The role of T cells in rheumatoid arthritis

Sir: Dr Gaston presented a scholarly review of current publications on the role of T cells in chronic rheumatoid synovitis.1 We would like to comment briefly on a few aspects of his editorial. It is interesting to see how the view of T cells in the rheumatoid joint has evolved over the past decade. In the mid-1980s it was assumed that T cells churned out lymphokines like interferon and interleukin 2 in the joint, and that in situ expansion of antigen specific T cells in synovium accounted for the plethora of T cells in synovial tissue. Only a few people would argue today with the fact that T cell products are, in fact, quite difficult to find in rheumatoid articular samples. Our current understanding of T cell recruitment and retention through non-antigen related adhesion molecules like selectins and integrins also suggests that the accumulation of CD4+ memory T cells in rheumatoid synovium is not due to local proliferation but is a direct reflection of local cytokine action on vascular endothelial cells and other interstitial cells. The simple T cell model of the past decade has been replaced by a far more complex paradigm that includes cytokine networks, activated mesenchymal cells, and possibly activated T cells responding to either an aetiological agent or perhaps a host of 'irrelevant' antigens. Hence, one of the major goals of the autocrine/paracrine model proposed in 1990 has been achieved—namely, to encourage people to think critically about the interpretation of data on soluble mediators in the joint.2

As Dr Gaston points out, we have always maintained that T cells might have a critical role in the initiation of rheumatoid arthritis, though we would have argued that this aspect from major histocompatibility complex (MHC) associations. An alternative view of these findings could be that the specific MHC molecules associated with rheumatoid arthritis result in a 'hole' in the T cell repertoire as the MHC clearly has a major role in thymus selection of the T cell repertoire. In a retrovirus mediated disease it would not be difficult to envisage that susceptible subjects lack the appropriate T cells to respond adequately to the infecting agent, as opposed to the traditional view that the MHC contributes to the disease by permitting specific autoimmune antigens to be presented to the appropriate T cells. With regard to the relative lack of T cell cytokines in rheumatoid arthritis being consistent with other immune responses, we would be wary of that conclusion. It is probably true that relatively small numbers of activated lymphocytes and small amounts of lymphokines can orchestrate inflammation and exuberant monocyte production. For instance, the insulins in NOD mice seems to be accelerated by antibodies to interferon γ, even though very little interferon γ is produced.3,4 However, in many other cases T cells in antigen specific processes express cytokine genes, and their products are easy to detect. In our own laboratory we have shown that granulocyte-macrophage colony stimulating factor (GM-CSF) is a major product of airway T cells in allergen induced asthma but have been unable to show any GM-CSF production by synovial T cells in rheumatoid arthritis.3,5 Interferon γ and mRNA are abundant in tuberculous pleurisy, a disease that all would agree has a significant T cell component.6,7 We would caution against dismissing evidence strongly implicating low T cell lymphokine production is 'typical' of antigen mediated processes and continue to await more definitive proof of T cell activation in rheumatoid arthritis. Furthermore, it is not even established that T cell factors such as interferon γ are detrimental in rheumatoid arthritis, and we have recently treated several patients with single or multiple intra-articular injections of recombinant interferon γ and have seen no evidence of flare (unpublished data).

Our current view of rheumatoid synovitis is more eclectic than the simple cytokine network proposed in 1990. Even though the data implicating T cells in chronic disease are unequivocal, we are now faced by a deeply rooted (almost religious) sense that T cells must be doing something in the joint because they are there in such abundance. Our more recent evidence, such as the four-axis network, involving macrophages, fibroblasts, and T cells, each of which is 'talking to the others and contributing to the perpetuation of the disease. While we understand the language in the first two, we have not yet established how (or even if) the T cells communicate with their neighbours. While we would happily embrace significant new data that would help resolve this conundrum, we expect that this approach will have significant therapeutic impact, as already a variety of specific and potent anti-T cell strategies have had rather disappointing clinical results—for example, anti-CD4, anti-CD5, anti-CD7, or CAMPATH-1 antibodies, interleukin 2/diphtheria toxin fusion proteins, and total nodal irradiation. Hence we encourage others to maintain a healthy measure of skepticism about the 'religion' of T cells until more data are available.

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Occurrence of arthritis in hyperimmunoglobulinemia D

Sir: We were interested by the brief report of Loeliger and colleagues on arthritis in hyperimmunoglobulinemia D.1 They report on four adult Dutch patients whose febrile attacks of the hyperimmunoglobulinemia D syndrome were accompanied by genuine arthritis. Their observation, however, indicating that arthritis should be incorporated within the clinical spectrum of the disease, is noteworthy.

In 1983 Prieur and Griselli described eight cases with juvenile onset of periodic fever and joint disease.2 All patients had lymphadenopathy, splenomegaly, skin lesions, and demonstrated leukocytosis with a neutrophilia and a raised erythrocyte sedimentation rate with attacks. Repeating antigenic triggers as a cause of the fever were ruled out. The attacks in the eight patients (six women, two men) were treated with the recurrent transient symmetric arthritis. The articular manifestations of these patients appeared only two to 13 years after the onset of the periodic fever. Clinical and radiological follow up showed no signs of residual joint disease in this group, emphasising the difference of joint manifestations when compared with systemic onset juvenile chronic arthritis. Laboratory analysis in all displayed a constant, raised serum IgD level typical for the hyperimmunoglobulinemia D syndrome.

More recently, Hiemstra et al described clinical and immunological studies in a group of eight children with hyperimmunoglobulinemia D syndrome and mentioned arthritis as a phenomenon of the disease.3 Furthermore, an immunological study in five children with the syndrome clearly referred to the occurrence of arthritis from the larger joints as a part of the clinical picture.4 As emphasised by Prieur and Griselli, it is important in children to differentiate between arthritis due to the hyperimmunoglobulinemia D syndrome and that in the systemic type of juvenile chronic arthritis.5 Indeed, besides arthralgias/ arthritis, these patients may present with recurrent intermittent fever, lymphadenopathy, organomegaly, and an evanescent maculopapular rash.6 Contrary to the hyperimmunoglobulinemia D syndrome cardio-pulmonary complications, such as pericarditis and pleuritis, were not observed in the systemic onset juvenile rheumatoid arthritis.7 A register of classifying criteria facilitating the diagnosis of systemic onset juvenile chronic arthritis has been recently published.8 Loeliger et al1 rightly emphasized the occurrence of arthritis as a symptom during febrile attacks of the hyperimmunoglobulinemia D syndrome.9 Their observations on the clinical manifestations of the disease, however, have been reported previously.

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