

Progress report

Oral ulceration and Behçet's syndrome

Ulcers in the mouth are common manifestations of many local or general disorders. Inadequate attention has been paid to the differential diagnosis of recurrent oral ulcers, perhaps because some of these ulcers may be trivial and they do not carry a threat of serious complications, as do ulcers in the gastrointestinal tract. However, a small but important proportion of patients suffer from frequent or continuous ulceration which causes severe pain, with associated difficulties in speaking and eating and loss of weight. Stomatology has been developing rapidly in this country, as a specialty concerned with the aetiology, differential diagnosis, pathogenesis, investigation, and management of oral disease. Ulceration is the most common lesion of the oral mucosa and the differential diagnosis can be complex. The frequent label of 'aphtha' to any oral ulcer is meaningless and can be harmful, as it may delay the diagnosis, at times, of a life-threatening disease.

Recurrent oral ulcers are the most common lesions and they will be considered with Behçet's syndrome, as there is no obvious line of division between focal oral ulcers and the multifocal involvement of different tissues. This syndrome is more common than was previously thought, if one allows for the definition of two or more major sites of involvement¹, especially with regard to oral and genital ulcers. The gastroenterological and haematological disorders will also be discussed, as considerable interest has been generated in the relationship between aphthous ulcers and those associated with anaemia and malabsorption.

Recurrent aphthous and herpetiform ulcers

There are three types of recurrent oral ulcers (ROU); the terms minor aphthous ulcers (MiAU)² was applied to 'aphthae'³ and major aphthous ulcers (MjAU) to the misleadingly named periadenitis mucosa necrotica recurrens lesion⁴. A third type have been termed herpetiform ulcers (HU)⁵. The differential diagnosis of minor and major aphthous and herpetiform ulcers, based on a series of 210 patients, is presented in Table 1⁶.

EPIDEMIOLOGY

The prevalence of ROU varies with the population studied, but the most reliable data show that 20.1% of a large hospital outpatient population and 10.6% of patients in general practice have ROU⁷. Although a very high prevalence of 55% was recorded in a student population⁸, if those with a doubtful history of ulcers were excluded^{8,9} the prevalence was 33.6%.

ROU is more often found in females than males, but the ratio varies from 2:1: to 1:1.3^{5-7,10}. The ulcers may appear at any age; the highest frequency of onset of ROU is during the second decade and 67% to 85% of patients develop ROU in the first three decades^{5-7,10}. It is noteworthy that ROU is common in children and the youngest child with MiAU observed by the author was 2 years of age.

Received for publication 30 November 1976

Table 1 *Differentiating features of three varieties of recurrent oral ulcers*

	<i>Minor aphthous ulcers</i>	<i>Major aphthous ulcers</i>	<i>Herpetiform ulcers</i>
Sex ratio F:M	1:3:1	0.8:1	2.6:1
Age of onset (yr) (peak incidence)	10-19	10-19	20-29
Number of ulcers	1-5	1-10	10-100
Size (mm)	<10	>10	1-2
Duration (days)	4-14	10-30	7-10
Healing by scar (%)	8	64	32
Recurrence (months)	1-4	<monthly	<monthly
Sites	Lips, cheeks, tongue	Lips, cheeks, tongue, pharynx, palate	Lips, cheeks, tongue, pharynx, palate, floor, gum
Total duration (yr)	<5	>15	>5
Associated oral lesions	—	Erythema migrans	—
Treatment (local)	Corticosteroids	Corticosteroids	Tetracycline

A family history is found in 24% to 46% of patients^{5,7,10}. The familial prevalence is not thought to be due to contact infection, as the frequency of ROU in the consorts is low (0% to 18%). A statistical analysis of 815 families with 1974 offsprings excluded dominant inheritance, as the observed values were considerably lower than the expected ones¹¹. Recessive inheritance could not be excluded, but the statistical data were conflicting.

CLINICAL FEATURES

A prodromal phase is recognised by most patients, as a soreness or burning sensation, one to two days before the onset of ulceration. With the breakdown of epithelium and associated inflammatory reactions the pain increases in severity for a few days, but then the pain gradually disappears, although the ulcer may be large. The salient points in the differential diagnosis of the three types of ROU is that MiAU are single, small, oval ulcers, usually affecting the mucosa of the lips, cheeks and sides of the tongue (Table 1). MjAU are single, large ulcers often involving the oropharynx and dorsum of the tongue. HU appears as crops of numerous minute ulcers, affecting several sites of the oral mucosa and the crops of ulcers coalesce to single lesions with an irregular margin. Although MjAU and HU account for less than 20% of ROU, they require most of the attention as ulceration is almost continuous, may cause severe pain and difficulties in speaking and eating, often with loss of weight. Nevertheless, the patients do not have a raised temperature; only occasionally are the submandibular or upper cervical lymph nodes palpable; and, as the lesions recur over many years, these patients learn to cope without losing much time from work.

Behçet's syndrome

Although originally Behçet's syndrome^{12,13} was defined as recurrent oral and genital ulceration with iridocyclitis, this is now extended to include cutaneous, vascular, joint, neurological, and intestinal manifestations. A precise definition of this syndrome cannot be given at present but the diagnosis is generally made when two or more major sites are involved¹.

A separation of Behçet's syndrome into mucocutaneous and neuro-ocular groups seems desirable on clinical and prognostic grounds¹⁴. The mucocutaneous syndrome may involve a combination of two or more of the following sites: mouth, genitals, conjunctiva, and skin. The neuro-ocular

syndrome, however, shows neurological or ocular involvement (usually uveitis, iritis, and hypopyon, but not conjunctivitis) or both, in addition to any of the mucocutaneous features. Of the patients with neurological manifestations 92% show ocular involvement¹⁵. Additional features, such as arthritis, vascular thrombosis, or intestinal lesions can be encountered in both groups. Although patients with the mucocutaneous syndrome may suffer pain and a great deal of discomfort for many years, ocular involvement commonly leads to blindness and neurological manifestations may result in death.

