The patient, a 62 year old Japanese woman, had been suffering from RA since 1987. She was treated by gold thiomalate, bucillamine and salazopyrine without dramatic response. There were no rheumatoid nodules or signs of cutaneous vasculitis at that time. Laboratory data revealed an erythrocyte sedimentation rate of 54 mm/h (Westergren), C-reactive protein of 5.4 mg/dl and positive rheumatoid factor (1:840 in RAHA test). Low dose corticosteroid therapy was started, and the response was moderate. MTX therapy was initiated in 1989, and the patient eventually responded to a weekly dose of 7.5 mg. Eighteen months after starting MTX, multiple painful nodules ranging from 5–15 mm in diameter gradually appeared and increased in number in the digits and soles. An infarcted area was observed in the centre of the nodules. Nailfold thrombi and periungual erythema were both present. However, no signs of visceral vasculitis or Raynaud’s phenomenon were observed. The biopsy specimen demonstrated small vessel obstruction as a result of fibrin thrombi and perivascular infiltration of neutrophils, lymphocytes and histiocytes, compatible with leukoclastic vasculitis. Granulomatous lesions with palisading layer were also observed. Immunohistochemical analysis revealed that ICAM-1 was strongly expressed in vascular endothelial cells of the vessels with pathological features of leukoclastic vasculitis (fig 1A). Some of the mononuclear cells around the vessels also reacted with anti-ICAM-1 antibody. Both VCAM-1 and ELAM-1 were faintly but exclusively expressed in the endothelial cells. IL-1, IL-6 and TNFα were identified in endothelial cells and cells in the palisading layer. Reverse-transcription polymerase chain reaction (RT-PCR) using primers for either inflammatory cytokines and adhesion molecules revealed that there was strong ICAM-1 mRNA expression together with upregulated expression of TNFα and IL-6 in the sample (fig 1B). IL-1 mRNA expression was extremely low. Both VCAM-1 and ELAM-1 mRNAs were more weakly expressed than that of ICAM-1. These data clearly indicated that MTX-induced nodulosis originated from inflammatory vascular lesions. We have already reported that significant amounts of IL-1 and TNFα were produced from rheumatoid nodules. In this sense, the pathophysiology of rheumatoid nodules and those induced by MTX may be quite similar. Augmented production of inflammatory cytokines in situ can cause upregulation of ICAM-1 on vascular endothelial cells, resulting in further recruitment of mononuclear cells, although an initial event that triggers endothelial cell injury remains to be clarified in MTX-induced nodulosis. At present we do not know how MTX induces nodulosis, as MTX itself did not directly stimulate the expression of either inflammatory cytokines or adhesion molecules of vascular endothelial cells and synovial cells in vitro in our preliminary experiments (data not shown). It is obvious, however, that MTX-induced nodulosis is a dose-dependent phenomenon.  

Susceptibility to MTX-induced nodulosis might be related to genetic factors, as most of the reported cases have had HLA-DR. Further study is necessary to elucidate the pathogenesis.

**Effect of milk product deprivation on spondyloarthropathy**

Certain fecal gram negative bacteria have been incriminated as provocative agents in the pathogenesis of ankylosing spondylitis and related spondyloarthropathies (SA)\(^1\). Despite ultra high temperature, milk and milk products might still contain bacterial fragments\(^2\) which could play an allergenic or activating role on the immune system.

An attempt was therefore made to show whether in SA a diet where patients were told to exclude milk, cheese, yoghurt, ice cream and butter, could exert a beneficial effect on the course of the disease.

Twenty five outpatients with SA and 10 with RA according to the ESSG and ACR criteria\(^3\) \(^4\) were enrolled in this study\(^2\) \(^3\) (they were paired for sex, age, duration of disease).

All patients complained of morning stiffness over 30 minutes, inflammatory low back pain and/or multiple joint swelling (at least one joint in SA).

Eighty five patients with SA and seven of 10 with RA also needed nonsteroidal anti-inflammatory drugs (NSAIDs). Some patients (7/25 SA and 4/10 RA) were receiving salazopyrine or methotrexate for more than six months. At each visit (after six weeks, three, six and nine months) the patients were asked the following questions about changes (worse, unchanged, better by comparison with the enrollment visit):

1. How do you feel?
2. What is the severity of your pain?
3. What is the duration of your morning stiffness?
4) How are your articular symptoms? (joint swelling, stiffness, tendinitis).

5) Did you modify your NSAID regime? (mean, unclear, reduced/discontinued).

6) Do you consider that the effect of the diet justifies continuing it?

When at least 4/6 variables were improved or positive, and none deteriorated the therapeutic effect was considered as good, and when 2/6 were improved and none deteriorated, as moderate. The compliance to the diet (poor, questionable or good) was assessed from the questions to the patient.

