Recurrent aphthous stomatitis (RAS; aphthae; canker sores) is a common condition which is characterized by multiple recurrent small, round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors typically presenting first in childhood or adolescence. RAS occurs worldwide although it appears most common in the developed world. The aetiology of RAS is not entirely clear. Despite many studies trying to identify a causal microorganism, RAS does not appear to be infectious. A genetic predisposition is present, as shown by strong associations with genotypes of IL-1β; IL-6 in RAS patients, and a positive family history in about one-third of patients with RAS. Haematinic deficiency is found in up to 20% of patients. Cessation of smoking may precipitate or exacerbate RAS in some cases. Ulcers similar to RAS may be seen in human immunodeficiency virus disease and some other immune defects, and drugs, especially non-steroidal anti-inflammatory drugs and nicorandil may produce lesions clinically similar to RAS. Topical corticosteroids can often control RAS. However, the treatment of RAS remains unsatisfactory, as most therapies only reduce the severity of the ulceration and do not stop recurrence.

**Epidemiology**

Depending upon the group examined, RAS may affect 5–60%. In the USA the highest incidence (60%) was found in female student nurses, male student dentists (56%) and professional school students (55%). The lowest incidence (5%) was found in male hospital patients (Ship, 1972). 56% of Danish dental students (Donatsky, 1973) have had a history compatible with RAS. 46.7% of one group of dental patients in Thailand were found to have had RAS (Pongissawaranun and Laohapand, 1991).

Population studies have found RAS in about 2% of Swedish (Axell and Henricsson, 1985b), 1.9% of Spanish (Garcia-Pola Vallejo et al, 2002) and 0.5% of Malaysian (Zain, 2000) examined adults, although 17.7% of Swedish and 9.7% of adults in Ljubljana (Slovenia) (Kovac-Kovacic and Skaleric, 2000) have a history of possible RAS. RAS seems to be infrequent in Kuwaiti Bedouins (5%; Fahmy, 1976) and it has been found in only 0.1% of Indians in Malaysia (Zain, 2000). However, RAS may be especially common in North America (Embil et al, 1975).

There may be female predominance of RAS in adults (Ship, 1972; Fahmy, 1976; Axell and Henricsson, 1985b; Pongissawaranun and Laohapand, 1991; Donatsky, 1973; Kovac-Kovacic and Skaleric, 2000) and in children (Field et al, 1992; Kleinman et al, 1994). In the USA, white people are three times more frequently affected than black people (Kleinman et al, 1994).

In a population study about 1% of children in the USA were found to have recurrent oral ulcers (Kleinman et al, 1994), but about 35–40% may have a history of RAS-like disease (Miller et al, 1980; Kleinman et al, 1994), with ulceration beginning before 5 years of age [19.7% (Miller et al, 1980); 21.7% (Kleinman et al, 1994)] and the frequency of affected patients rising with age. However, a study of elderly dental patients in
Thailand found RAS in only 0.7% of persons over 70 years of age (Jainkittivong et al, 2002).

Children of higher socioeconomic status may be more commonly affected [21.4% (Axell, 1975; Axell and Henricsson, 1985b); 19% (Crivelli et al, 1988)] than those from low socioeconomic groups [5% (de Muniz et al 1981); 2% (Crivelli et al, 1988)].

**Aetiopathogenesis**

A genetic predisposition is present, as shown by an increased frequency of certain human leucocyte antigen (HLA) types, and a positive family history in some patients with RAS. Attempts to implicate a variety of bacteria or viruses in the aetiology have failed. Reactions to heat shock proteins (hsp) are one possibility: patients with RAS have circulating lymphocytes reactive with peptide 91–105 of hsp 65–60.

Haematinic deficiency is found in up to 20% of patients, cessation of smoking may precipitate or exacerbate RAS in some cases, and stress may underly RAS in some individuals. It has been suggested in some, but not all, studies that sodium lauryl sulphate (SLS), a detergent in some oral healthcare products may give rise to ulceration akin to that of RAS. Ulcers similar to RAS may be seen in human immunodeficiency virus (HIV) and some other immune defects, and drugs, especially non-steroidal anti-inflammatory drugs (NSAIDS) and nicorandil may produce lesions clinically similar to RAS in appearance, but not periodicity.

In RAS, microscopically, mononuclear (lymphocytic) cells begin to infiltrate the epithelium and oedema develops (Figures 1–3). This preulcerative stage is followed by an increase of pain and the development of a localized papular swelling because of keratinocyte vacuolization surrounded by a reactive erythematous halo representing localized vasculitis with a dense mononuclear cell infiltrate.

The painful papule then ulcerates and a fibrous membrane covers the ulcer which is infiltrated mainly by neutrophils, lymphocytes and plasma cells. Finally there is healing with epithelial regeneration and coverage of the ulcer.

The immunopathogenesis probably involves a cell-mediated immune response mechanism, and involves generation of T-cells and tumour necrosis factor alpha (TNF-α) by these other leucocytes (macrophages and mast cells) (Natah et al, 2000). The TNF-α cytokine, a major inflammatory mediator, induces initiation of the inflammatory process by its effect on endothelial cell adhesion and a chemotactic effect on neutrophils (Natah et al, 2000). Studies have shown that RAS can be prevented by treatments that prevent the synthesis of endogenous TNF-α such as thalidomide (Sampaio et al, 1991) and pentoxifylline (Natah et al, 2000).

Elevated levels of interleukin-2 (IL-2) (Sun et al, 2000) as well as those of TNF-α (Taylor et al, 1992) (both pro-inflammatory cytokines) and lower levels of IL-10 (an anti-inflammatory cytokine) (Buno et al, 1998) have been reported in lesional mucosa of RAS patients. IL-10 usually stimulates epithelial proliferation in a healing process therefore its low levels in RAS patients may delay epithelization and prolong the duration of the ulcers.

TNF-α also has some important immune regulatory activities including stimulation of class I major histocompatibility (MHC) expression. An increase in class I and class II MHC antigen expression has been detected in the basal epithelial cells in the preulcerative and ulcerative stages of the RAS lesion (Savage et al, 1986). As almost no MHC antigens were detected after healing (Savage et al, 1986), they probably play a role in the local tissue damage by targeting these cells for attack by cytotoxic T-cells (CD8+ cells) in the ulcerative process.

