LETTERS TO THE EDITOR

Cytokines in rheumatoid arthritis

Sir: In a recent interesting article Westacott *et al* reported on concentrations of the five cytokines interleukin 1 β , interleukin 2, tumour necrosis factor α , interferon gamma and alfa in synovial fluids from patients with rheumatic diseases.¹ As is common in such studies, patients with rheumatoid arthritis were compared with those with osteoarthritis and other arthritides. As previously reported by some but not all investigators, Westacott *et al* found significantly increased concentrations of interleukin 1 β and significantly decreased concentrations of interleukin 2 and tumour necrosis factor α as well as tendential decreases of interferons alfa and gamma in rheumatoid arthritis compared with osteoarthritis.¹ Although osteoarthritis is not a systemic inflammatory disease, osteoarthritic synovial fluids are of course not normal, and one cannot therefore be completely certain that the differences between osteoarthritis and rheumatoid arthritis are of relevance to pathophysiological processes in rheumatoid arthritis. What made the study of Westacott *et al* especially interesting in this respect was the unusual inclusion of synovial fluids from two non-arthritic subjects, which were also shown to contain lower concentrations of interleukin 1 β than rheumatoid synovial fluids, but higher concentrations of the other cytokines measured.

We recently completed a study of cytokine concentrations in synovial fluid, in which we measured interleukin 1 β , tumour necrosis factor α , and interferon gamma (using commercially available assay kits from the same sources as Westacott *et al*) and tried to obtain values for 'normal' controls by aspirating synovial fluid from knee joints of cadavers not known to have had rheumatic disease. Data from the cadavers were then compared with those from patients with rheumatoid arthritis with the results shown in the table.

The differences between results in patients with rheumatoid arthritis and in cadavers were all significant ($p < 0.001$, Mann-Whitney U test). These results are therefore consistent with the limited data of Westacott *et al* whose two non-arthritic synovial fluids contained < 20 pg/ml of interleukin 1 β , but 11 and 16 U/ml of interferon gamma, and 1.3 and 1.4 ng/ml of tumour necrosis factor α .¹ The concentrations of the last two cytokines were higher than in osteoarthritis, but still lower than in our cadavers, possibly reflecting the fact that the controls of Westacott *et al* did in fact have swollen knee joints.¹

Although these results confirmed the correlation of interleukin 1 concentrations with disease activity in rheumatoid arthritis, they suggest that a rethinking of the role of the 'inflammatory' cytokines tumour necrosis factor α and interferon gamma in the pathology of joint destruction in rheumatoid arthritis may be necessary. In contrast, these data might rather suggest that a relative lack of these cytokines is associated with the disease process, and, further, imply that therapeutic interventions aimed at increasing tumour necrosis factor α and interferon gamma concentrations may be more appropriate than those aimed at decreasing them. This would be consistent with some reports showing decreased interferon gamma and tumour necrosis factor α production in patients with rheumatoid arthritis³ and the possible therapeutic benefit of interferon gamma treatment,⁴ as well as the fact that antirheumatic drugs may stimulate immune responses rather than inhibiting them, even to the extent of enhancing interleukin 2 production.⁵

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Sir: The novel study by Pawelec *et al* of cytokines in synovial fluids from non-rheumatic cadavers seems to corroborate our measures of cytokine concentrations in synovial fluids from healthy subjects using the same methods. The subjects in our study, however, although showing no clinical signs and symptoms of arthritis, provided fluid far in excess of the microlitre volumes usually available for aspiration from normal knee joints. For this reason we were reluctant to call the fluids 'normal'. Similarly, synovial fluid

from cadavers is likely to contain serous exudate together with molecules released from dead and dying cells and is therefore hardly representative of normal synovial fluid. Although these two data sets are intriguing in their comparability, whether they are meaningful in terms of control for disease activity is open to conjecture. By comparing one disease group with another, however, our study did show distinct differences between cytokine patterns in inflammatory disease and those in non-inflammatory disease. In osteoarthritis tumour necrosis factor α concentrations were indeed significantly higher than those in rheumatoid arthritis and apparently correlated with patient age ($n = 24$, $r = 0.56$, $p = 0.007$). In addition, examination of synovial fluids from patients with evidence of osteophytosis, as judged by x ray evidence of bony increase, showed that interferon alfa and gamma concentrations were significantly higher than in fluids from patients without osteophytosis ($p < 0.01$; $p < 0.05$).

