

RECURRENT APHTHOUS STOMATITIS

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Of all the common illnesses of man few are as baffling to medical science as oral ulcers. Despite their high prevalence little is known about what causes them. Equally distressing to patient and physician is the lack of effective treatment or preventive measures. The Greek word *apthae* introduced by Hippocrates comes from two other words meaning "mouth ulcer" and "to set on fire". This is a most appropriate name for intense pain and burning sensation are some of the most characteristic symptoms of aphthous ulcer (Anon, 1965). Recurrent aphthous stomatitis (RAS) is a chronic inflammatory disease characterized by painful recurring ulcerations of the oral mucosa. Prevalence studies by Sircus *et al.* (1957) and Shapiro *et al.* (1970) indicate the incidence rate in a hospital to be 20% and Ship *et al.* (1960, 1961) found the incidence to be 60% among university students. RAS can be clinically subdivided into four varieties of recurrent oral ulcers.

MINOR APHTHOUS ULCER:

1 - 5 recurrent and moderately painful ulcers, which are less than 1.0 cm in diameter and affect the non-keratinized part of the oral mucosa (lips, cheeks, sulci, tongue and floor of the mouth) and last 4 - 14 days (Fig 1). The patients show a high incidence of antibodies to oral mucosa. The lesions pass through well recognised phases (Stanley, 1972; Reade and Hay 1978):

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Prodromal phase

(up to 24 hours). At the site which eventually becomes ulcerated, a tingling, burning, roughened or hyperanaesthetic sensation occurs with no clinical changes evident.

Pre-ulcerative phase

(18 hours to 3 days). A small erythematous macule or papule develops on the mucosa at the site of future ulceration. The region is slightly indurated, painful and eventually becomes surrounded by a dusky-red halo.

Ulcerative phase

(1 to 16 days). The central part of the erythematous lesion blanches and resembles a minute infarct. It eventually sloughs to produce a small shallow exquisitely painful ulcer which may continue to enlarge for 4 to 6 days.

Healing phase

(4 to 20 days). After a variable period of time the ulcers heal spontaneously without obvious scar formation. It is interesting to note for comparison that a single small traumatic ulcer of

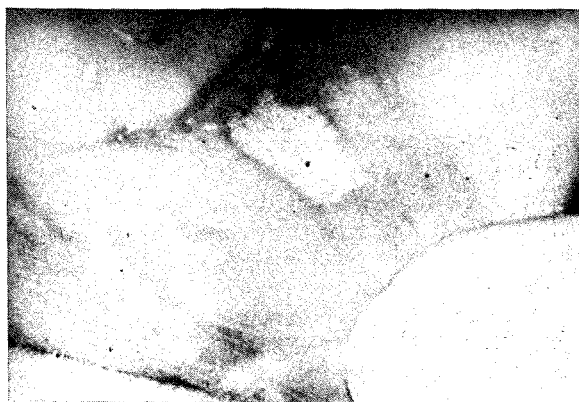


FIGURE 1 — Shows a minor aphthous ulcer on the lower lip.

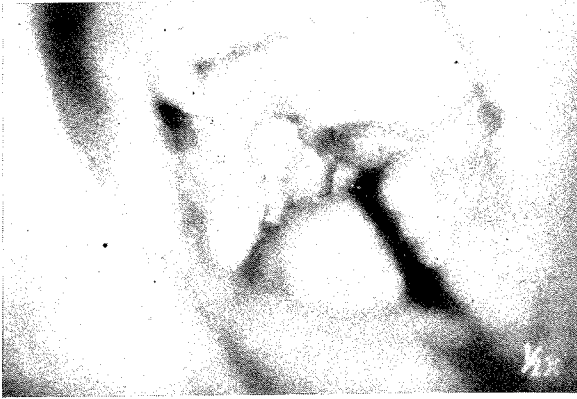


FIGURE 2 — Shows a major aphthous ulcer on the right side of the soft palate with evidence of severe scarring.



FIGURE 3 — Shows herpetiform ulcers on the tongue.

the oral mucosa heals completely in 3 to 4 days while minor aphthae often take more than twice as long.

Major Aphthous Ulcer

[Periadenitis Mucosa Necrotica Recurrens]:

1 - 10 very painful ulcers that measure more than 1.0 cm in diameter (De Meyer *et al*, 1977), recur at frequent intervals, affect the fauces and soft plate in addition to the sites of minor aphthous ulcers, last up to 6 weeks and leave a scar on healing (Fig.2). These patients show a high incidence of antibodies to oral mucosa.