A markedly increased plasma level of IL-2 was recorded in the active stage of RAS (Sun et al, 2000). Natural killer (NK) cells activated by IL-2 may play a role in the process of this disease. An increased activity of these cells was noted in active lesions, diminishing during periods of remission (Sun et al,
1991). As NK cells are also associated with antiviral activity against varicella zoster virus (VZV) and cytomegalovirus (CMV) (Hayward et al, 1986), a viral antigenic source may be considered for RAS in some patients. Other studies, however, failed to demonstrate any significant difference in fractions of NK subsets between patients with RAS and controls (Pedersen and Pedersen, 1993).

Studies have shown circulating autoantibodies against the cytoplasm of autologous oral epithelial cells of RAS patients. Enhanced cytotoxic destruction of epithelial cells by TNF produced by peripheral blood mononuclear cells (lymphocytes) (Dolby, 1969) and leucocytes (Taylor et al, 1992) from RAS subjects was demonstrated by in vitro studies. As a similar enhanced cytotoxicity has been shown against a fibroblast cell line (Thomas et al, 1988), the damage to the underlying connective tissue may also be part of the pathogenesis of the disease.

Figure 2  Major aphthous ulcer, active phase (lower lip, HIV positive 44-year-old male). (a) Segmental arteritis deeply located beneath the ulcer. (b) Detail of arteritis, with occlusive thrombosis of the vessel lumen. (c) Recurrent major aphthous ulcer, cicatrical fibrous artery in scar tissue (58-year-old female)

Figure 3  Herpetiform ulcers (lower lip mucosa, 48-year-old female). (a) Small erosions and foci of heavy inflammatory exocytosis in the epithelium. (b) Polymorphous infiltrate and pyknotic neutrophils around occluded capillaries.
Genetic basis

At least 40% of RAS patients have a vague familial history of RAS (Sircus et al., 1957). It has been suggested that patients with a positive family history of possible RAS may develop oral ulcers at an earlier age and have more severe symptoms than affected individuals with no family history of oral ulceration (Ship, 1965). The probability of a sibling developing RAS may be influenced by the parents’ RAS status (Ship, 1972) and there is a high correlation of RAS in monozygote but not dizygote twins (Miller et al., 1977).

A variety of associations or non-associations with HLA antigens and RAS have been reported. An association with HLA-B12 was reported (Lehner et al., 1982; Malmstrom et al., 1983) but not confirmed by others (Gallina et al., 1985; Ozbakir et al., 1987). In groups of RAS patients of different ethnic origin a significant association between HLA-DR2 (usually in the haplotype HLA-DR2/B12) and RAS was observed, but the study groups were only comprised of a few patients (Lehner et al., 1982; Albanidou-Farmaki et al., 1988). In a study of Turkish patients with RAS the frequency of HLA-B5 was not significantly raised compared with healthy control subjects (Ozbakir et al., 1987). The frequency of HLA-DR4 was reduced in a cohort of Greek patients (Albanidou-Farmaki et al., 1988). In Sicilian patients with RAS the frequency of HLA-B5 was reduced, but HLA-DR7 was significantly increased (Gallina et al., 1985). A small study of 22 Israeli Arabs with probable RAS found a non-significantly raised frequency of HLA-B52 and B44 (Jaber et al., 2001). In some, but not all groups (Shohat-Zabarski et al., 1992), there may be a negative association of RAS with MT2 and MT3 (now HLA-DQ series). A comparison of HLA phenotypes of patients of Chinese origin established that the frequency of HLA-DR5; DRw8; Dwq1 were increased in mucocutaneous Behcet’s disease, compared with RAS as well as haplotypes DR5/DRw1 and DRw8/DRw1 (Sun et al., 2001). There would seem to be no consistent significant association between RAS and any particular serologically determined HLA antigen haplotypes except possibly HLA-B51 (Shohat-Zabarski et al., 1992).

The close association both of Behcet’s syndrome and RAS with HLA-B51 (Shohat-Zabarski et al., 1992) suggests a relationship in which this locus may not be the primary locus responsible – rather some other gene close to those controlling hsp and TNF (Mizuki et al., 1995). However no association was observed in polymorphism of TNFα, TNFβ or vitamin D receptor genes in a study of 95 white patients with RAS attending a clinic in London (Bazrafshani et al., 2002a) but a strong correlation was observed in the inheritance of an allele of interleukin-1 (IL-1β-51). In addition, the allele of IL-6-174 was strongly associated with RAS, this being greatest with α/α homozygosity. Other less strong associations occurred with IL-1RN-wNTR 1/1 homozygosity.

Such strong associations with these genotypes of IL-1β and IL-6 thus suggest that RAS does indeed have some sort of genetic basis (Bazrafshani et al., 2002b). It may be that an unopposed or excessive production of IL-1β or IL-6 (e.g. response to local trauma) may be pivotal to the development of RAS (see below).

There is evidence that patients with RAS have changes in cell-mediated immunity. Patients with RAS may have increased levels of peripheral blood CD8+ T lymphocytes and/or decreased CD4+ T lymphocytes (Bachtai et al., 1998; Sistig et al., 2002) although levels of total (CD3+) lymphocytes may be reduced (Sistig et al., 2002). There may be a reduced percentage of CD4+ (CD5+ 2H4T) ‘virgin’ T cells and an increased percentage of CD4+ (CD29+ 4B4+) ‘memory’ T lymphocytes (Pedersen et al., 1989). Patients with active RAS have an increased proportion of γδ T cells compared with healthy control subjects and RAS patients with inactive disease (Pedersen and Ryder, 1994). The γδ T cells may play a role in antibody-dependent cell-mediated cytotoxicity (ADCC), however, the exact stimulus for the increased generation of γδ T cells in RAS is unclear.

In contrast to peripheral blood there is a decrease in the number of mononuclear cells, including CD4+ and CD8+ T lymphocytes in the affected and non-affected oral mucosa of RAS patients (Hayrinen-Immonen et al., 1991). In the preulcerative phase of RAS there is a local mononuclear infiltrate consisting initially of large granular lymphocytes (LGL) and T4 (CD4+) helper-induced lymphocytes (Hayrinen-Immonen et al., 1991). The ulcerative phase is associated with the appearance of CD4+ cytotoxic suppressor cells, but these are replaced by CD4+ cells during healing (Savage et al., 1985). Polymorphonuclear lymphocytes (PMNL) also appear in the lesion (Figures 1, 2 and 3).

As noted above, there can be an increase in γδ T cells, important in ADCC. In vitro studies have indicated that peripheral blood leucocytes of patients with RAS may demonstrate increased cytotoxicity towards oral mucosal epithelium (Lehner, 1967; Dolby, 1969; Rogers et al., 1974, 1976; Greenspan et al., 1981; Burnett and Wray, 1985) or sheep red blood cells (Sistig et al., 2002), and it is thus possible that RAS may represent an ADCC-type reaction to the oral mucosa. This concept is supported by the knowledge that peripheral blood mononuclear cells of patients with RAS (but no active disease) lyse oral mucosal cells expressing class I and II MHC antigens. More importantly peripheral blood CD4+ T cells from RAS patients can also cause epithelial lysis (Savage and Seymour, 1994). It is thus feasible that CD4+ and CD8+ T cell mediated cytotoxic reactions occur in RAS.

