striking feature of these smears is the profusion of multinucleated epithelial cells, the result of the great reparative power of the oral mucosa, for such cells are not often seen in epithelial smears from the skin.

These patients are treated by my dermatological colleagues with systemic steroids. Nevertheless, extremely high doses are sometimes needed in the initial stages to control the lesions. The dose of steroids which is sometimes quite adequate to control the skin lesions fails in fact to completely suppress the oral ones. This is a real problem and sometimes patients may be otherwise fit except for the occasional oral lesion.

Oral lesions sometimes persist in a patient whose skin manifestations of pemphigus are controlled with steroid therapy. This gives rise to the problem of whether the oral lesions are due to the pemphigus or to the steroids. A steroid ulcer took sixteen weeks to heal in a patient on a maintenance dose of 25 mg of prednisolone daily for severe asthma. It was shallow, shelving, and without inflammatory features.

In a patient with pemphigus vulgaris that had been adequately controlled by steroids, the steroids were discontinued. The problem here was whether the ulcer, or rather a deep fissure at the site of trauma at the occlusal line of both cheeks, was the result of steroid therapy or a recurrence of the pemphigus. During biopsy, part of the epithelium became detached, and, in fact, there was a 'histologic Nikolsky'. Where the epithelium had come away, the basal cells were left behind, and elsewhere there was the earliest sign of separation of the prickle cells from the basal layer. Although there were no obviously acantholytic cells in this section, epithelial smears from the depth of the fissure showed an abundance of them.

*Summary*

In conclusion then, whereas there is an unequivocal histological diagnosis of pemphigus, the diagnosis of the oral lesions of erosive lichen planus, erythema multiforme and benign mucous membrane pemphigoid affecting the oral mucosa alone must be made on the clinical features. In highlighting these I would like to reiterate the importance in atrophic lichen planus of the white striæ radiating from the smooth yellow fibrin sloughs covering the shallow erosions on the atrophic mucosa, together with the picture of desquamative gingivitis; in erythema multiforme the acute febrile disturbance and the hæmorrhagic nature of the ulceration with the predilection for the lips, tongue and cheeks, sparing the masticatory mucosa; and in benign mucous membrane pemphigoid the predilection for the masticatory mucosa of bullæ and thick white sheets of necrotic epithelium and the almost constant association with the conjunctival lesions.

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## 'Aphthous' and Herpetic Lesions of the Oral Mucosa

The terms 'aphtha' and 'aphthous ulceration' appear to date back to Hippocrates, and they have been used in varying and often conflicting ways since that time. Nowadays the terms are usually used to indicate the state in which there are recurrent crops of painful ulcers of unknown ætiology affecting various parts of the oral mucosa. However, within this broad group, a number of relatively well-defined conditions or variations can be detected.

First, there are those patients who experience recurrent crops of one to four ulcers affecting the non-keratinized mucosa and lasting for seven to fourteen days. Then there are the patients who have recurrent attacks in which there are up to twenty or more ulcers at a time, and these are not confined to the non-keratinized parts of the mouth. This condition or variation, sometimes termed 'recurrent herpetiform stomatitis', is more usually included under the heading of 'aphthous ulceration'. Thirdly, there are the patients who suffer recurrent attacks in which there are usually only one or two ulcers at a time but these are deep, destructive, and may take six or more weeks to heal. Both in this condition, often

termed 'periadenitis mucosa necrotica recurrens', and in ordinary aphthous ulceration, the oral lesions may be accompanied by similar ulcers of the genital mucosa or skin, and some of these patients later develop a typical Behçet's syndrome.

Sircus *et al.* (1957) listed 11 synonyms for lesions of the aphthous and periadenitis group, and many more names still could be added to this list. Therefore, it is always necessary to define the terms that are to be used in discussing lesions of this type.

In this communication, 'periadenitis mucosa necrotica recurrens' will be regarded as a distinctive type of disorder – and the term 'aphthous ulceration' will be used mainly for the condition in which there are one to four ulcers at a time on the non-keratinized mucosa. However, some of the investigators whose work will be cited include both the recurrent herpetiform type of lesion and the periadenitis lesions in the 'aphthous' category.

