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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- Westacott C I, Whicher J T, Barnes I C, Thompson D, Swan A J, Dieppe P A. Synovial fluid concentration of five different cytokines in rheumatic diseases. *Ann Rheum Dis* 1990; 49: 676-81.
- Eastgate J A, Wood N C, Di Giovine F S, Symons J A, Grinlinton F M, Duff G W. Correlation of plasma interleukin 1 levels with disease activity in rheumatoid arthritis. *Lancet* 1988; ii: 706-9.
- Franchimont P, Reuter A, Vrindts-Gevaert Y, *et al*. Production of tumour necrosis factor- α , interferon-gamma and interleukin-2 by peripheral blood mononuclear cells of subjects suffering from rheumatoid arthritis. *Scand J Rheumatol* 1988; 17: 203-12.
- Cannon G W, Pincus S H, Emkey R D, *et al*. Double-blind trial of recombinant gamma-interferon versus placebo in the treatment of rheumatoid arthritis. *Arthritis Rheum* 1989; 32: 964-73.
- Oben J A, Wallace G R, Chain B M, Foreman J C. The stimulation of IL-2 production by anti-rheumatic drugs. *Immunology* 1989; 67: 328-32.

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