In rheumatoid fluids the significantly higher concentrations of interleukin 1 β were found to correlate with x ray evidence of bone destruction ($r = 0.33$). In sequential samples in this study some patients had increases in interleukin 1 β concentrations accompanied by decreases in interleukin 2 and tumour necrosis factor α , thereby substantiating the suggestion that a lack, rather than excess, of certain cytokines may contribute to the pathology of inflammatory arthropathies. The converse situation was apparent in many cases, however, while in other patients no distinct pattern between cytokines emerged. Great variation in cytokine measurement was apparent not only between patients but between fluids taken at different clinical appointments from the same patient, and probably, therefore, the concentration of one particular cytokine is less important than the balance between them.

Owing to the many and varied interactions between cytokines, as well as between cytokines and other molecules, only by studying longitudinal cytokine data in sequential samples and attempting to relate the findings to clinical evidence of disease activity will it be possible to clear up the controversy about the role of the so called inflammatory cytokines. It would therefore seem inappropriate at the present time to place too much significance on high or low concentrations of particular cytokines.

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Comparison of data from cadavers with those from patients with rheumatoid arthritis. Results are given as means (SD)

Cytokine	Patients with rheumatoid arthritis	Cadavers
Interleukin 1 β (pg/ml)	193 (57)* (n=26)	<20 (n=14)
Interferon gamma (U/ml)	<1* (n=26)	38.8 (13.8) (n=17)
Tumour necrosis factor (ng/ml)	0.17 (0.04)* (n=27)	2.89 (0.89) (n=18)

* $p < 0.001$, Mann-Whitney U test for results in patients *v* cadavers.

Munchausen's syndrome simulating reflex sympathetic dystrophy

Sir: The case report on Munchausen's syndrome, which was published recently in the *Annals*,¹ illustrates the confusion in conceptions and terminology inherent in many cases of reflex sympathetic dystrophy. The clinical presentation with marked demineralisation on radiography and increased articular uptake by technetium-99m bone scan is to paraphrase

the authors 'indistinguishable from reflex sympathetic dystrophy'. It is therefore illogical to suggest that the condition is a 'mimic of reflex sympathetic dystrophy' rather than a genuine case of 'traumatic self induced reflex sympathetic dystrophy'. Certainly, the clinical criteria fulfil Kozin's 'probable category'—that is, symptomatic pain and swelling with observed swelling²—and the bone scan changes are classical for reflex sympathetic dystrophy using either Kozin's criteria or the more comprehensive criteria of Demangeat (acute stage I category).³ Incidentally, the bone scan figure in the article is incorrectly labelled—the early blood pool phase is b and the late bone phase a.

Part of the confusion in diagnosis of reflex sympathetic dystrophy relates to expecting a 'full house' of symptoms and signs in every case and this is due to a poor understanding of the epidemiology—that is, the limits of clinical expression. Central to this process is a basic understanding of the sympathetic nervous system's involvement in somatic pain.

Involvement of the sympathetic nervous system is common in many pain states (somatosympathetic responses)^{4, 5} and readily demonstrated with medical thermographic imaging and triple phase bone scan.^{2, 6} Thomas *et al* in a recent study comparing medical thermal imaging and triple phase bone scan in 50 patients with chronic limb pain and variable clinical expression of sympathetic disease showed abnormalities in 74% with medical thermal imaging and in 68% with triple phase bone scan.⁶ Many studies correlating clinical presentation with medical thermal imaging changes confirm Chard's observation that pain and vasomotor changes may be the only manifestation of reflex sympathetic dystrophy.⁷

Also, in the present case (after viewing the blood pool scan changes) I believe that significant thermal abnormalities would have been detected with medical thermal imaging. A more useful terminology, rather than the term reflex sympathetic dystrophy, is sympathetically related pain state (SRPS), which has two subdivisions: (a) sympathetically maintained pain (SMP)—that is, pain relieved by sympathetic blockade, implying that sympathetic efferent activity causes pain, and (b) sympathetically associated pain (SAP)—that is, pain that is not relieved by sympathetic blockade because sympathetic activity is not causal but is a response to the pain. This terminology excludes the confusion when sympathetic blockade fails to relieve what seems to be a classical case of reflex sympathetic dystrophy. It correctly focuses treatment on pain and anxiety in cases of sympathetically associated pain, where sympathetic manifestations resolve once causative factors have been eliminated. This was well shown in this case.