Herpetiform ulcers:

Recurrent crops of up to 100 small and painful ulcers that may involve any part of the oral mucosa (Fig.3). The patients have a low incidence of antibody to oral mucosa.

Behcet's Syndrome:

Behcet's syndrome which was first described as a clinical entity by Behcet (1937), a Turkish dermatologist, is characterized by oral and genital ulceration and ocular inflammation. At least two of these major signs are customarily required to establish the diagnosis (Curth, 1946). There appears to be a greater incidence of Behcet's syndrome in the Middle East and Japan.

In a series of 85 patients examined by Oshima *et al*. (1963), 36 had the classical triad and the remaining 49 were partially affected. Oral ulcera-

tions were present in 98% of the patients and eye lesions occurred in 80% of the patients. Genital ulcerations were noted in 64% of the cases. In that series skin lesions were found in 84% of the patients, arthritis in 60% and gastrointestinal involvement in 60%. Neurologic involvement occurred in 20 to 50% of patients and the prognosis for these patients was poor; 65% dying within one year of the appearance of the neurologic lesions (Schotland *et al*. 1963).

Mason and Barnes (1969) reported a series of 25 patients with definite Behcet's syndrome. They divided the diagnostic criteria into major and minor criteria:

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|-------|---|--------------------------|
| Major | — | Oral ulceration |
| | | Genital ulceration |
| | | Eye lesions |
| | | Skin lesions |
| Minor | — | Gastrointestinal lesions |
| | | Thrombophlebitis |
| | | Cardiovascular lesions |
| | | Arthritis |

Central Nervous System
lesions

Family history

These authors suggested that to make a diagnosis of Behcet's syndrome a minimum of three major or two major and two minor criteria was required.

MATERIAL AND METHODS

This study was based on the records of the Department of Stomatology, Institute for Medical Research, Kuala Lumpur. The period of study was based from 1st July 1967 up to 30th June 1979. Only cases seen for the first time were included in the study. In all there were 134 patients consisting of 26 Malay males, 29 Malay females, 27 Chinese males, 17 Chinese females, 19 Indian males and 16 Indian females (Table 1). The male:female ratio was 1.2:1. Table II shows the distribution of the types of RAS by race and sex. Minor aphthous ulcer (63%) followed by major aphthous ulcer (29%) were the most frequent. Fourteen patients during the period of study developed two or more types of RAS.

DISCUSSION

Our group of patients was a highly biased sample for study for most of them were patients who were referred by practitioners who failed to register adequate response to treatment. As such very limited interpretations can be made. It has been estimated that approximately 2% of the patients with RAS present the more severe, chronic and persistent form of the disease (Stanley, 1973). It would therefore appear that the frequency of RAS in Malaysians may be as high as it has been reported in the literature. It can also be said that all the four variants of RAS are prevalent in Malaysians.

There is need for practitioners to be aware of the changing views on RAS so that more valuable studies can be carried out locally. Although isolation studies on the major and minor aphthous ulcers and Behcet's syndrome for a persistent or latent virus have been negative so far, these studies however cannot exclude a viral etiology. In fact the hypothesis of an infectious and viral etiology seems reasonable (Hooks, 1978). Treatment with tetracycline showed significant reductions in ulcer duration, size and pain. Tetracycline treatment apparently alters the seve-

Table 1

DISTRIBUTION BY AGE GROUPS, RACE AND SEX

AGE IN YEARS	MALAYS		CHINESE		INDIANS		TOTAL	PERCENTAGE
	M	F	M	F	M	F		
0 - 10	1	1	3	1	-	-	6	4.5%
11 - 20	3	5	3	1	3	3	18	13.4%
21 - 30	7	7	9	8	2	6	39	29.1%
31 - 40	8	8	8	4	4	2	34	25.4%
41 - 50	5	6	1	1	4	2	19	14.2%
51 - 60	2	2	1	-	5	2	12	9.0%
61 - 70	-	-	1	2	-	1	4	3.0%
71 - 80	-	-	1	-	1	-	2	1.5%
TOTAL	26	29	27	17	19	16	134	100.0%
PERCENTAGE	19.4%	21.6%	20.1%	12.7%	14.2%	11.9%	100%	