The incidence of aphthous ulceration varies with the population examined, but there can be no doubt that it is a common and widespread condition. In a sample of over 1,500 consecutive out-patients, Sircus *et al.* (1957) found that one out of every 5 suffered from this form of mouth ulceration at some time, whilst in a survey of a professional school (mainly University) population, Ship *et al.* (1960) found an incidence of 55%. Women are affected more commonly than men, and this disparity is especially marked over the age of 50 years.

The first attack may occur in the first few months of life but most commonly the onset is between the ages of 10 and 20 years. Thereafter, the incidence of first attacks declines steadily and few individuals develop the disorder after the age of 50; of those who do have such a late onset, almost all are women.

Many factors appear to predispose to aphthous ulceration or to precipitate an individual attack. The condition is noticeably more common in intelligent, conscientious people, and Kelleher (in Sircus *et al.* 1957) found a high incidence of anxiety, obsessional and hypochondriacal features amongst a group of 55 individuals suffering from aphthous ulceration who were examined both by a physician and by a psychiatrist. An interesting feature of this group was that 73% were non-smokers.

The first attack of oral ulceration may be associated with a period of severe emotional or environmental stress and a similar relationship may be observed between stress and subsequent attacks.

There can be little doubt that in the more susceptible individuals minor local trauma may precipitate the lesions, and in many women attacks of oral ulceration appear to be associated with the menses. In these patients the oral lesions tend to develop most often in the week preceding menstruation (Ship *et al.* 1961).

The clinical features of an attack of aphthous ulceration are well known, and the majority of cases follow the same general pattern. After a period of twenty-four hours or less, in which there is a pricking or burning sensation in the affected mucosa, and during which there may be slight reddening, ulceration occurs, and during the next three to six days the ulcer enlarges. It is shallow, and its base is covered by a yellow or grey pyogenic membrane. The margin is slightly raised, but there is only a little induration. The shape of the ulcer depends partly on the site; those on the lip or cheek mucosa are usually rounded or reniform, whilst in the sulci or on the floor of the mouth they tend to be elongated.

The patient experiences little constitutional disturbance, and the ulcers have usually healed within ten to fourteen days of the onset.

Histologically the aphthous ulcer presents a very nonspecific appearance. The lesion is usually shallow and the base is covered by a small amount of fibrinous exudate. At the margins the epithelium thins and then abruptly terminates, and there is no evidence of virus inclusion bodies or other distinctive change. The inflammatory cell infiltration extends quite deeply, and often down to the underlying fat and muscle. This infiltrate is quite dense and it consists mainly of lymphocytes and plasma cells.

Periadenitis mucosa necrotica recurrens affects individuals of similar type to those affected by aphthous ulceration. The lesion, which is often solitary, starts as a tender submucous nodule. Over a period of a few days the nodule enlarges, the overlying mucosa becomes necrotic, and an ulcer forms (Fig 1). However, unlike the ordinary aphthous ulcer this lesion is deep, it has a necrotic core, and it may be accompanied by considerable induration. These lesions occur mainly on the lips and tongue, but their relationship to the sub-

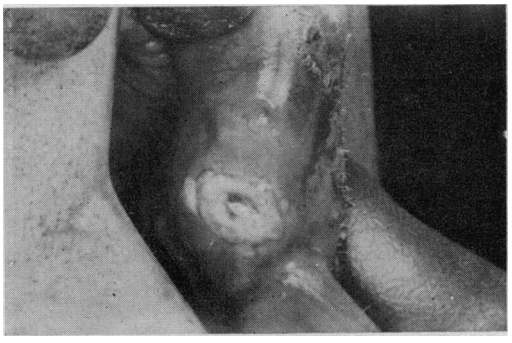

Fig 1 *Periadenitis mucosa necrotica recurrens. Ulcer on lip with large area of induration*

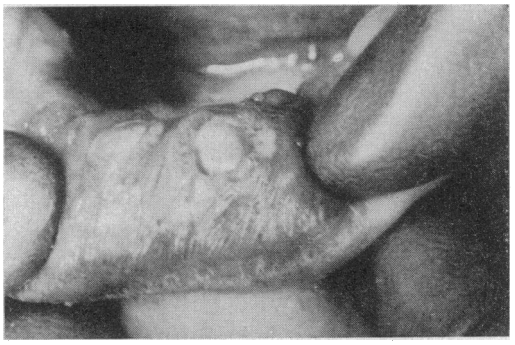

Fig 2 *Periadenitis mucosa necrotica recurrens. Two early lesions on the lower lip*