EPIDEMIOLOGY

The world literature of 907 patients has been surveyed; this included 716 patients reviewed in 1966¹⁶ and eight series of 10 or more patients reported between 1966 and 1976. The geographical distribution is given in Table 2. Although this type of survey, at best, gives only a general trend of the prevalence of BS, nevertheless the very large number reported in Japan (more than 412 patients) is striking and does not include a large series of 335 patients¹⁷, as there may have been an overlap with the previous series reported by the author's group^{18,19}. The true prevalence of BS has not been determined but in an epidemiological study from the Hokkaido district a prevalence of 1 in 10,000 of the population has been recorded²⁰. The prevalence is also very high in countries bordering the Mediterranean (312 patients), where the disease was first reported (Turkey). Somewhat surprisingly, a relatively high prevalence has been reported from Britain (98 patients), with second position among the list of 33 countries. It is difficult to account for the geographical distribution by some common environmental factor, viral agent, or susceptibility to BS.

Although BS may develop at any age, the mean age of onset is between 20 and 30 years²¹. BS may follow ROU after an interval ranging from one to 24 years²². There is no way of predicting in any patient with ROU the development of BS, but this must be rather infrequent. Although most commonly oral, genital, and cutaneous manifestations precede neuro-ocular or joint involvement, the order can be reversed.

BS occurs more often in men than women and the mean M:F ratio calculated from a review of 683 patients was 2.3:1²¹. It should be noted that the sex ratio in BS is the reverse of that found in ROU. A family history has been recorded in some patients but it seems unlikely that genetic factors are significant²³⁻²⁵.

CLINICAL FEATURES

The range of frequencies of involvement of various systems in BS is given in Table 3 and this is based on five published series of 618 patients^{14,18,19,26}.

Oral ulcers

These ulcers are present in almost all patients and MiAU, MjAU, and HU can be found, so that BS cannot be distinguished on the basis of the oral ulcers¹⁴. The oropharynx is also involved.

Genital ulcers

Genital ulcers involve most often the vulva or vagina in females, and the penis or scrotum in males. The prevalence varies between 64% and 88%.

Table 2 *Geographical distribution of Behçet's syndrome**

Order	Country	No. reported			
1	Japan	412+			
2	Britain	98			
3	Israel	74	} 213 (East Mediterranean countries)	} 312 (Countries bordering Mediterranean)	
5	Greece	37			
6	Turkey	34			
7	Egypt	26			
8	Lebanon	18			
12	Jordan	14			
14	Syria	10			
4	Italy	68			} 99 (North, West, and South Mediterranean countries)
13	France	13			
16	Spain	7			
17	Algeria	4			
	Tunisia	1			
9	United States	18			
10	Australia	18			
18	Sweden, Norway and Denmark	9			
15	Russia	8			
†	Belgium, Holland, Switzerland, Argentina, Bulgaria, Canada, Chile, China, India, New Guinea, Poland, Portugal				

*Based on nine series: 14, 16, 21, 25, 31, 82, 117, 118, 152.

†Less than five patients.

Table 3 *Frequency of clinical manifestations of Behçet's syndrome**

	(%)
Oral ulcers	90-100
Genital ulcers	64- 88
Ocular lesions	27- 90
Cutaneous lesions	48- 88
Joint manifestations	18- 64
Neurological features	10- 29
Intestinal manifestations	0- 59
Thrombophlebitis	10- 37

*Data from five published series of 618 patients: 14, 18, 19, 21, 26.

twice as many females as males are affected and the ulcers are similar to the three types found in the mouth.

Cutaneous lesions

These are found in 48% to 88% of patients and three main groups have been described; erythema nodosum, pustules, and erythema multiforme^{26, 27}.

Ocular manifestations

These manifestations have been reported in 27% to 90% of patients. The most common manifestations are relapsing iridocyclitis, or uveitis with hypopyon, optic atrophy, and alteration of the retinal vessels. Less frequently chorooiditis, relapsing conjunctivitis, keratitis, and haemorrhage may occur¹⁶.

Neurological features

These are less frequent (10% to 29%) and three of the most common manifestations are pseudobulbar palsy, multiple sclerosis, and general paresis¹⁵.

Joint manifestations

These are found in 18% to 64% of patients. Relapsing pain, swelling, tender-

ness, and redness involves usually the knees, ankles, hands, wrists, elbows, and feet, and, unlike in rheumatoid arthritis, small joints are rarely affected^{25,28}.

Vascular involvement

Recurrent thrombophlebitis has been found in 10% to 37% of patients²⁹ and obstruction of the inferior or superior vena cava is relatively frequent^{21,30-34}. Arterial aneurysms have been reported in a few patients^{18,152-155}.

Intestinal manifestations

These are ill-defined and except for isolated cases of ulcerative colitis being reported³⁵⁻³⁷, it appears that the small intestine is most frequently involved¹⁸. A systematic study has only been carried out in Japan and gastrointestinal manifestations have been recorded in 59% of patients. The symptoms included diarrhoea (28%), distension (43%), nausea (16%), and anorexia (31%). Radiological examination revealed abnormalities affecting most commonly the small intestine, with dilatation, gas and fluid retention, and segmentation. A high prevalence of intestinal involvement (eight out of 16 patients) was recorded in another Japanese series³⁸. All but one of the 16 patients had some radiological finding of the small intestine; thickening of folds and fragmentation or stippling were observed in more than half of the patients. However, no clinical manifestations of gastrointestinal involvement have been recorded in a recent review of 41 patients with BS in Israel²¹.