In the subgroup results at six weeks (table 1) showed a relatively good compliance to the diet (18/25). When patients were questioned about its benefit, 13/25 reported good efficacy (no precise symptom was more sensitive), and 4/24 a moderate improvement; among the good responders, 8/13 could discontinue their NSAID therapy. Conversely, despite good compliance, no patients with RA improved at six weeks or could reduce NSAID, and they all decided to discontinue the trial.

When follow up of the 17 SA responders was carried out, 12/15 were still satisfied and kept up the diet at three months, 10/10 at six months, and 9/10 at nine months. Our longest follow up is now over two years; six patients are still observing the diet and remain free from any other therapy; interestingly, none reported discomfort or frustration with the diet even for the longest duration.

No association between response and variables such as sex, age, axial versus peripheral involvement, enthésopathies, sacroiliitis, HLA-B27, entérocolitis, genito-urinary or cutaneous symptoms, duration and type of disease could be demonstrated. According to some patients, psoriatic lesions remained unchanged but the number of such patients was rather low.

In summary, this study indicated that more than half of the patients with SA felt a subjective improvement of their symptoms with a diet without milk products; they felt better, pain was reduced, morning stiffness improved, joint and spine symptoms got better, NSAID consumption was reduced and a large number of patients agreed to continue the diet for a longer period. So far, prolongation of its heterogeneous subgroup of responders could not be further characterised.

Benefit to the patients appeared within six weeks and most of the responders decided to keep up the diet for months or years. Interestingly, three patients reported a transient relapse of their complaints within a few days when there was a relapse in the diet and one patient on the diet was free of recurrent episodes of uveitis for over two years.

Yet before interpreting these data, one should be aware of the numerous biases: small, heterogenous and not randomised groups, subjective evaluation of efficacy, diet without excluding all milk products, no control diet, subjective measures of outcome and compliance, and in addition the course of SA which can be spontaneously favourable.

A placebo effect is present in this study; yet a high proportion of SA responders – in contrast to RA patients – continued the trial for a relatively long period of time and in the six weeks period for analysis, NSAID and salazopyrine/methotrexate could be discontinued in respectively 8/10 and 3/3 patients. The reasons for possible benefit from the diet remain unclear. Digestion is capable of producing a hypersensitivity reaction and certain associations between connective tissue diseases and food (ingredients) have been proposed. Approximately one third of SA patients “believe” that certain foods can increase morning stiffness, pain and swelling. A diet free of dairy products could modify the content of the intestinal flora and consequently reduce the proliferation of pathogenic bacteria. Some gram negative bacterial fragments could persist despite the ultra high temperature processing of milk. Alternately, a chronic intestinal allergy to milk products could contribute to the gut permeability alterations in SA.

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MATTERS ARISING

The relationship between rheumatoid arthritis and bronchiectasis

We enjoyed the recent article by McMahon et al which attempted to rationalise the relationship between rheumatoid arthritis (RA) and bronchiectasis. There is now good evidence that bronchiectasis is associated with RA and this paper brings the important hint that gastrosesophageal reflux and bronchiectasis in patients with bronchiectasis and RA may be more pronounced than in those with bronchiectasis alone. The reason for this remains unclear but the suggestion that it may be mediated by the presence of secondary Sjogrens syndrome was novel. However, we would like to provide two items of evidence which appear to make this theory less tenable.

1) Neither physiological nor pathological studies of the airways of patients with primary Sjogrens syndrome (PSS) have we found evidence of bronchiectasis, although high resolution computed tomography (HRCT) demonstrated bronchiolar infiltrates in 30% of PSS patients complaining of dyspnoea. Of more direct relevance we have recently completed a HRCT study of 40 patients with RA, 10 of whom had evidence of bronchiectasis.4 Schirmer’s tear tests were measured in all patients and abnormal results were found in 60%. Using the same criteria as McMahon et al we found 18 of 30 patients with RA without bronchiectasis and 10 of 10 RA patients with bronchiectasis to have 5 mm or less wetting from either eye over five minutes. Thus we have been unable either to demonstrate the presence of bronchiectasis in patients with PSS, or to show a relationship between Schirmer’s tear test results and the presence of bronchiectasis in RA patients. The difference between our results and those of McMahon et al may be explained by the relatively low percentage of RA patients without bronchiectasis (controls) with an abnormal Schirmer’s tear test in their study (22%). This is lower than found in their patients with pure bronchiectasis and may represent an underestimate of the true value.

We conclude that the case for Sjogrens syndrome contributing to the development of bronchiectasis in patients with RA remains at best unproven.

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Author’s reply: We thank Drs Kelly and Gardiner for their interest in our paper and for their informed comments on our hypothesis that elements of Sjogrens syndrome may account for the link between RA and bronchiectasis. We acknowledge the limitations of inferring a diagnosis of Sjogrens syndrome from a Schirmer’s test and that the small numbers of patients involved make confident
Effect of milk product deprivation on spondyloarthritis.

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