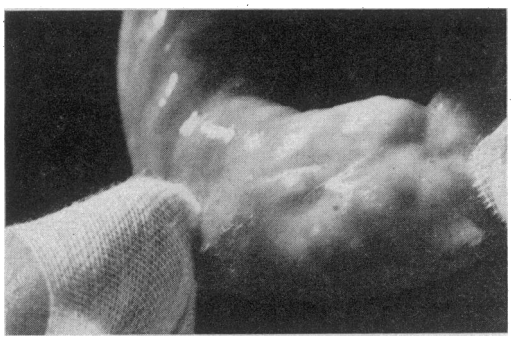

Fig 3 *Same patient as Fig 2, showing tissue distortion following healing of periadenitis mucosa necrotica recurrens lesions*

mucous glands in these sites is uncertain. Healing may take six weeks or more, and when it is complete there may be marked scarring. Fig 2 shows a patient with two such ulcers developing on the lower lip. At this stage the submucous nodules are present, and the overlying mucosa is becoming necrotic, but gross ulceration has not yet developed. Fig 3 shows the lip of the same patient after the ulcers have formed and healed and illustrates the distortion of the tissues that has resulted.

Aphthous and periadenitis mucosa necrotica recurrens lesions of the mouth are unpleasant enough, but of even greater concern is the possibility that these lesions may herald a more generalized disorder, and especially Behçet's syndrome. It is well known that in this syndrome lesions in one or two sites may appear months, or even years, before a third site is involved. Furthermore, in some patients a third site is never involved, yet the existing lesions appear essentially the same as in the classical 'triple symptom complex'.

In patients with oral aphthous or periadenitis type lesions, ulceration in other sites (especially the genitalia) appears to occur in about 8–13% (Sircus *et al.* 1957, Farmer 1959), but there do not appear to be reliable figures to show how many of these will proceed to a typical Behçet's syndrome.

The character of the individual oral lesions also seems to give little guidance as to the likelihood of more serious developments. However, here it may be possible to exclude the 'recurrent herpetiform' type of stomatitis, for experience suggests that these mouth lesions are unlikely to be the forerunner of Behçet's syndrome. It also seems that, in the periadenitis type of lesion, ulceration of the soft palate and fauces is an ominous sign.

Microscopically the periadenitis mucosa necrotica recurrens lesion shows evidence of considerable tissue destruction, so that the mucous glands of the submucosa or even the muscle may lie almost at the surface of the lesion. As in the ordinary aphthous lesions, there are no characteristic changes in the epithelium at the margin of the ulcer and the inflammatory cell infiltrate consists principally of lymphocytes and plasma cells. The mucous glandular tissue is involved in the inflammatory changes but there seems little to suggest that it plays any dominant role.

The treatment of oral aphthosis and periadenitis is far from satisfactory. A great variety of remedies has been tried, and this very variety testifies to the shortcomings of them all. General supportive measures, including the administration of γ-globulin and the stimulation of immunity mechanisms by repeated vaccination have proved disappointing. Folic acid, aneurine hydrochloride, betamethasone and the systemic administration of prednisone all achieve some measure of relief in some patients, and a careful double-blind study by Cooke & Armitage (1960) with hydrocortisone hemisuccinate showed that in a selected group of cases the patient-ulcer-days could be reduced by half. It has also been reported that patients taking 'the pill' may show relief from their oral lesions as a fringe benefit. However, all of these treatments fall far short of the ideal, and emphasize our lack of knowledge regarding the ætiology of the disorders.