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Sir: I thank Dr Thomas for the interest that he has shown in our paper. I agree with the interesting comments that he made about the involvement of the sympathetic nervous system in some pain states, based on evidence from medical thermographic imaging and triple phase bone scan. We must not forget, however, that both techniques only reflect circulatory or metabolic alterations and not direct injury of the sympathetic nervous system, which could only be shown by electrophysiological studies. To our knowledge these studies do not exist in reflex sympathetic dystrophy, but undoubtedly they would be revealing.

It is obvious that the patient whose case we reported fulfils the reflex sympathetic dystrophy diagnostic criteria of Kozin, Daman-geat, and other experienced authors.¹ Even so, as we mentioned in the discussion, the patient presented characteristics ruling out a typical shoulder-hand syndrome (absence of cyanosis and hyperhydrosis, shoulder not affected, prolonged duration, and rapid healing after suppression of the causal agent), and for this we prefer to use the term 'mimic'. In our view this case is an example of the conceptual, terminological, and diagnostic confusion that exists around reflex sympathetic dystrophy that we have already mentioned on other occasions² and that Dr Thomas has alluded to.

(As Dr Thomas notes, in fig 3 the bone scan phases were incorrectly labelled. Additionally, fig 2 should show the left hand affected rather than the right.)

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Rheumatoid factors and the disease state in rheumatoid arthritis

Sir: I read with interest the paper by Jones *et al*¹ on the reactivity of rheumatoid factors with IgG of various species; and, in particular, their finding that in solid phase capture assays rheumatoid factors specifically bind human and baboon IgG but not the IgG of other subhuman primates.

In a study carried out in our laboratory some years ago² we modified the standard Waaler-Rose haemagglutination method of assaying rheumatoid factor by using sheep red cells sensitised with a subhuman primate IgG antibody. This would show a greater degree of immunochemical cross reactivity with human IgG than does rabbit IgG antibody customarily used for this purpose, and would

therefore permit the use of the system in the inhibition-agglutination mode for the study of the interaction of rheumatoid factors with human IgG isotypes and their enzymatic cleavage fragments. We chose to produce IgG antibodies against sheep red cells in baboons for two reasons—firstly, because we were using these subhuman primates at the time in other investigations in the allergy field and, secondly, radioimmune inhibition studies³ had shown a high degree of cross reactivity between the IgG of this species and human IgG heavy chain.

When sheep red cells sensitised with baboon instead of rabbit IgG were used it was possible to show inhibition-haemagglutination by human myeloma proteins of the IgG1, IgG2, and IgG4, but not the IgG3 isotype, nor rabbit IgG; while heat aggregated forms of all four human IgG isotypes were inhibitory. We also found that aggregated baboon IgG, unlike aggregated rabbit IgG, possessed inhibitory activity comparable to that of aggregated human IgG in this system.

In summary, our findings from that early study of the inhibition of haemagglutination by rheumatoid factors of sheep cells coated with baboon IgG are very much in line with the results now reported by Jones and colleagues obtained by more modern solid phase capture assay systems.

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Sir: We were very interested to read Dr Stanworth's comments on our recent paper.¹ Stanworth's original work,² which we admit should have been quoted in our paper, clearly showed that baboon IgG and human IgG, compared with IgG of other species, are the preferred antigens for rheumatoid factors. Using our solid phase capture assay we were also able to show that human IgG and baboon IgG are the preferred antigens for rheumatoid factors. We feel it would be worthwhile comparing the sequences of both baboon and human IgG with those of other species of IgG so as to disclose common epitope between the human and baboon IgG which may be missing from the IgG of other species. Any common sequences between human and baboon IgG could then be synthesised as a putative antigen for rheumatoid factors.

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