AETIOLOGY OF RECURRENT ORAL ULCERATION AND BEHÇET'S SYNDROME

Although a large variety of causes have been suggested, the aetiology of recurrent aphthous ulcers has not been fully established. A family history of recurrent aphthous ulcers is often present and the highest incidence of ulcers is recorded in siblings in whom both parents have recurrent aphthous ulcers¹¹. A hormonal disturbance may play a part, as in some female patients there is a relationship between the ulcers and menstrual period. Furthermore, the onset of ulceration may coincide with puberty and the ulcers often disappear during pregnancy. While emotional stress may influence the pattern of the disease, it is unlikely to be the direct cause. Trauma is also unlikely to play an essential role, though it might precipitate ulceration.

Food allergy

Food allergy has been postulated as an aetiological factor in ROU on the basis of a history of food allergy³⁹, or the increased prevalence of ROU among patients with allergic conditions^{40,41}. This has received some support from the finding of relatively high titres of serum antibodies to casein and to a lesser extent α -lactalbumin, β -lactoglobulin, and a gluten fraction⁴². Recently, an immunological response to some dietary agent such as gluten has been invoked: (1) because of finding a flat jejunal biopsy in eight of 33 patients with ROU, in all of whom the ulcers cleared on a gluten-free diet, and (2) a mean increase in plasma cells and decrease in lymphocyte counts in the jejunum of the remaining patients⁴³.

The food allergy hypothesis was examined by skin tests with foods, but these failed to show a relationship between ROU and a variety of

foods^{39,44,45}. Elimination diets³⁹ or removal of patients from dietary and contact allergens⁴⁶ failed to eliminate the ulcers. A case for food allergy has not been established, but it seems that in a small proportion of patients with ROU coeliac disease may be responsible for the ulcers.

Viral, L form or microplasma infection

ROU and herpetic stomatitis have been often confused, although the two conditions have been clearly differentiated³. Any causative association between Herpes simplex virus and ROU has been based on case histories. Evidence against this hypothesis is that material from 10 out of 11 patients with ROU failed to induce corneal lesions in rabbits and neutralisation tests also proved negative in nine out of 11 patients⁴⁷. The negative results were supported by the inability to grow the virus or to find inclusion bodies in several studies^{7,48-52}. Furthermore, 28% of a series of patients with ROU had no antibodies to Herpes simplex virus and seronegative patients do not show a rise in antibody titre during convalescence^{39,49}. Stimulation of lymphocytes by Herpes simplex virus also failed to show any significant difference between patients with ROU and controls⁵³. Idoxuridine is effective in the treatment of Herpes simplex virus lesions but not in HU⁵⁴.

However, a very rare type of recurrent, intraoral ulceration caused by Herpes simplex virus is now recognised⁵⁵, with clinical and cytological features clearly distinguishable from ROU. Recently adenovirus type 1 has been implicated in recurrent oral ulceration by culturing the virus and by immunofluorescence staining of scrapings of cells from the ulcers⁵⁶.

Streptococcus sanguis or its L form has been claimed to be isolated preferentially from the ulcers and the organisms elicited a delayed hypersensitivity skin reaction in 27 of 30 patients and one of six controls^{57,58}. However, *Strep. sanguis* is commonly found in normal subjects, and it stimulates lymphocyte transformation in patients to a less extent than in controls⁵⁹, though significant inhibition of leucocyte migration was elicited by the same organism in patients with recurrent oral ulceration⁶⁰.

In BS a virus was isolated from the eyes of two patients⁶¹ and from the eye and brain of another patient⁶². In both studies a raised titre of neutralising antibodies to these unidentified viruses was found in patients but not in controls. A careful review of the literature in 1961⁴⁹ concluded that a viral aetiology could not be established, as there were many unsuccessful attempts at growing viruses.

A different approach has been recently adopted in examining the hypothesis that viruses may be responsible for some autoimmune diseases⁶³. Viruses replicate in phytohaemagglutinin stimulated cultures of mononuclear cells from normal blood, but not in mononuclear cells from patients with known virus infections or putative viral infections in autoimmune disease. Herpes simplex virus was used in many of these studies and failed to replicate in mononuclear cells of more than half of the patients with recurrent herpetic lesions, untreated patients with BS, systemic lupus erythematosus, polyarteritis, and Crohn's disease. However, Herpes simplex virus replication was not impaired in patients with localised disease and this is particularly significant with reference to RAU and rheumatoid arthritis. There is, nevertheless, some evidence that those mononuclear cells which do not permit replication of Herpes simplex virus may preferentially localise in the synovial effusion⁶⁴. The true significance of this phenomenon cannot be yet assessed and, al-

though some viral specificity has been found, it is not envisaged that Herpes simplex virus is a causative agent of all the diseases in which lymphocytes do not permit viral replication. Interference is a nonspecific phenomenon⁶⁵ and interference with growth of Herpes simplex virus in lymphocytes previously exposed to a virus is thought to be a more likely interpretation.

The possibility that *Mycoplasma pneumoniae* may be associated with the aetiology of BS has been raised by finding cold agglutinins in two patients⁶⁶. However, cold agglutinins and complement fixing antibodies to *M. pneumoniae* were not found in 12 sera from patients with BS (unpublished). Furthermore, *M. orale* and *hominis* were not related immunologically to ROU, as these sera yielded antibody titres to the mycoplasmas that were comparable with those from controls⁶⁷.