The aggregation of lymphocytes is likely to be mediated by the adhesion molecules intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function-antigen-3 (LFA-3) binding to their counterpart ligands LFA-1 and CD-2 on lymphocytes (Hayrinen-Immonen et al., 1992; Verdickt et al., 1992). ICAM-1 is expressed on the submucosal capillaries and venules suggesting that it may control the trafficking of leucocytes into the submucosa (Savage et al., 1986; Eversole, 1994) while LFA-3 and its lingual counterpart CD-2 are likely to be involved in T-cell activation in RAS.
There is an elevation of serum levels of IL-6, IL-2R and soluble ICAM compared with controls, but these changes do not correlate with disease activity, and their pathogenic significance remains unclear (Yamamoto et al., 1994).

The HLA class I and II antigens appear on basal epithelial and perilesional cells in all layers of the epithelium in the early phases of ulceration (Savage et al., 1986) presumably mediated by interferon gamma (IFN-γ) released by T-cells. Such MHC antigens may target these cells for attack by cytotoxic cells: indeed, activated mononuclear cells infiltrate the epithelium, especially the prickle cell layer (Honma, 1976) and are in contact with apoptotic prickle cells, which they and neutrophils sometimes phagocytose (Honma et al., 1985). Factor XIIIa – positive (FXIIIa+) cells are present in significantly greater numbers in RAS lesions than traumatic ulcers (Natah et al., 1997). The FXIIIa+ cells are present in the mononuclear – rich inflammation cell infiltrate and perivascular areas of the RAS lesions. As FXIIIa cells are considered to have antigen presenting functions these observations do suggest that the pathogenic trigger of RAS may indeed be some as yet unknown local factor. A local trigger for RAS may also be suggested by the increased number of activated mast cells in RAS as compared with traumatic ulcers (Natah et al., 1998).

Although there are cell-mediated immune changes within RAS, a B lymphocyte-mediated mechanism involving ADCC and, possibly, immune complexes have also been observed. Although circulating immune complexes have not reliably been demonstrated in RAS (Levinsky and Lehner, 1978; Lehner et al., 1979; Burton-Kee et al., 1981; Bagg et al., 1987), immune deposits do occur in lesional biopsy specimens (Ullman and Gorlin, 1978) especially in the stratum spinosum (Schroeder et al., 1984) and there can be evidence of leucocytoclastic or immune complex vasculitis (Lunderschmidt, 1982; Schroeder et al., 1984) leading to the non-specific deposition of immunoglobulins and complement.

Serum immunoglobulin (Ig) levels are generally normal although increases in serum IgA, IgG, IgD and IgE have all been reported in different groups of RAS patients (Lehner, 1969a,b; Ben Aryeh et al., 1976; Scully et al., 1983). Normal or reduced immunoglobulin levels have been observed in other groups of RAS patients. Serum levels of C9 have been reported to be raised in some patients (Adinolfi et al., 1976; Lehner and Adinolfi, 1980) and, together with elevated serum levels of β2-microglobulin, (Scully, 1982) may represent a non-specific acute phase response. IgG subclass deficiencies were not observed in one study of UK patients with quiescent RAS (Porter et al., 1992b), but a significant reduction in IgG2 (important in bacterial immunity) was observed in a study of Spanish patients (Vicente et al., 1996). The IgG2 subclass deficiency may predispose to infection by (an unknown) bacteria and the resultant immune response raises IgG2 antibody levels. However, oral ulceration is not a common feature of patients with known IgG2 subclass deficiency and is uncommon in selective IgA deficiency – where IgG2 and IgG4 can predispose to significant bacterial infection (Porter et al., 1992b). Salivary levels of total IgA are not abnormal in RAS (Lehner, 1969b; Bennet and Reade, 1982).

In the ulcerative phase of RAS salivary levels of IgG1-4 as well as IgA1 and IgA2 may increase, but levels of IgA2, IgG1, IgG3 remain increased in the non-ulcerative phase of disease (Sistig et al., 2002). However, it remains unclear if such changes have any true bearing upon the pathogenesis of RAS. If local humoral immunity was to be of relevance to the development of RAS it would be expected that patients with xerostomia would develop RAS-like ulcers – but they do not.

Salivary prostaglandin E2 and epidermal growth factor (that may potentially aid mucosal healing) are reportedly reduced in the early stages of ulceration of RAS and then rise in the healing phase (Wu-Wang et al., 1995). A stage-dependent fall in salivary levels of vascular endothelial growth factor (VEGF) was also observed in patients with major (but not minor) RAS (Brozovic et al., 2002). It remains to be determined however, if the fluctuation in these potentially tissue-healing agents is of any true significance to the pathogenesis of RAS. It would seem more likely that these changes are merely the normal homeostatic response to the tissue damage of RAS. Such a notion would also explain the increase in levels of circulatory vascular cell adhesion molecule-1 (VCAM-1) and E-selectin (Healy et al., 1997) in patients with RAS.

The role of NK cells seems doubtful in the pathogenesis of RAS. In RAS levels of peripheral blood NK cells may be increased (Thomas et al., 1990) or similar to those of control subjects and NK subsets (e.g. CD16+ , CD56+ and CD14+) are not altered in RAS (Pedersen and Pedersen, 1993). Likewise the function of NK cells in RAS shows no consistent pattern, baseline NK cell function is not notably altered in RAS (Pedersen and Pedersen, 1993; Ueta et al., 1993), although may be reduced during exacerbation of major RAS, late ulcerative stage of minor RAS (Sun et al., 1991) or indeed during quiescent phases of disease (Sistig et al., 2002).

In contrast to Behcet’s disease, peripheral blood neutrophils of patients with RAS do not have any enhanced in vitro chemotaxis (Dagalis et al., 1987). Phagocytosis by neutrophils has likewise been reported to be not significantly defective, though one recent study reported that peripheral blood neutrophil haemotaxis and phagocytosis may be reduced in the ulcerative phase of RAS, although ingestion may be enhanced during the non-ulcerative phase (Sistig et al., 2002).

