Cytokines in rheumatoid arthritis

Sir: In a recent interesting article Westacott et al. reported on concentrations of the five cytokines interleukin 1β, interleukin 2, tumour necrosis factor α, interferon gamma and alfa in synovial fluids from patients with rheumatic diseases. 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 1β and significantly decreased concentrations of interleukin 2 and tumour necrosis factor α in 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 1β, 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 1β, but 11 and 16 U/ml of interferon gamma, and 1.3 and 1.4 ng/ml of tumour necrosis factor α. The concentrations of these two cytokines were higher 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.

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 arthritis and the possible therapeutic benefit of interferon gamma treatment, as well as the fact that antirheumatic drugs may stimulate immune responses rather than inhibiting them, even to the extent of enhancing interferon production.

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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 osteoporosis, 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 osteoporosis (p = 0.01; p = 0.05).

In rheumatoid fluids the significantly higher concentrations of interleukin 1β 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 1β 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 interleukin 1β measurements is 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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Munchausen's syndrome simulating reflex sympathetic dystrophy

Sir: The case report on Munchausen's syn- drome, which was published recently in the Annals, suggests the confusion in concep- tions 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