Immunological responses

HUMORAL RESPONSES

A slight increase in serum IgA and IgG was found especially in MjAU, but in BS there was an increase in serum and salivary IgA⁶⁸. Complement components have received scanty attention, though recently, normal concentrations of C3 and C4⁶⁹, but high levels of total haemolytic complement titre and concentrations of C9, were found in patients with BS^{69,70}. Furthermore, C3, C4, and C2 were markedly reduced before an attack of uveitis, suggesting complement consumption by the classical pathway⁷⁰. Estimation of the concentration of C9, c-reactive protein (CRP), and α 1-antitrypsin in 40 sera from patients with BS and ROU showed significantly increased amounts of CRP in BS and C9 in BS and ROU⁷¹. It is not certain if the complement components might play a part in lysis of the affected cells in BS or if they are acute phase reactants released during epithelial inflammation.

It is possible that CRP might modulate the immunological mechanism by inhibiting T cells, promoting phagocytosis, and activating complement⁷²⁻⁷⁴. As CRP and C9 are significantly increased in BS as compared with ROU they might be implicated in the transition from focal oral ulceration to the multifocal BS⁷¹.

Although immune complexes (IC) have not been demonstrated by the immunofluorescent technique⁷⁵, preliminary studies using C3 haemagglutination inhibition assay of the macromolecular fraction of plasma⁷⁶ suggest that IC are present in some patients with BS⁷⁷. This is consistent with the clinical manifestations of BS, as erythema nodosum²⁷, arthritis²⁸, and uveitis²⁹ have been commonly ascribed to immune complexes. Histological examination of erythema nodosum and oral and genital ulcers disclosed vascular endothelial proliferation, with obliteration of the lumen, thrombosis, occasional fibrinoid necrosis, and perivascular leucocytic infiltration in BS but not in ROU^{27,75,78,79}. These features raise the possibility that transition from focal oral ulceration to the multifocal BS might be associated with complement activation and IC formation and this concept is now being examined.

Nuclear, thyroid, and gastric antibodies are not found in ROU or BS and the Rose-Waaler test is also negative even with joint involvement. However, autoantibodies to saline homogenates of oral mucosa were found in patients with ROU and BS^{14,80}. Significant haemagglutinating antibodies were found in 72 to 80% of MiAU and MjAU and BS but not in HU (20%) and a variety

of controls (10%). These antibodies belong predominantly to the IgM and, to a less extent, IgG classes. Haemagglutinating antibodies to oral mucosa in another study were, however, found mostly in BS¹⁸. These antibodies were not specific to oral mucosa, as common antigenic determinants were shared between the saline extract of oral mucosa, pharynx, larynx, oesophagus, conjunctiva, vagina, skin, and colon⁸¹.

Direct immunofluorescent staining of predominantly IgG and IgM was found in the cytoplasm of spinosal cells in biopsies of ulcers from patients with MiAU, MjAU, and BS⁷⁵. As indirect immunofluorescent staining of normal human buccal mucosal cells with serum from patients with ROU was not detected, non-specific inflammatory binding could not be excluded. However, cytoplasmic antibodies to epithelial cells of human oesophagus were found by the indirect method in all five patients with BS tested and in none of the 20 controls⁸². This was confirmed by finding a significantly higher titre of cytoplasmic fluorescence with sera from patients with RAU than controls, using human buccal mucosa⁸³.

CELLULAR RESPONSES

The intense lymphomonocytic infiltration seen on histological examination is consistent with a delayed hypersensitivity reaction^{58,75}. This is also supported by the electron-microscopical findings of intracytoplasmic phagosome-like bodies of epithelial cells adjacent to mononuclear cells⁷⁵ and the association of phagocytosing macrophages with prickle cells⁸⁴.

Delayed hypersensitivity skin reactions have been produced by injecting a homogenate of non-ulcerating scrotal lesion from a patient with BS⁸⁵⁻⁸⁷. It should be, however, noted that a non-specific vesicular lesion develops by pricking the skin and this is used by some as a diagnostic test of BS^{27,87}.

Significant lymphocyte transformation was induced by homogenates of oral mucosa in MiAU, MjAU, and BS and to a less extent in HU, but not in controls⁸⁸. Skin homogenates also induced a significant response in lymphocytes from patients with MjAU and BS. There has been considerable support for the involvement of cell-mediated immunity, by finding that lymphocytes from patients with ROU, but not from control subjects, induce cytotoxicity in cultures of gingival epithelial target cells^{89,90}. The tissue specificity of the cytotoxic response of lymphocytes from patients with ROU to oral epithelial cells was suggested by the lack of cytotoxicity to skin, vaginal, or colonic mucosal cells^{90,91}. Recently, homogenates of oral mucosa induced significant leucocyte migration inhibition in patients with ROU but not controls⁹². A correlation was found in sequential studies between the clinical features and cell-mediated immunity, as assessed by lymphocyte transformation, cytotoxicity, and leucocyte migration inhibition but not haemagglutinating or fluorescent antibodies to oral mucosa^{81,89,90,93}.

The result of three different markers of cell-mediated immunity are in agreement that the cellular responses play an important effector part in the recurrences of ROU and that this occurs in the presence of a constant level of antibodies. As the cytotoxicity is antibody independent^{89,90}, it is suggested that the antibodies may be involved in immune complex formation. The relationship between increased cellular responses and immune complexes is not clear; while immune complexes may modulate cellular immunity, they might be the principal agents in the change from focal oral ulceration to the involvement of many tissues in BS. Antigenic cross-reactivity between oral

mucosa and some microbial agent might account for the autoimmune manifestations. There have been few systematic studies of cross-reactivities, except for that found between oral mucosa and *Lactobacillus acidophilus*⁹⁴. This suggests the possibility that lipoteichoic acids might be responsible for this observation. There is some evidence that *Strep. sanguis* may share antigens with oral mucosa⁹⁵.