It is thus evident, that although there is no unifying theory of the immunopathogenesis of RAS, it would seem that the ulceration is because of the cytotoxic action of lymphocytes and monocytes upon the oral epithelium, but the trigger for these responses remains unclear. Patients with RAS may be liable to uncontrolled or excessive release of locally active inflammatory mediators, perhaps in response to local trauma (Bazrafshani et al., 2002a). Levels of IL-2, IFN-γ and TNF-α mRNA are raised in lesional tissue of RAS (Buno et al., 1998), while levels of IL-10 mRNA were
reduced in the normal mucosa of RAS patients when compared with that of control subjects. Local levels of IFN-γ are higher in the mucosa of RAS patients as compared with suitable controls, and in contrast IL-10 levels remain low in the former but not the latter. Local production of TNF-α is higher in RAS lesions than traumatic ulcers (Natah et al., 2000) and unstimulated peripheral blood leukocytes of patients with RAS produce much greater amounts of TNF-α than healthy controls (Taylor et al., 1992).

Microbial aspects of RAS

A local microbial basis for RAS might explain why only the oral mucosa is affected in patients with RAS. However, as there is no evidence of clustering of affected patients (other than via vague family associations), an infectious basis for RAS seems unlikely.

Oral streptococci were previously suggested as important in the pathogenesis of RAS, either as direct pathogens or as antigenic stimuli in the genesis of antibodies that may conceivably cross-react with the oral mucosa (Martin et al., 1979; Lindemann et al., 1985). An L-form streptococcus isolated from RAS patients was initially typed as S. sanguis (Barile et al., 1963) (but later this was found to be S. mitis (Hoover and Greenspan, 1983). While some studies have disclosed elevated serum antibody titres to viridans streptococci among RAS patients, other investigations have yielded contradictory results (Barile et al., 1968; Donatsky, 1976). Furthermore, lymphocyte mitogenic responses to S. sanguis and S. mitis in RAS patients are not significantly different from those in control subjects (Barile et al., 1968; Gadol et al., 1985; Greenspan et al., 1985), although this may simply indicate that there is no predominant cell-mediated pathogenesis to RAS.

Cross-reactivity between a streptococcal 60–65 kDa hsp and the oral mucosa has been demonstrated and significantly elevated levels of serum antibodies to hsp have been detected in patients with RAS (Lehner et al., 1991). Lymphocytes of RAS patients have reactivity to peptide 91–105 (Hasan et al., 1995), and there is a significantly increased lymphoproliferative response to this peptide in the ulcerative stage as opposed to the period of remission. There is some cross-reactivity between the 65 kDa hsp and the 60 kDa human mitochondrial hsp. As monoclonal antibodies to part of the 65 kDa hsp of Mycobacterium tuberculosis react with S. sanguis (Lehner et al., 1991), it has been suggested that RAS may be a T-cell mediated response to antigens of S. sanguis that cross-react with the mitochondrial hsp and induce oral mucosal damage (Hasan et al., 1995).

An association between RAS and Helicobacter pylori has also been suggested, but the evidence suggests such a link is unlikely. A study of 39 patients with both RAS and HIV disease found that 71.8% of samples of ulcers had polymerase chain reaction (PCR) evidence of local H. pylori carriage, and that 68.8% of the patients had circulating antibodies to H. pylori (Birek et al., 1999). In contrast no raised frequency of local carriage of H. pylori has been detected in four other studies of non-HIV infected individuals with RAS (Mravak-Stipetic et al., 1998; Pavelic et al., 2000; Shimoyama et al., 2000; Victoria et al., 2003) and no raised frequency of H. pylori seropositivity was observed in a study of patients from the UK (Porter et al., 1997).

It has been suggested that viruses may play a role in RAS (Hooks, 1978). An association with adenoviruses (Sallay et al., 1971, 1973, 1975) has been suggested, but these are ubiquitous organisms and the results need confirmation. The possible association of RAS with herpes viruses 1–6 has been reviewed (Pedersen, 1993). Herpes virus virions and antigens are not demonstrable in RAS (Dodd and Ruchman, 1950; Driscoll et al., 1961; Ship et al., 1961a; Griffin, 1963). RNA complimentary to herpes simplex virus (HSV) has been detected in circulating mononuclear cells (Eglin et al., 1982) and HSV-1 in circulating immune complexes (Hussain et al., 1986) in some RAS patients. However, serum levels of IFN-γ which tend to rise in viral infections, are not increased in RAS (Hooks et al., 1979). HSV has not been successfully isolated from leisonal material (Donatsky et al., 1977; Rothe et al., 1978), only about a third of RAS patients are HSV seropositive (Ship et al., 1967), and HSV is rarely detected in lesional tissue by PCR (Studd et al., 1991).

IgM and IgG antibodies to VZV may be elevated in some RAS patients (Pedersen and Hornsleth, 1993) suggesting an association between reactivation of VZV and RAS. Furthermore VZV-DNA can be detected in lesional tissue by PCR (Pedersen et al., 1993), but contamination is possible and may underlie these observations (Pedersen et al., 1993). The evidence on the potential therapeutic benefits of aciclovir also requires further investigation (Wormser et al., 1988; Pedersen, 1992).

Antibodies to CMV may be significantly elevated in some RAS patients (Pedersen and Hornsleth, 1993) and CMV-DNA has been detected in ill-defined oral ulceration in non-HIV-infected persons (Leimola-Virtanen et al., 1995). Additional support for a link with CMV was suggested by the detection of elevated levels of circulating antibodies to CMV in patients with RAS (Sun et al., 1996). However, CMV was not detected more frequently in RAS when compared with the titres in some of the same group of patients (Sun et al., 1996). Two further studies did not report an increased local carriage of CMV (as detected by PCR) in patients with RAS (Ghodratnama et al., 1997; Brice et al., 2000). Human herpes virus 6 (HHV-6) and HHV-7 DNA have not been demonstrated in RAS, but HHV-8 DNA is present in HIV-related oral ulcers (Di Alberti et al., 1998). However, the detection of herpes viruses in oral lesions may well not be of clinical relevance as these viruses are commonly latent, and can often be detected in oral fluids of even healthy individuals.