It has often been suggested that the aphthous and periadenitis lesions are due to infection with the herpes simplex virus but this suggestion is quite unjustified by the available evidence. In acute herpetic gingivo-stomatitis, the initial oral lesions are usually – perhaps always – vesicles, but these rupture quickly and consequently they are not often seen. Very soon after the vesicles break, and especially if they are on a keratinized part of the mucosa, the loose ring of epithelium that formed the walls of the vesicle may be seen (Fig 4). This stage is a fruitful one for the collection of epithelial cells showing the characteristic changes of the disease; these cells are readily

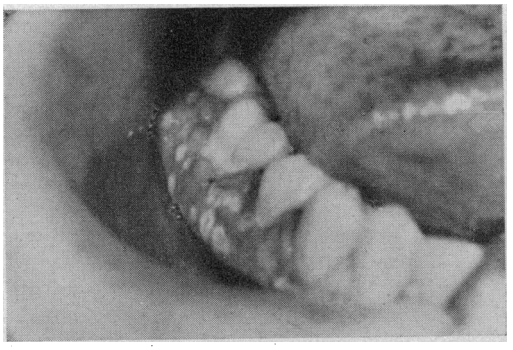

Fig 4 *Rings of detached epithelium at the sites of recently ruptured herpetic vesicles on keratinized oral mucosa*

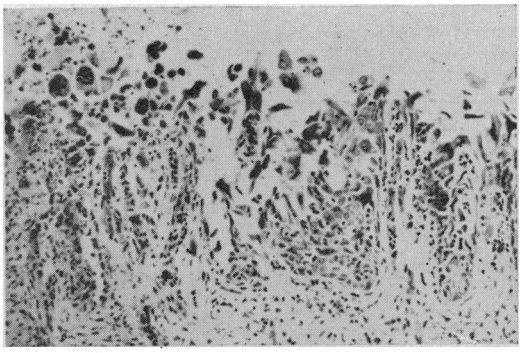

Fig 5 *Floor of recently ruptured herpetic vesicle of oral mucosa. The deeper layers of the epithelium are still present, and there are many multinucleate epithelial cells.* ×110

harvested by gentle scraping, and a stained smear provides a simple and rapid method for confirming the diagnosis. Histologically, also, the picture is typical. Fig 5 shows the floor of a recently ruptured vesicle, and the deeper part of the epithelium can still be distinguished.

Closer inspection of the floor or margins of the lesion shows the multinucleate epithelial cells, and within these cells it is possible to see the intranuclear inclusion bodies, displacing the chromatin outwards to form a darkly staining ring lying against the nuclear membrane.

Initially the ulcers are small, but they are exquisitely painful, and each may be surrounded by a broad area of injection. Gradually, the ulcers enlarge, and as they are doing so the diagnostic histological features of the lesion are lost. Fig 6 shows a herpetic lesion of the oral mucosa that is five days old, and it can be seen that the multinucleate epithelial cells are so degenerate that their nuclear outlines are hardly visible.

The original vesicles tend to develop in clusters, and as the consequent ulcers enlarge they coalesce, thus giving a compound ulcer with a serpiginous outline.

Oral herpetic lesions, especially in the child, vary both in their severity and their distribution; for example, sometimes one encounters gross gingival ulceration, and this form is often incorrectly diagnosed as Vincent's infection. However, whatever form the herpetic lesions take, they share certain features that reveal their ætiology – histologically, there are the multinucleate epithelial cells with inclusion bodies, culturally the virus can readily be isolated, and serologically there is a rising antibody titre.

None of these features is to be found in the aphthous and periadenitis type of lesion. What, then, is the ætiology of recurrent aphthous ulceration? Very recently there have been two new approaches to this problem, one examining the possible role of autoimmunity, and the other

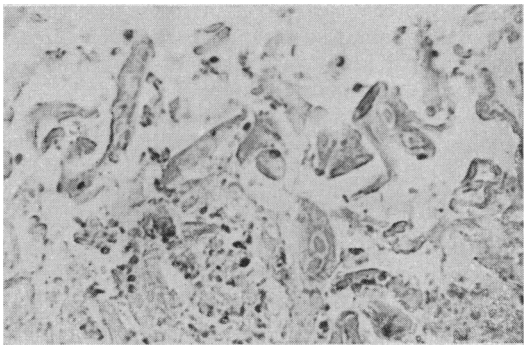

Fig 6 *Herpetic lesion five days old; the multinucleate epithelial cells are now necrotic.* ×270

suggesting that infection with pleuropneumonia-like or L-form organisms may be responsible.