HLA-antigens in oral ulceration

HLA-antigens have been studied recently in 143 patients with ROU or BS and the results were compared with those of 100 controls⁹⁶. The frequency of five selected HLA-antigens out of the 26 antigens tested are given in Table 4. The results suggest that the antigen-frequency of HLA-A2, B12, and AW29 are significantly raised in patients with ROU, although these were not significant after correcting for the number of antigens tested⁹⁷. No previous association of HLA antigens with ROU have been reported, except in a study of 44 Japanese patients with BS⁹⁸, in which it was found that 75% had HLA-B5. An increased frequency of HLA-B5 in BS was not confirmed in the two small British studies^{96,99} in which HLA-B5 was found in 3/24 and 2/10 (total of 5/34) patients, but HLA-A2 was found in 14/24 and 5/10 (total of 19/34) patients. Although the total number of patients with BS in the British series is small, nevertheless they indicate that HLA frequency in BS is different from that of the Japanese patients. Both studies, however, suggest that the susceptibility to BS is associated with a gene near the HLA region which is in linkage disequilibrium with the HLA genes. It is possible that HLA-A2/B12 which is significantly increased in ROU might function as specific receptors for pathogens or that the antigenic determinants of some exogenous pathogens might mimic the HLA antigens¹⁰⁰. The most likely mechanism is that immune responses (Ir) genes are in linkage disequilibrium with the HLA loci and that genes might be significantly associated with ROU. It is of interest that in most of the diseases which are associated with HLA-antigens in man, the immune response is thought to play a major role in the pathogenesis of the disease¹⁰¹. Preliminary family studies are consistent with the hypothesis that susceptibility to ROU may be linked to HLA haplotypes⁹⁶.

Treatment

RECURRENT ORAL ULCERS

The differential diagnosis of the large variety of oral ulcers is the most

Table 4 Frequency of selected HLA antigens in groups of patients with recurrent oral ulceration

HLA antigen	Recurrent oral ulcers 143		Minor aphthous 80		Major aphthous 19		Herpetiform 20		Behçet's syndrome 24 100		
	(No.)	(%)	(No.)	(%)	(No.)	(%)	(No.)	(%)	(No.)	(%)	(%)
A2	84	58.8*	48	60.0*	9	47.4	13	65.0	14	58.3*	44
B5	18	12.6	11	13.8	2	10.5	2	10.0	3	12.5	12
B8	19	13.3*	11	13.8	2	10.5	2	10.0	4	16.7	23
B12	57	39.9*	30	37.5*	9	47.4*	11	55.0*	7	29.2*	22
AW29	24	16.8*	12	15.0*	5	26.3*	2	10.0	5	20.8*	6
A2/B12	40	28.0†	21	26.3*	6	31.6*	8	40.0†	5	20.8*	11

*Uncorrected $P < 0.05$.

†Corrected $P < 0.05$ (multiplying the P value by the number of antigens tested).

important aspect in the management of ROU. Attention has been drawn to the folate and vitamin B12 deficiencies, with or without anaemia, which may be due to coeliac disease, dietary restrictions, or drug interference with folate metabolism. Specific replacement of the deficiency, eliminating the dietary restriction or offending drug, and gluten-free diet in cases of coeliac disease, may eliminate the ulcers. Iron deficiency with or without anaemia should be treated in its own right, but the ulcers may improve in only a limited number of patients. It should, however, be emphasised that over 90% of patients with ROU have no systemic disorder and will need some topical treatment with corticosteroids, antibiotics, immunostimulants, or analgesics.

Topical steroids

These are most helpful in controlling MiAU and MjAU¹⁰², provided that they are applied during the prodromal stage of ulceration. This requires that the patient applies the steroid when the first symptoms develop, a day or two before the epithelium breaks down; during this phase lymphocytes may be reaching peak activity⁸¹. The most useful preparations are 0.1% triamcinolone in Orabase, 2.5 mg tablets hydrocortisone sodium succinate, and 0.1 mg tablets betamethasone valerate; these drugs are usually applied three to four times daily. Suppression of the adrenal cortex does not occur if the dosage is kept within reasonable limits^{103,104}, and betamethasone disodium phosphate is not used¹⁰⁵. Systemic prednisone or ACTH (tetracosactrin) is needed in some patients with severe MjAU, in whom the ulcers cannot be controlled by topical treatment and the patients have difficulties with speaking and eating, leading to loss of weight. Prednisone given in daily doses of about 40 mg for seven to 10 days often clears the ulcers and should then be discontinued.

Topical antibiotics

Tetracycline is the drug of choice in the treatment of HU¹⁰⁶, but it is also useful in controlling some MjAU. The mode of action is not clear, though it is noteworthy that, in addition to its broad antibacterial properties, tetracycline has antimycoplasma and some antiviral properties. In order to prevent acute candidiasis, which develops in most patients using topical tetracycline for any length of time¹⁰⁷, Mysteclin capsules containing 250 mg tetracycline and 250 000 units nystatin should be prescribed. The capsules are used four times daily, by dissolving the contents in about 5 ml of water and keeping the fluid in the mouth for two minutes.