There are thus no definitive data to support the notion of RAS having an infectious aetiology. A viral cause seems unlikely. Current evidence suggests that cross-reactivity between bacterial heat shock proteins and epithelial components may play a role.
Local factors predisposing to RAS

Local, physical trauma may initiate ulcers in susceptible people (Ross et al., 1958; Wray et al., 1981) and RAS are uncommon where mucosal keratinization is present (Sallay, 1968; Banoczy and Sallay, 1969) or in patients who smoke tobacco (Brookman, 1960; Dorsey, 1964; Chellemi et al., 1970; Shapiro et al., 1970; Axell and Henricsson, 1985a; Salonen et al., 1990). A recent study of 34 patients in Turkey with minor and/or major RAS found a significantly reduced frequency of tobacco smoking in individuals with RAS compared with an appropriate control group (8.8% vs 25.2% respectively) (Tuzun et al., 2000). In an effort to correct for any error caused by the self-reporting of patients about their tobacco habits, cotinine levels of 84 UK patients with RAS were compared with a group of 81 control subjects. The study found that the frequency of tobacco smokers was significantly less in RAS than control group. In addition, the mean cotinine levels of RAS patients who smoked, was significantly less than that of healthy control smokers (Atkin et al., 2002). Of course it may be that these individuals who did smoke may be less psychologically stressed than those did not smoke and thus some psychological trigger may be at play.

An increased frequency of recurrent oral ulceration because of use of SLS-containing toothpaste was previously reported, together with some reduction in ulceration following the use of SLS-free toothpaste. This supposed adverse effect of SLS does not reflect any increased oral retention of SLS (Fakhry-Smith et al., 1997). However, while another study also suggested that SLS-free dentifrice might reduce the number of ulcers that patients with RAS might develop (Chahine et al., 1997), a large double-blind study did not observe any significant change in the frequency or severity of RAS (Healy et al., 1999). In view of the widespread use of SLS in dentifrices it seems unlikely that this agent truly predisposes to, or causes, most RAS.

Systemic factors predisposing to RAS

Most patients with RAS appear otherwise well. Oral ulceration similar in clinical appearance to RAS can arise in a number of disorders in which the patient has other systemic problems (Table 1). These include Behcet’s disease (Hoopen-Neumann et al., 1999; Krause et al., 1999; Whalley et al., 1999; Al-Otaibi et al., 2005); mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome (Orme et al., 1990; Le Thi et al., 1993; Sweet’s syndrome (acute febrile neutrophilic dermatosis) (Delke et al., 1981; Driban and Alvarez, 1984; Mizoguchi et al., 1988; von den Driesch et al., 1989; Bruyn et al., 1990; von den Driesch, 1994; Femanino et al., 2003a, b); cyclic neutropenia (Lange and Jones, 1981; Scully et al., 1982; Sucker and Diawari, 1999; Lubitz et al., 2001), benign familial neutropenia (Porter et al., 1994); a periodic fever with aphthae, pharyngitis and adenitis (sometimes termed PFAPA syndrome) (Marshall et al., 1987; Feder, 2000; Kawasaki et al., 2001) various nutritional deficiencies with or without underlying gastrointestinal disorders (Grattan and Scully, 1986; Eversole, 1994); and some other primary immunodeficiencies (Porter and Scully, 1993a–d) and secondary immunodeficiencies (Porter et al., 1994) including infection with HIV (MacPhail and Greenspan, 1997; Zakrzewska et al., 1997). Rarely, drugs such as NSAIDS can give rise to oral ulcers, similar to RAS, along with genital ulceration (Healy and Thornhill, 1995). Superficial ulceration similar to that of RAS can arise in response to nicorandil therapy (Cribier et al., 1998; Scully et al., 2001; Boulinguez et al., 2003). However, unlike RAS, this drug associated ulceration is not recurrent and resolves upon cessation of nicorandil therapy.

There is particular interest in the association between RAS and Behcet’s disease. RAS-like ulceration can occur in Behcet’s disease, however patients with the latter have multisystem disease, particularly affecting

<table>
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<th>Disease</th>
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<tr>
<td>Behcet’s disease</td>
<td>RAS-like ulceration is a cardinal feature of Behcet’s disease. The ulceration may be more severe, and more likely to comprise major and/or herpetiform ulcers from RAS. Patients with Behcet’s disease also have recurrent genital ulceration, cutaneous disease (usually papulopustular lesions or erythema nodosum), ocular disease (typically posterior uveitis) and a range of other gastrointestinal, neurological, renal, joint and haematological abnormalities.</td>
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<td>MAGIC syndrome</td>
<td>Comprises major aphthae and generalized inflamed cartilage. A variant of Behcet’s disease. Also termed acute neutrophilic dermatosis. Affected patients have superficial ulceration similar to RAS. In addition, there is sudden onset fever, leucocytosis and well demarcated cutaneous, plum-coloured papules or plaques. Usually arises in middle-aged females. In 50% of patients there is an associated malignancy (e.g. acute myeloid leukaemia).</td>
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<td>Sweet’s syndrome</td>
<td>Comprises periodic fever, aphthae like oral mucosal ulceration, pharyngitis and cervical adenitis. Although rare, PFAPA tends to occur in young children. Tends to be self-limiting, and non-recurrent. May respond to cimetidine (via suppression of T lymphocyte function).</td>
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<tr>
<td>PFAPA syndrome</td>
<td>Comprises periodic fever, aphthae like oral mucosal ulceration, pharyngitis and cervical adenitis. Although rare, PFAPA tends to occur in young children. Tends to be self-limiting, and non-recurrent. May respond to cimetidine (via suppression of T lymphocyte function).</td>
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<td>Cyclic neutropenia</td>
<td>Cyclic reduction in circulating levels of neutrophils about every 21 days. Affected patients develop oral ulceration, fever, cutaneous abscesses, upper respiratory tract infections and lymphadenopathy. Other oral complications include severe gingivitis and aggressive periodontitis. Treated with recombinant granulocyte colony stimulating factor (rG-CSF). Other neutropenias (e.g. chronic neutropenia) can give rise to superficial oral mucosal ulceration without any significant periodicity.</td>
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<td>HIV disease</td>
<td>Aphthous-like ulceration may occasionally arise in HIV disease. However, it remains unclear, if there is a significantly raised frequency of recurrent idiopathic oral ulceration in HIV disease.</td>
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other mucocutaneous surfaces, the eyes (e.g. uveitis), and musculoskeletal, neurological, haematological, gastrointestinal, and other systems. As detailed in this paper, RAS does not have a notable geographic distribution, has no HLA associations similar to those of Behcet’s disease and has few of the immunological abnormalities that arise in Behcet’s disease. Unlike Behcet’s disease, RAS does not lead to significant morbidity nor mortality (Mittal et al, 1985; Schreiner and Jorizzo, 1987; Arbesfeld and Kurbán, 1988; Jankowski et al, 1992; Stratigos et al, 1992).

