MATTERS ARISING

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 γ 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 The simple T cell model of the past decade has been replaced by a far more complex paradigm that includes cytokine networks, activated mesenchymal cells, and possibly activated T cells responding to either an aetiological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 there have been few data to support this apart 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 inciting agent, as opposed to the traditional view that the MHC contributes to the disease by permitting specific arthritogenic 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 monokine production. For instance, the insulinitis in NOD mice seems to be ameliorated by antibodies to interferon γ , even though very little interferon γ is produced by islet T cells.³ 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.^{4,5} Interferon γ protein 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 assuming that low T cell lymphokine production is 'typical' of antigen mediated processes and continue to await more definite proof of T cell activation in rheumatoid arthritis. Furthermore, it is not even established that T cell factors like 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 circumstantial, we too are influenced 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 paradigms have suggested a three-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 of 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 do not 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, -CD5, -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 hyperimmunoglobulinaemia D

Sir: We were interested by the brief report of Loeliger and colleagues on arthritis in hyperimmunoglobulinaemia D.¹ They report on four adult Dutch patients whose febrile attacks of the hyperimmunoglobulinaemia D syndrome were accompanied by genuine arthritis. Their observation, however, indicating that arthritis should be incorporated within the clinical spectrum of the syndrome, is not unique.

In 1983 Prieur and Griscelli described eight cases with juvenile onset of periodic fever and joint disease.² All patients had lymphadenopathy, splenomegaly, skin lesions, and demonstrated leucocytosis together 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 associated with 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 hyperimmunoglobulinaemia D syndrome.

More recently, Hiemstra *et al* described clinical and immunological studies in a group of eight children with hyperimmunoglobulinaemia 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 Griscelli, it is important in children to differentiate between joint disease in the hyperimmunoglobulinaemia D syndrome and that in the systemic type of juvenile chronic arthritis.² Indeed, besides arthralgias/arthritis, these patients may present with recurrent intermittent fever, lymphadenopathy, organomegaly, and an evanescent maculopapular rash.⁵ Contrary to the hyperimmunoglobulinaemia D syndrome cardiopulmonary complications, such as pericarditis and pleuritis, occur frequently in systemic onset juvenile rheumatoid arthritis.⁶ A register of classifying criteria facilitating the diagnosis of systemic onset juvenile chronic arthritis has been published recently.⁵

Loeliger *et al* rightly emphasise the occurrence of arthritis as a symptom during febrile attacks of the hyperimmunoglobulinaemia D syndrome.¹ Their observations on the articular manifestations of the disease, however, have been reported previously.

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Buerger's disease and antiphospholipid syndrome

Sir: Casellas *et al* reported a patient in whom arterial occlusions were found in association with anticardiolipin antibodies.¹ The authors discussed the diagnosis of Buerger's disease (thromboangiitis obliterans) and the relation with the antiphospholipid syndrome.

Buerger's disease is an uncommon vasculitis of unknown cause, in which tobacco is implicated. Diagnosis is difficult because clinical, anatomopathological, and arteriographic features are not specific. Cell mediated sensitivity to collagen was reported to be helpful in diagnosis,² but was not specific.³ Several diagnostic criteria have been proposed.⁴ Adar and Mozes suggested that positive and negative criteria might be used for diagnosis.^{2,5} Thus these authors considered that other causes of arterial occlusions, such as coagulation disorders, systemic diseases, or embolism, rule out the diagnosis of Buerger's disease.²

The patient described by Casellas *et al* presented with repetitive intrauterine fetal deaths, mild thrombopenia, and a significant level of anticardiolipin antibodies without evidence of systemic lupus erythematosus. A diagnosis of primary antiphospholipid syndrome could be made. The major arterial lesions of the patient were in agreement with those now well recognised in the antiphospholipid syndrome.⁶⁻¹⁰ The range of histopathological changes seen in antiphospholipid arterial vasculopathy is quite different from changes in Buerger's disease.¹⁰ The acute lesions of Buerger's disease are associated with an intense mixed cell inflammatory infiltrate. This is not present in patients with antiphospholipid vasculopathy, in whom thrombosis appears at various stages of thrombus organisation, and not vasculitis.⁹

We conclude that the patient described by Casellas *et al*, even if she fulfilled the criteria

of probable Buerger's disease according to McPherson, should not be considered to have this disease. The negative criteria of Adar and Mozes should be taken into account, thus preventing overdiagnosis of Buerger's disease and avoiding the risk of misdiagnosis of a more common and curable disease and delay of urgent specific treatment.

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AUTHORS' REPLY: Puéchal *et al* suggest that the patient we described recently in the *Annals*¹ had primary antiphospholipid syndrome (PAS) rather than Buerger's disease.

The authors adduce histological differences between these two conditions: in Buerger's disease the primary lesion is vasculitis, whereas in PAS it is thrombosis. Although correct, this fact does not exclude, in our opinion, a possible association: it is theoretically possible that vasculitis, by causing endothelial cell damage, might have triggered the reaction of antiphospholipid antibodies with negatively charged phospholipids on these cells, as described by Alarcón-Segovia *et al*.²

Puéchal also suggests, based on the negative criteria of Adar and Mozes,³ that diagnosis of another associated disease should exclude Buerger's disease. The paper published by Adar was designed to examine the 'possible relationship between Buerger's disease and atherosclerosis by clinical and radiological analysis of young patients with ischaemic disease of the lower extremities'. Patients with evidence of embolism, trauma, or collagen disease were excluded from the study group, but, in our opinion, these diseases were not defined as negative criteria for the diagnosis of Buerger's disease. A clinical diagnosis of Buerger's disease was

made by Adar when, in addition to ischaemic manifestations in the legs, two or more of the following systemic manifestations were present: migrating phlebitis; vasospastic elements—such as Raynaud-like phenomena—in hands or legs, or both; and ischaemic manifestations in the arms.

Although there were grounds for diagnosing Buerger's disease in our patient in accordance with McPherson, we did in fact point out in our paper that the clinical picture might be attributed entirely to PAS. However, given the possible association, we tested 13 patients diagnosed in our hospital as having Buerger's disease over the past three years for the presence of antiphospholipid antibodies; these were absent in all cases. Although this suggests that these two conditions are not related, further studies are needed to confirm this. Otherwise there will be a risk of failing to establish a possible, though unlikely, association between two conditions of as yet unknown cause.

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LETTERS TO THE EDITOR

Erythema induratum and pulmonary tuberculosis

Sir: Erythema induratum, first described by Bazin in 1861,¹ is an uncommon inflammatory skin disease pathologically characterised by nodular vasculitis.² Erythema induratum occurs mainly in women and features recurrent, painful, subcutaneous nodules generally found on the lower legs, which usually deteriorate in winter.² A direct correlation with *Mycobacterium tuberculosis* infection has been found. Rarely, however, an active tuberculous focus has been reported.³ On the other hand, it is well known that mycobacterial infections can be associated with raised titres of rheumatoid factor (RF).⁴ Recently, we studied a woman with erythema induratum who had high levels of RF and active pulmonary tuberculosis. After specific chemotherapy the skin lesions disappeared and RF fell to normal.

A 35 year old woman was referred to the rheumatology unit of this hospital because of