Immunostimulant drugs

Levamisole (2, 3, 5, 6,-tetrahydro-6-phenyl imidazo 2, 1-b thiazole) is a drug which potentiates cell-mediated immune responses¹⁰⁸. The drug seems to be effective in ROU¹⁰⁹⁻¹¹¹. A double-blind, crossover trial of Levamisole was carried out in 47 patients with ROU and a significant decrease in the number of ulcers and ulcer days has been found after two months of intermittent administration of Levamisole¹¹¹. About 64% of patients responded to the drug by a decrease in the number of ulcers by more than 50% for two or more months. The remaining 36% of patients failed to respond to Levamisole and 23% of these had an increased number of ulcers. An important side-effect of Levamisole is a neutropenia which has been recorded predominantly in patients with rheumatoid arthritis receiving Levamisole daily. Although

neutropenia has not been found in patients with ROU receiving intermittent doses of 150 mg Levamisole for two days every week, nevertheless this complication must be borne in mind and monthly differential white blood counts carried out. Among the other less serious complications, a flu-like syndrome and urticaria may affect the patient. The mechanism of action of Levamisole in ROU is not known, but it is suggested that Levamisole may correct a deficiency of suppressor cells, or potentiate the cellular responses to cross-reacting microbial agents.

The apparent paradox that both immunosuppressive drugs (steroids) and immunopotentiating drugs (Levamisole and transfer factor) can be beneficial in the same disease may be interpreted by both types of drugs exerting immunosuppression as an end result, though through different pathways and subpopulations of lymphocytes. Levamisole may correct a deficiency of T suppressor cells, thus resulting in immunosuppression, whereas corticosteroids act directly on effector cells causing immunosuppression in addition to other functions.

Miscellaneous

A very small proportion of women have ROU which appear regularly before the onset of the menstrual period; in these cases treatment with ethinyl oestradiol 0.05-2 mg daily can suppress ulceration¹¹². In spite of expectations to the contrary, the contraceptive pill does not seem to improve these ulcers and in some patients it may exacerbate them.

Cromoglycate has been reported to be useful in two patients¹¹³, but in a double-blind trial of 15 patients it reduced only the pain and not the number of days with oral ulceration¹¹⁴. The author has not detected a beneficial effect from using cromoglycate in eight patients.

Chlorhexidine has been tried in a small double-blind trial and some improvement in ulceration has been reported¹¹⁵. Irrespective of the efficacy of chlorhexidine in ROU, patients with severe, continuous ulceration find it very difficult to maintain their oral hygiene, and may accumulate large deposits of bacterial plaque which may further aggravate oral ulceration. As chlorhexidine is effective in controlling bacterial plaque, mouthwashes used once or twice daily can be helpful, especially in patients who are unable to carry out routine oral hygiene.

Topical azathioprine has been tested in a double-blind trial using doses of 2 mg daily, but it was not found to be helpful¹¹⁶. It is not clear, however, whether a therapeutic dose had been achieved and, as the drug was tested for only two weeks, the assessment of the results is fraught with uncertainties.

The place for tranquillisers, such as chlordiazepoxide, in treatment of ROU is rather doubtful, and their use should be limited to patients having to cope with severe emotional problems. A number of proprietary preparations based on astringent, antiseptic, anaesthetic, and some anti-inflammatory functions are freely available and may give transient relief.

BEHÇET'S SYNDROME

All the topical therapeutic agents noted in ROU have also been used in BS with mucocutaneous manifestations. Systemic treatment of BS has to be resorted to, particularly in BS with neuro-ocular manifestations. However, as BS is not a common disease and shows marked fluctuation in its clinical

features, the results of treatment have been assessed on the basis of case histories and this is rather unsatisfactory.

Immunosuppressive and anti-inflammatory agents

Systemic corticosteroids have been commonly used and control the disease in some patients and not others. This is especially indicated with the neuro-ocular manifestations and remissions have been reported^{117,118}. However, there is little evidence that corticosteroids may prevent the development of neuro-ocular features.

Azathioprine¹¹⁹, cyclophosphamide^{120,121}, and chlorambucil¹²² have been used in a few patients and found to be beneficial, particularly in the management of uveitis.

Immunopotentiating agents

Transfer factor prepared from the leucocytes of unrelated blood donors has been effective in one patient with BS and one with ROU¹²³. Striking clearance of genital ulcers after 16 years of almost continuous ulceration was maintained for three years in one of two patients treated with 5 units of transfer factor¹²⁴, but the effect on oral ulcers was less convincing. Severe swelling of the entire arm has been recorded as one of the complications of using transfer factor in this disease¹²³.

Levamisole has also been used in BS and the response of the oral ulcers is similar to that found in ROU¹¹¹. The drug can be very effective in vulvo-vaginal ulcers, but it has not been tested in BS with neuro-ocular manifestations. It is possible that the beneficial effect from transfusion of fresh blood or plasma^{82,125} might also be due to an immunopotentiating effect.

Fibrinolytic deficiency

This deficiency has been described in plasma of patients with BS and there are reports that fibrinolytic drugs (Phenformin and ethyloestrenol) are helpful, especially in the presence of thrombophlebitis^{21,34,126,127}.

Haematological disorders

Isolated cases of anaemia have long been reported in ROU¹²⁸⁻¹³¹ but attempts to relate anaemia with ROU in systematic examinations of larger series have failed^{10,52,132,133}. Nevertheless, about 8% of patients referred to specialised stomatology clinics with ROU may have iron, folate, or B12 deficiency anaemias^{132,133}. As the ulcers may clear up with treatment of some of the iron deficiency and all of the macrocytic anaemias, routine haematological examination of these patients has to be carried out.