Haematinic (iron, folic acid or vitamin B₁₂) deficiencies may be twice as common in some groups of patients with RAS as in healthy control subjects (Wray et al, 1975; Challacombe et al, 1977a, 1983; Hutcheon et al, 1978; Tyldesley, 1983; Rogers and Hutton, 1986; Field et al, 1987; Porter et al, 1988). About 20% of patients with RAS may have a haematinic deficiency, although one US study did not report any haematinic problem (Olson et al, 1982). A study of Japanese patients with RAS suggested that affected individuals may have reduced dietary intake of iron and vitamin B₁₂, which might underlie some of the aforementioned observations (Ogura et al, 2001). However, this investigation did not examine for correlations between dietary intake and haematologic evidence of deficiency.

A novel study of Indian patients reported a correlation between high nitrate concentration of drinking water, resultant increased blood cytochrome b₅ reductase activity, and susceptibility to recurrent episodes of ‘stomatitis’ (presumed to be RAS) (Gupta et al, 1999). The rationale for these associations was that excess oxidation of NADH would predispose to oral mucosal inflammation (Courtois et al, 1994).

Deficiencies in vitamin B₁ (thiamine), B₂ and B₆ were observed in 28.2% of a group of patients with RAS from Scotland (Nolan et al, 1991), but the cause of the deficiencies was never established, and it is interesting to note, that this group of workers found vitamin B complex deficiencies in other patients with quite disparate clinical disease. Low levels of thiamine were observed in substantial number of adult patients from Israel with RAS (Haisraeli-Shalish et al, 1996). The reasons why thiamine deficiency could cause RAS are not known.

Reduced iron storage is the most commonly reported relevant abnormality, arising in up to 37% of reported patient groups (Porter et al, 1988, 1993) and can affect children (Field et al, 1987) as well as adults. Vitamin B₁₂ deficiency has been observed in 1–6% of adults or children with RAS (Field et al, 1987; Porter et al, 1988, 1993; Barnadas et al, 1997; Weusten and van de Weil, 1998) in developed countries, but a more recent study observed low serum vitamin B₁₂ levels in about 23% of a group of teenagers and adults with RAS (Piskin et al, 2002). The reasons for such a high frequency of vitamin B₁₂ deficiency in this group of patients were not established.

The present evidence thus suggests that some patients with RAS may have deficiency of one or more haematinics, or occasionally an unrelated vitamin. That these deficiencies are truly important in the pathogenesis of RAS however, seems doubtful, as current data suggest that iron or vitamin supplement significantly only infrequently produce resolution of RAS (Nolan et al, 1991; Porter et al, 1992a; Haisraeli-Shalish et al, 1996).

Oral ulceration akin to RAS can be a feature of gluten sensitive enteropathy (GSE; coeliac disease) but only 5% of outpatients who initially present with RAS (Ferguson et al, 1976, 1980; Veloso and Saleiro, 1987; Nolan et al, 1991) have GSE. Folate deficiency can occur in RAS and reticulin antibodies (Ferguson et al, 1980) including IgA class reticulin antibodies (Merchant et al, 1986) and/or anti-gliadin antibodies (O’Mahony et al, 1985) are occasionally detected in patients with RAS. The haplotype of HLA-DRw10 and DQw1 has been suggested to predispose patients with GSE to RAS (Majorana et al, 1992; Meini et al, 1993), but this haplotype is not similar to the suggested HLA associations of RAS (see above). There may also be occasional patients who have RAS with no detectable clinical or histological evidence of coeliac disease on jejunal biopsy, yet who may respond to dietary withdrawal of gluten (Wray, 1981; Wright et al, 1986). However, the withdrawal of gluten does not often result in significant benefit (Hunter et al, 1993), may be difficult for the patient to comply with and may simply reflect the pronounced placebo response in RAS.

Hypersensitivity reactions to other identifiable exogenous antigens appear not to have a significant aetiological role in RAS. There is no consistent association with atopy (Tuft and Ettleson, 1956; Spouge and Diamond, 1963; Wilson, 1980; Eversole et al, 1982; Wray et al, 1982; Hay and Reade, 1984). Some RAS patients correlate the onset of ulcers with exposure to certain foods, but controlled studies have failed to disclose a causal role (Wilson, 1980) and dietary manipulation rarely produces clinical improvement (Spouge and Diamond, 1963; Eversole et al, 1982; Hay and Reade, 1984).

Aphthous-like ulceration can be a feature both of Crohn’s disease (Rehberger et al, 1998; Hegarty et al, 2003) and ulcerative colitis (Thornhill et al, 1992) but this ulceration may reflect associated haematinic deficiencies.

It is unlikely that an association between RAS and zinc deficiency exists, although one reported patient with RAS and zinc deficiency did have clinical benefit from zinc supplementation (Endre, 1991).

A minority of women with RAS have cyclical oral ulceration related to the luteal phase of the menstrual cycle, presumed progestogen driven defective oral mucosal epithelial turnover (Dolby, 1968; Segal et al, 1974; Ferguson et al, 1984). However, a detailed review of relevant data did not find any association between RAS and altered female sex corticosteroids (McCartan and Sullivan, 1992). It is of course possible, that occasional patients with RAS-like disease may have autoimmune progesterone dermatitis (Moghadam et al, 1998).

Psychological illness has been suggested to initiate some episodes of RAS (Ship et al, 1961b; Miller and Ship, 1977) but there has never been an appropriate study to
examine this possible link. A study of Irish patients with RAS, using the hospital anxiety and depression (HAD) scale, observed an increased level of anxiety (and increased salivary cortisol levels) in some patients (McCartan et al., 1996). There are sparse data to suggest that antidepressant therapy may lessen symptoms of RAS (Yaaacob and Ab, 1985). Nevertheless, no significant objective measure of neurosis has been observed in patients with RAS (Pedersen, 1989; Buajeeb et al., 1990).

**Clinical features**

RAS comprises recurrent bouts of one or several rounded, shallow, painful ulcers at intervals of a few months to a few days. RAS has three main presentations – minor (MiRAS), major (MaRAS) or herpetiform (HU) ulcers.

The MiRAS is the most common (Field et al., 1992), affecting about 80% of patients with RAS: ulcers are round or oval usually < 5 mm in diameter with a grey-white pseudomembrane and an erythematous halo (Figure 4). MiRAS usually occur on the labial and buccal mucosa and floor of mouth, but are uncommon on the gingiva, palate or dorsum of the tongue. The ulcers heal within 10–14 days without scarring.

Major RAS is a rare, severe form of RAS, sometimes termed periadenitis mucosa necrotica recurrens (Figure 5). These ulcers are oval and may exceed 1 cm in diameter and have a predilection for the lips, soft palate and fauces. The ulcers persist for up to 6 weeks and often heal with scarring. MaRAS usually has its onset after puberty and is chronic, persisting for up to 20 or more years (Scully and Porter, 1989).