The investigations into the role of autoimmunity have been reported recently by Lehner (1964). In this investigation sensitized sheep erythrocytes were prepared by tanning followed by exposure to a saline extract of oral mucosa from a stillborn infant. These sensitized cells were added to serial dilutions of sera from patients in five categories: controls who were healthy, controls who had systemic disease but without oral ulceration, patients with non-ulcerating mouth lesions, patients with a variety of ulcerative conditions of the mouth excluding aphthous lesions and, in the last category, patients with typical oral aphthæ. In this latter group, the duration of the aphthous ulceration had varied between six months and thirty years (Table 1). Table 1 also summarizes Lehner's findings on the titre of antibodies against the sensitized erythrocytes, dividing the results broadly into sera with titres above and below 1 in 48. Whereas three-quarters of the sera from patients with aphthous lesions had an antibody titre of 1/48 or abov

*Table 1*
**Titres of antibodies against erythrocytes treated with extract of oral mucosa (based on findings of Lehner 1964)**

| | *Titre* | |
|---|---|---|
| | *Under 1/48* | *Over 1/48* |
| Controls: | | |
| Healthy | 100 | 0 |
| Systemic disease | 100 | 0 |
| Oral lesions: | | |
| Non-ulcerating | 93 | 7 |
| Ulcerating | 90 | 10 |
| Aphthous lesions | 25 | 75 |

only 17% of patients with other oral lesions showed similar titres, and none of the controls either healthy or with systemic disease not involving the mouth. As Lehner cautiously comments, this evidence suggests that the part played by an autoimmune reaction or an antibody cross-reacting with an infective agent and oral mucosa deserves further consideration.

In the past, many searches have been made for a possible infective agent in aphthous ulceration, and recently a group in the United States has been studying the relationship between these lesions and an organism that they believe to be a transitional L-form, probably of an α hæmolytic streptococcus (Barile *et al.* 1963, Barile & Graykowski 1963, Graykowski *et al.* 1964, Stanley *et al.* 1964). The organisms have been isolated from the ulcers and grown in culture using a variety of media; on occasions they have also been cultured from the bloodstream of patients during exacerbations of the oral lesions. The organism has also been grown in tissue culture with young rabbit kidney cells, and this material has been injected intradermally into rabbits (Graykowski *et al.* 1964). Within twelve hours at the site of inoculation there was a nodule 0·5 cm in diameter on an erythematous base, and within forty-eight hours the nodule was 2 cm diameter. About four days after inoculation ulceration occurred over the nodule and the ulcer continued to enlarge. These rabbit lesions were reported to be similar to the oral lesions of periadenitis mucosa necrotica recurrens. Cultures of a biopsy from one of the rabbit lesions again yielded the L-form organisms, the organisms could also be demonstrated histologically in the biopsy from the nodule, and they showed the same morphological features as the organisms in culture.

Stanley *et al.* (1964) report that the L-forms can be demonstrated in the shallow aphthæ, and in the periadenitis type lesions, but they can also be found in a variety of other circumstances. The specimens in which the L-forms have been sought can be divided into three groups as shown in Table 2, which also shows the percentage of specimens in which L-forms were found. Clearly, as yet, it is not possible to say more than that the association between the L-forms and the aphthous lesion merits further investigation, and Stanley *et al.* (1964) indicate that fluorescent and ferritin antibody techniques may throw further light on this association. Thus, the work of this group, and the work of Lehner appear to be drawing closer together. It may well be that during the next year or two we shall have significant further information on the ætiology of the aphthous and periadenitis lesions.

*Table 2*
**Incidence of 'transitional L-forms' in oral mucosa (based on findings of Stanley *et al.* 1964)**

| | *Percentage showing L-forms* |
|---|---|
| Aphthous and periadenitis lesions | 93 |
| Non-aphthous lesions | 40 |
| Post-mortem specimens of oral mucosa | 47 |

*Acknowledgment:* Dr Harold Stanley (National Institute of Dental Research, National Institutes of Health, Bethesda) kindly provided slides, shown at the meeting, illustrating the demonstration of L-forms in human oral lesions and in animal lesions produced by the inoculation of pure cultures.

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