IRON DEFICIENCY ANAEMIA AND SIDEROPENIA

Systematic haematological examination in a series of 130 patients with ROU revealed only four patients (3%) with iron deficiency anaemia¹³² and in another series of 193 patients nine (4.7%) had iron deficiency anaemia¹³³. Whereas the prevalence of anaemia was comparable in these two series, the prevalence of sideropenia was three times greater in one series (18.6%)¹³³ than the other (6.1%)¹³². This might have been due to the high proportion of MjAU (22.3%) and Behçet's syndrome (8.3%) in the former series, but unfortunately the types of ulcers in the latter series were not given. A more

important difference was the success claimed in treatment with oral iron of all 15 patients with iron deficiency anaemia or sideropenia¹³², in contrast with the response of only eight out of 23 patients¹³³, six of whom were given oral iron and two had courses of 10 intramuscular injections of iron. However, only a formal double-blind trial of iron therapy in ROU can establish whether iron is beneficial in patients with iron deficiency, with or without anaemia. Routine administration of iron by the author over 10 years in patients with ROU and iron deficiency suggests that iron is beneficial only in a few selected patients. Nevertheless, iron should be given on general grounds, to correct the haematological deficiency, even if there is no improvement in the ulceration.

An alternative and more plausible interpretation of the high prevalence of sideropenia¹³³ is that iron is lost as a result of ulceration and the associated loss of epithelium^{134,135}. This hypothesis is consistent with the findings that the prevalence of sideropenia in ROU (20%) was identical with that found in other oral ulcers (20%), and both were significantly higher than those found in normal controls, or in another diseased control series of patients with non-ulcerating oral lesions¹³³. Furthermore, ranking of the oral ulcers in a descending prevalence of sideropenia seems to be associated with a descending order of severity of ulceration. This suggests that the more severe the ulceration, in terms of surface area, duration, and rate of recurrence, the more epithelium and therefore iron is lost and the more severe is the depression of serum iron. An alternative explanation is that the low serum iron concentration is due to the disease itself; sideropenia is a common finding in other chronic diseases.

FOLATE DEFICIENCY WITH AND WITHOUT ANAEMIA

Folate deficiency anaemia is also infrequent and was found in 4/130 (3%)¹³² and 4/193 (2.1%)¹³³ of patients with ROU. Folate deficiency was even less common, 3/130 (2.5%)¹³² and 3/193 (1.5%)¹³³, and is usually revealed in routine blood examination with macrocytosis and raised MCV. Although the number of patients with folate deficiency of $<3 \mu\text{g/l}$ is very small, most of those associated with other abnormal blood indices responded to administration of oral folate. There is no benefit from giving folate to unselected patients with ROU^{7,10} or to patients with folate levels in the equivocal range of 3-5 $\mu\text{g/l}$ and without macrocytosis¹³³.

It should be noted that nine of the 14 patients^{132,133} with folate deficiency, with or without anaemia, can be accounted for by malabsorption, mostly due to coeliac disease. Of the remaining five patients, two were epileptics taking the anticonvulsant drug primidone (Mysoline), which interferes with folate metabolism. Thus all but three patients with folate deficiency were accountable for by malabsorption or drug interference with folate metabolism.

VITAMIN B12 DEFICIENCY ANAEMIA

This is the least common haematological association with ROU; pernicious anaemia was found in 3/130 (2.3%)¹³², 1/193 (0.5%)¹³³ and latent anaemia in 1/130 (0.8%)¹³² and 2/193 (1%)¹³³ patients. Replacement therapy of vitamin B12 results in complete disappearance of oral ulceration, as long as the treatment is maintained, so that it is important to make the diagnosis.

COMPARISON BETWEEN HAEMATOLOGICAL DISORDERS IN ROU AND CONTROLS

The prevalence of anaemia and haematological deficiencies in ROU was

compared with three control groups consisting of patients with other oral ulcers, non-ulcerating oral lesions, and healthy subjects with no oral lesions (Table 5)¹³³. Folate and vitamin B12 deficiency with anaemia (2.6%) and without anaemia (2.5%) were not significantly greater in ROU than the three control groups. Although 5.1% of patients had macrocytosis, with or without anaemia, the diagnosis is an important one, as most of the patients respond to replacement of vitamin B12 or folate. The part that iron deficiency anaemia or sideropenia plays is much less certain, as they are commonly found in the control groups and only a small proportion of patients respond to treatment with iron. Furthermore, in a selected control group of 50 inpatients with macrocytic, microcytic, and normocytic anaemias only three had ROU at the time of examination, and three other patients gave a past history of ROU, so that anaemia does not appear to play a primary role in the pathogenesis of ROU¹³³.

A critical review of the clinical features of ROU secondary to haematological abnormalities suggests that, although they mimic ROU, there are many distinguishing features. The terminology of pseudo-minor, -major, and -herpetiform ulcers is applied to ulcers secondary to haematological abnormalities. The most important factors to be considered in the diagnosis of pseudo-MjAU are the greater prevalence in males, the very late age of onset, duration of each episode as well as total duration of ulceration, and associated general disease; laboratory tests are then used to confirm iron deficiency anaemia and sometimes malabsorption. Pseudo-MiAU and pseudo-HU can be differentiated from their classical counterparts by the shorter duration of each episode as well as the total duration of ulceration, depapillated tongue, associated general disease, dietary restrictions, or drugs interfering with metabolism and confirmed by laboratory tests showing macrocytic anaemia, B12 or folate deficiency, malabsorption, and a raised ESR.

CYCLICAL NEUTROPENIA

Neutropenia or agranulocytosis, secondary to bone marrow aplasia caused by some drugs or diseases, may result in oral and particularly pharyngeal ulcers. There are, however, severe systemic manifestations, with oral ulcers being of secondary importance.