Herpetiform ulceration is the least common variety and is characterized by multiple recurrent crops of widespread small, painful ulcers. As many as 100 ulcers may be present at a given time, each measuring 2–3 mm in diameter (Figure 6), although they tend to fuse producing large irregular ulcers. HU may have a predisposition for women and have a later age of onset than other types of RAS (Lehner, 1977; Scully and Porter, 1989).

**Management**

The diagnosis of RAS is invariably based upon the history and clinical findings. It is essential however to always consider a possible systemic cause, especially when adult patients suddenly develop what appears to be RAS. It is common practice to assess the full blood cell count, red cell folate and serum levels of ferritin (or equivalents) and vitamin B₁₂ (Porter et al., 1993). These investigations may also reveal potential gastrointestinal causes of oral ulceration but, in the absence of other manifestations, screening of patients with RAS for GSE is usually fruitless (Sedghizadeh et al., 2002).

There are currently few agents that have been found in randomized controlled trials (RCTs) to be clinically effective in the management of RAS. Nevertheless there is a need to provide patients with treatment to lessen the severity and/or frequency the associated painful symptoms, and reduce the likelihood of associated tissue damage. A wide variety of different agents have been suggested for the treatment of RAS (Table 2) (Porter and Scully, 2005). A consensus approach to the management of RAS was recently published (Scully et al., 2003). There is no curative treatment available. The best that can be achieved is to suppress the local immune
Topical corticosteroids

Topical corticosteroids are the mainstay of RAS treatment in most countries (Siegel, 1999), but there are few well-controlled studies. There is only one systematic review of aspects of therapy of RAS (Porter and Scully, 2005), showing topical corticosteroids to be the most frequent means of treating RAS, although the available data do not demonstrate consistent benefits.

The corticosteroids vary in their degree of potency and may be given as mouth rinses, ointments, creams or in adhesive vehicles. Several different topical corticosteroids may reduce symptoms and hasten healing of RAS (Cooke and Armitage, 1960; Zegarelli et al, 1960; Merchant et al, 1978; Yeoman et al, 1978; Fisher, 1979; Pimlott and Walker, 1983; Scaglione et al, 1985; Miles et al, 1993). The major concern of possible adrenal suppression with long-term and/or repeated application has rarely been addressed, although there is evidence that even some of the more potent, such 0.05% fluocinonide in adhesive paste and betamethasone-17-valerate mouth rinse do not cause this problem (Porter et al, 2000).

Cyclodextrin-based corticosteroid mouthrinses may be useful as corticosteroids are better released from the cyclodextrin preparations than from carboxymethylcellulose-based pastes (Holbrook et al, 1998). Topical clobetasol propionate 0.05% in an adhesive denture paste seems to be even more effective and does not cause adverse effects (Lo et al, 2001), however, some authors disagree (Gonzales-Moles et al, 2002). A 0.1% solution of mometasone furoate has been suggested as an effective treatment of RAS (Teixeira et al, 1999). However, corticosteroids applied topically do not stop the recurrence of RAS.

Other topical anti-inflammatory agents

Benzydamine
Benzydamine hydrochloride mouthwash may provide transient relief of painful symptoms but does not aid ulcer healing (Matthews et al, 1987) and is the only ‘over the counter’ topical agent (Edres et al, 1997) to have been formally assessed.

Amlexanox
Amlexanox has been suggested to be of some benefit in the treatment of RAS. Amlexanox has anti-allergic and anti-inflammatory activities, but its exact mode of action in the treatment of RAS remains unknown (Khandwala et al, 1997). One RCT of 335 patients with RAS in the US reported that 5% amlexanox significantly reduced the pain and time of healing. Other open studies have also suggested that amlexanox may result in some improvement in the signs and symptoms (Greer et al, 1993; Binnie et al, 1997; Khandwala et al, 1997).

Cromoglycate
Lozenges of the anti-allergic sodium cromoglycate may provide mild symptomatic relief (Dolby and Walker, 1975; Kowolik et al, 1978), but cromoglycate-containing toothpaste is not of benefit (Potts et al, 1984). In one double blind study carbenoxolone sodium mouthwash reduced the severity of RAS (Poswillo and Partridge, 1984).

Others
Topical non-corticosteroid based immunomodulatory agents which have been suggested to be of some benefit in the management of RAS include azelastine (Ueta et al, 2005).
et al, 1994), human alpha-2-interferon in cream (Ham-uryudan et al, 1990, 1991), topical ciclosporin (Eisen and Ellis, 1990), deglycurrhizinated liquorice (Das et al, 1989), topical 5-aminosalicylic acid (5-ASA; Collier et al, 1992), prostaglandin E2 (PGE2) gel (Taylor et al, 1993) and topical granulocyte-macrophage colony-stimulating factor (at least in HIV disease) (Herranz et al, 2000). However, few of these agents have been subjected to detailed clinical evaluation. Despite the knowledge that non-steroidal anti-inflammatory agents can cause oral ulceration, one study suggests that aspirin mouth rinse may reduce the pain of RAS (Angirish, 1996). A more detailed RTC observed that diclofenac in hyaluronate reduced the pain associated with RAS; indeed this preparation was more effective than lidocaine (Saxen et al, 1997).

In a double-blind study sucralfate mouth rinse was found to reduce the duration of pain and healing time of RAS (Ricer, 1989). A recent study of Italian patients suggested that 20% sucralfate is of some benefit in reducing the symptoms of RAS (Campisi et al, 1997).

A gel of silicone dioxide, aloe and allantoin – suggested to be useful in aiding wound healing – failed to significantly influence the clinical course of RAS (Garnick et al, 1998).

**Systemic immunomodulation**

Patients with especially frequent or severe RAS may require systemic immunosuppressive therapy.

**Corticosteroids**

Prednisolone (Stanley, 1973) and/or azathioprine (Brown and Bottomley, 1990) can help healing of large ulcers but their long-term use should be avoided as the risk of their many associated adverse systemic side-effects will usually outweigh any clinical benefit.

**Anti-TNF agents**

As TNF-α may be implicated in the pathogenesis of RAS (see above), it might be expected that anti-TNF-α agents could be beneficial in the treatment of RAS.