Male: female ratio
= 1.2:1

Male: female ratio = 1.2:1

Table II
DISTRIBUTION OF TYPES OF RECURRENT APHTHOUS
STOMATITIS [RAS] BY RACE AND SEX

TYPES OF RECURRENT APHTHOUS ULCERS	MALAYS		CHINESE		INDIANS		TOTAL	PERCENTAGE
	M	F	M	F	M	F		
1. Minor Aphthous Ulcer	16	19	17	14	13	14	93	62.8
2. Major Aphthous Ulcer	11	10	9	5	7	1	43	29.1
3. Herpetiform Ulcers	1	4	1	-	1	1	8	5.4
4. Behcet's Syndrome	-	1	-	1	2	-	4	2.7
TOTAL	28	34	27	20	23	16	148*	100%
PERCENTAGE	18.9%	23.0%	18.2%	13.5%	15.5%	10.8%	100%	

*Fourteen patients had two or more types of RAS during the period of study.

rity of the ulcer, but does not appear to affect those factors responsible for recurrences (Graykowski and Kingman, 1978).

A series of 330 patients with RAS were screened for deficiencies of iron, folate and vitamin B12. In 47 patients (14%) such deficiencies were found; 23 were deficient in iron, seven in folic acid, six in vitamin B12 and in addition 11 patients had combined deficiencies. The 39 patients with a proven nutritional deficiency who were available for follow-up showed a favourable response to corrective therapy; 23 showed a complete remission of ulcers, 11 were improved and 5 were not helped (Wray *et al.*: 1978).

Immunological factors play an important part in RAS. HLA markers seem to differentiate Behcet's syndrome from the other three clinical variants (ROU). Immune complexes have now been found in about 55% of patients with Behcet's syndrome and fewer patients with ROU so that the transition from the focal ROU to the multifocal Behcet's syndrome might be mediated by immune complexes. Immunopathological studies have shown that a vasculitis is the essential lesion in Behcet's syndrome and this

might be secondary to immune complexes inducing complement activation and damage. It is not clear at present whether the increased levels of C9 and C-reactive protein are a manifestation of acute phase reactants. C9 could be involved in complement dependent lysis and C-reactive protein in modulating the cell-mediated immune responses by its effect on T lymphocytes. It seems that at least two types of damaging immune mechanisms have been identified; cell-mediated and immune complex induced reactions and these might account for the association between ROU and Behcet's syndrome (Lehner, 1978).

Cohen (1978) had suggested that normal levels of antinuclear factors permit the suggestion that RAS is not an autoimmune disease arising from a central immunological fault but could be a local immune response against an antigenically altered mucosa. From these findings he postulated that the etiology of RAS is the result of diffusion of bacterial toxins, foods and other substances acting as allergens or haptens which initiate an immune response. These same substances could also react with epithelial cell surface antigens, producing a change resulting in an adverse inflammatory response. BenEzra and Nussenblatt

(1978) have suggested that Behcet's syndrome might be a sequence of events triggered by an interaction between a virus and specific receptors on the host cell membrane (HLA determined?). This initial interaction is followed by a malregulation of the host immune mechanism leading to autoimmune phenomena which are characteristics of the disease.

Recent studies on the value of levamisole in the treatment of RAS has been conflicting (De Cree et al, 1978; Drinman and Fischman, 1978; Gier et al. 1978; Kaplan et al., 1978; Kaplan et al., 1978; Miller et al., 1978; Olson and Silverman, 1978 and Sampson, 1978). The workshop committee on treatment of RAS (Graykowsky et al., 1978) has recommended that additional clinical trials with levamisole should be performed on small groups of patients with severe RAS. This committee recommended two treatment regimes for further clinical studies i.e. high and low dosage therapy. In addition in-depth studies of these patients with respect to the immunological effects of this drug are indicated. The studies should include assessment of B and T lymphocyte function and should be done before, during and after the course of therapy.

In conclusion it is worth emphasizing that in the differential diagnosis of RAS the following merit consideration - intra oral herpes simplex infection, erythema multiforme, erosive and bullous lichen planus, pemphigus vulgaris, cicatricial pemphigoid, bullous pemphigoid, herpangina, herpes zoster, cyclic neutropenia, Reiter's syndrome, discoid lupus erythematosus and hand-foot and mouth disease.

SUMMARY

Despite the high prevalence of oral ulcers little is known about what causes them and how best they can be treated. Recurrent aphthous stomatitis (RAS) is a chronic inflammatory disease characterized by painful recurring ulcerations of the oral mucosa. RAS can be clinically subdivided into four varieties viz - minor aphthous ulcer, major aphthous ulcer, herpetiform ulcers and Behcet's syndrome. A report on 134 patients with RAS is reported. Minor aphthous ulcer (63%) followed by major aphthous ulcer (29%) were the most frequent. A review of current research on RAS is summarized.

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