In contrast, ROU can be the only clinical manifestation in cyclical neutropenia. ROU was reviewed in 25 patients with cyclical neutropenia¹³⁶; the

Table 5 Comparison between haematological disorders in recurrent oral ulcers, other oral diseases, and controls

	ROU		Other oral ulcers		Non-ulcerating oral lesions		No oral lesions	
	193 patients		80 patients		204 patients		100 subjects	
	(No.)	(%)	(No.)	(%)	(No.)	(%)	(No.)	(%)
Anaemia								
Iron deficiency	9	4.7	4	5	7	3.4	2	2
Folate deficiency	4	2.1	1	1.3	0		0	
Vitamin B12 deficiency	1	0.5	0		2	1	0	
Total	14	7.3	5	6.3	9	4.4	2	2
Deficiency								
Iron deficiency	36	18.6	16	20	18	8.8	5	5
Folate deficiency	3	1.5	3	3.8	1	0.5	0	
Vitamin B12 deficiency	2	1	0		2	1	0	
Total	41	21.1	19	23.8	21	10.3	5	5

ulcers resembled MjAU and showed a periodicity in parallel with the neutropenia. The neutrophil count fell to zero every 21 days, for three to four days and the ulcers recurred one day before the onset of the complete neutropenia. In a detailed haematological study of 20 patients with cyclical neutropenia, nine patients had ROU and in four patients oral ulceration was the sole clinical feature¹³⁷. A familial pattern was found in eight out of the nine patients with ROU.

The prevalence of cyclical neutropenia in ROU cannot be assessed but must be exceedingly low. The author has been unable to diagnose a new case during 10 years of awareness of the condition.

Gastroenteropathies

ROU has been reported in a variety of gastrointestinal diseases. However, few epidemiological studies have been carried out, to find out if any of the associations between ROU and a particular intestinal disease is significantly higher than would be expected from the prevalence of these diseases in the population.

COELIAC DISEASE

Oral manifestations have been recorded in coeliac disease, but in one series 90% of patients with idiopathic steatorrhoea had glossitis and some of these had ROU¹³⁸. However, examination of patients with ROU in gastroenterological departments revealed only one patient with steatorrhoea in a series of 120 patients⁷ and one among 52 patients².

In a recent investigation of 33 patients with MiAU (30) and MjAU (3), all of whom had jejunal biopsies taken, eight patients had a flat mucosa compatible with coeliac disease⁴³. When these eight patients were given a gluten-free diet their oral ulcers and intestinal symptoms disappeared and the haematological values in those with anaemia and folate deficiency were restored. The remaining 25 patients were also thought to have some immunological disorder, because the jejunal biopsies showed an increased number of plasma cells and decreased number of lymphocytes. These important observations need confirmation, for if there was no selection of their patients, the implications are that 24% of patients with ROU have coeliac disease. If one considers the lowest estimate of ROU in the population to be 10%⁷, and the estimates range up to 54%^{8,9}, then the prevalence of coeliac disease in this country would be 2.4%. This seems an extremely high estimate if one considers that the prevalence of coeliac disease is of the order of 0.05%¹³⁹.

Jejunal biopsies were examined in 15 patients with BS, all of whom had ROU and none showed atrophic villi¹⁴⁰; a marked lymphangiectasia was found in the lamina propria of four patients. Coeliac disease was found in five out of 130 patients with ROU (3.8%) in one series¹³², and in four out of 193 patients with ROU (2.1%) in another series¹³³. Although a systematic study of malabsorption has not been carried out in the latter series, all patients with diarrhoea and many with low serum folate and iron levels have been investigated by barium meal, jejunal biopsy, and estimation of faecal fat. It might also be relevant that, whereas HLA-B8 is found in 80% of coeliac disease^{141,142}, the prevalence of HLA-B8 in a series of 143 patients with ROU was significantly less (13.3%) than in a control group of 100 subjects (23%)⁹⁶. The doubts expressed about the true prevalence of coeliac disease in

ROU should soon be settled by jejunal biopsies in unselected series of patients with ROU. A preliminary investigation of 50 and 40 unselected patients with ROU independently at two centres revealed a flat jejunal biopsy in one patient in each series^{143,144}.

ULCERATIVE COLITIS

In a large series of patients with ulcerative colitis ROU was found in 51 out of 624 patients (8.2%) and it was the second most common complication¹⁴⁵. ROU recurred more frequently during severe attacks of colitis (25 patients) than with moderate (11 patients) or mild attacks (seven patients). As ROU affect at least 10% of the population, it has not been established if the association between ROU and ulcerative colitis is significantly higher than could occur by chance.

CROHN'S DISEASE

As in ulcerative colitis, oral lesions have been described in Crohn's disease and substantiated by biopsy examination showing granulomas with epitheloid cells and giant cells. This can be found in the mouth of patients with established Crohn's disease of the intestines¹⁴⁶⁻¹⁵¹ or the oral manifestation may be the presenting feature of the disease^{149,150}. The prevalence of oral ulcers in Crohn's disease has been estimated on the basis of a history of oral ulcers to be 6% (20/232 patients)¹⁴⁹. A comparable figure of 9% (9/100) was reached when oral manifestations of Crohn's disease were assessed in another series¹⁵¹. The clinical features to be considered are: (1) labial and facial swelling, (2) shallow, irregular, and often linear ulcers affecting the buccolabial mucosa or any part of the mouth, (3) granulomatous hypertrophic lesions often involving the buccolabial sulci, and (4) a cobblestone appearance of the buccolabial mucosa. Secondary oral manifestations of Crohn's disease are acute pseudomembranous candidiasis (thrush), angular cheilitis, and a sore, depapillated tongue. These features may well be related to the depressed serum iron and folate found in Crohn's disease.

The treatment of oral Crohn's disease, with or without the intestinal manifestations, is that used conventionally in this disease but, in addition to sulphasalazine (Salazopyrin), topical oral steroids are helpful. Iron and folate deficiencies should be corrected.

THOMAS LEHNER

*Department of Oral Immunology and Microbiology
Guy's Hospital Medical and Dental Schools
London*

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