Results of limited open studies from two centres suggested that the anti-TNF-α agent pentoxifylline (400 mg three times daily) significantly reduced the number of RAS for up to 9 months after 1 month of therapy (Pizarro et al, 1995, 1996; Wahba-Yahav, 1995a,b). Nevertheless, this interesting carry-over effect was not confirmed in a more recent study (Chandrasekhar et al, 1999) and furthermore, about 10% of treated patients had some degree of gastrointestinal upset. Thalidomide is effective and is proven to be the most reliably effective agent for the management of RAS, producing remission in almost 50% (Revuz et al, 1990). Thalidomide probably acts by virtue of its anti-TNF-α actions but, in one study, the reduction in blood TNF-α levels did not correlate with ulcer healing (Jacobson et al, 1997), suggesting that thalidomide could also be acting via its action upon Th1/Th2 immune response and/or its anti-angiogenic properties (Porter and Jorge, 2002).

Open and double-blind studies on patients with HIV-related oral ulceration (Nicolau and West, 1990; Paterson et al, 1995), and non-HIV-related RAS (de Wazieres et al, 1999), and several case studies, confirm that thalidomide (e.g. 50–100 mg daily) is of clinical benefit (Mascaro et al, 1979; Grinspan, 1985; Grinspan et al, 1989). Nevertheless, its adverse effects seriously limit its application to short-term use. The main concern is the real risk of teratogenicity (just one tablet taken about day 20 of pregnancy can cause phocomelia) (Porter and Jorge, 2002), particularly as most females with RAS are of childbearing age. Polyneuropathy – typically a peripheral neuropathy, is an unpredictable but significant adverse effect of long-term thalidomide treatment, necessitating regular assessment of sensory nerve action potentials (SNAPs) (Porter and Jorge, 2002). Recently the risk of polyneuropathy has been shown to be minimal at doses below 25 mg day⁻¹ (Bastuji-Garin et al, 2002). Somnolence is common but can be reduced by dosing prior to sleep.

**Levamisole**

In the 1970s there was considerable interest in the possible benefits of levamisole in the management of RAS (Sun et al, 1994). The exact mode of action of levamisole remains unclear but the current data do not suggest this agent to be the clinical panacea once suggested. Five RCTs did not report a significant benefit with levamisole while four suggested that this agent might decrease the duration, number, size and frequency of ulceration of RAS. However the benefit, while statistically significant, was not likely to be of clinical significance, and the associated adverse effects (nausea, hyperosmia, dysgeusia and agranulocytosis) discourage its use (Lehner et al, 1976; Meyer et al, 1977; Drinnan and Fischman, 1978; Gier et al, 1978; Kaplan et al, 1978; Miller et al, 1978; Olson and Silverman, 1978). Levamisole combined with Chinese medical herbs has produced a decrease in the frequency, duration and number of oral ulcers (Sun et al, 2003).

**Colchicine**

Results of one open study and several smaller investigations suggested that colchicine may be of some clinical benefit in the management of RAS, causing a significant reduction in pain scores and frequency of self-reported ulcers (Gatot and Tovi, 1984; Ruah et al, 1988). It was suggested that colchicine shortens the recovery period of RAS by reducing neutrophil phagocytic function (Altinor et al, 2003). Unfortunately, not all patients benefit from colchicine, and at least 20% can have painful gastrointestinal symptoms or diarrhoea (Katze et al, 1994) and long-term use can induce infertility in young males. Combined colchicine and thalidomide therapy has been suggested to be of occasional benefit in the treatment of recalcitrant RAS (Genvo et al, 1984), although long-term therapy might be expected to give rise to clinically significant adverse side-effects.
Oral Diseases

**Antimicrobials**

**Chlorhexidine**

Despite there being no evidence that RAS is caused by any bacterial infection there are good data to indicate that some topical antimicrobials (particularly chlorhexidine gluconate) will lessen the duration of ulceration of RAS. Several RCTs have established that chlorhexidine either as a 0.2% w/w mouth rinse or a 1% gel can reduce the duration of ulcers and increase the number of ulcer-free days (Addy et al, 1974, 1976; Addy, 1977; Hunter and Addy, 1987) in patients with RAS. However, one study found little objective benefit of chlorhexidine mouth rinse over placebo (Matthews et al, 1987).

**Tetracyclines**

Placebo-controlled studies of topical tetracyclines (e.g. aureomycin, chlortetracycline and tetracycline) suggest that these may also reduce healing times and/or reduce the associated pain of RAS (Guggenheimer et al, 1968; Graykowski and Kingman, 1978; Denman and Schiff, 1979; Hayrinen-Immonen et al, 1994). An open study indicated that the local application of doxycycline under cyanoacrylate caused rapid healing of the ulceration of RAS (Ylikontiola et al, 1997). However this approach is of limited clinical application (dental professionals or patients have to apply the agent to the lesions) (Ludlow et al, 2000; Kutcher et al, 2001) and the other agents may cause dysgeusia, oral candidosis and a burning-like sensation of the pharynx, and/or are not suitable for young children who might ingest the antibiotic leading to later dental staining. One placebo-controlled study of 25 patients with RAS suggested that the oxygenating agent carbamide peroxide in glycerol was not effective in reducing the number of ulcers, relief pain and shorten the ulcerative phase. It has been suggested that tricosan has not only antimicrobial, but also anti-inflammatory and analgesic effects (Kjaerheim et al, 1995).

**Other agents**

Monoamine oxidase inhibitor (antidepressant) therapy in the treatment of three patients with RAS produced benefit (Rosenthal, 1984; Lejoe and Fourieste, 1985) but this may have been because of accompanying dietary modifications rather than any alteration in psychological status. The lack of association between significant mental illness and RAS suggests that therapeutic approaches of this type are likely to be fruitless.

There are reports that systemic zinc sulphate (Orbak et al, 2003), irsogladine maleate (Hara et al, 1999), *Eupatorium laevigatum* (Paulo et al, 2000) paste and photophoresis of oxolin ointment (Prikuls, 2000) may be of benefit in the treatment of RAS, but any real benefit from these agents is unclear.

**Physical treatment**

A range of physical methods of locally managing RAS have been proposed for the treatment of RAS, but most are impractical. Suggested physical therapies have included surgical removal, debridement or laser ablation of ulcers (Potoky, 1981; Howell et al, 1988; Convissar and Massoumi-Soureyy, 1992), low dense ultrasound (Brice, 1997) chemical cautery (Debacterol) (Rhodus and Bereuter, 1998) and the use of physical barriers such as cyanoacrylate adhesives (Yel et al, 1994).

**Conclusion**

Although common, RAS remains an elusive disorder, as the precise aetiology and long-term behaviour of disease are ill understood. No therapies are available to stop the bouts of ulceration and not give rise to adverse side-effects. The management of RAS is thus presently directed towards lessening physical trauma to the oral mucosa, and reducing the inflammatory response.

**References**


Recrurent aphthous stomatitis
S Jurge et al


