Author's reply

We were interested to read Dr Stanworth's letter, in which he recalled his thoughts in the 1970s about the mechanism of action of d-penicillamine and his more recent experiments on the IgA-α, anti-trypsin complex. Dr Israel Jaffe, very reasonably, had suggested that his studies of perivascular-arterial injection of penicillamine, that this drug degraded IgM rheumatoid factor (IgM RF) by sulphydryl reduction of the IgM RF molecule. We are uncertain that this was the mechanism because we reasoned that the therapeutic effect should occur more rapidly than the several months required if a simple chemical reduction of IgM RF took place. It seemed to us that it was more likely that the delayed onset of clinical improvement was associated with a gradual change in the cellular immune response in the synovial membrane due, perhaps, to a progressive inactivation of a crisis factor or factor playing a part in this response. We reasoned that this should be reflected in a gradual fall in the titre of rheumatoid factor. The fall in titre might not necessarily be the reason for the joint improvement but, rather, an associated change.

It was for this reason that we decided to measure the titres of IgM RF over time in patients receiving penicillamine. It turned out that there was a gradual fall over a period of months. As pointed out by Dr Stanworth, in subsequent experiments carried out in collaboration with Dr Jaffe, our laboratory showed that there was no correlation between RF titre and clinical improvement in patients treated with penicillamine. Similar results have been reported by several other groups. In later experiments carried out in Dallas Olsen et al noted a correlation between spontaneous synthesis of IgM RF by peripheral blood mononuclear cells and disease activity in patients treated with penicillamine. This result suggested that penicillamine suppressed the release of cytokines producing RF in the circulation, possibly from the inflamed synovium itself. Thus this observation was also compatible with a cellular mechanism. Lipsky and Ziff have, in fact, shown that penicillamine inhibits helper T cell function in the presence of copper.

We are aware of the observations that the complex of immunoglobulin A and α, antitrypsin is reduced by gold and d-penicillamine. Recent work showing that the levels of serum IgA-α, antitrypsin complex might be a predictive indicator of erosions in early rheumatoid arthritis are of interest. Undoubtedly, further studies will tell us if this is the only predictor. If indeed α-penicillamine can reduce this complex, then we would expect erosions to heal, or perhaps not occur, if the complex level is reduced by treatment. We are not aware that studies to date have provided overwhelming evidence for such a role for d-penicillamine.

Fortunately, many treatments introduced into medicine for the wrong reason have still been effective and have stimulated subsequent excellent research.

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von Willebrand factor antigen in giant cell arteritis

SIR: We were surprised at Dr Nordborg and colleagues somewhat negative appraisal of their findings in following on von Willebrand factor (vWF) and plasminogen activator inhibitor levels in a large cohort of patients with giant cell arteritis. Although showing that vWF levels are not useful in monitoring clinical relapse, they did establish that vWF levels gradually fall to control values after 18–24 months, which corresponds with the natural history of the disease in most patients. This is an important observation as several studies have concluded that vWF is raised but not useful in assessing clinical activity and have noted a trend of increased vWF after successful corticosteroid treatment.24

The logical conclusion from Dr Nordborg's data is that vWF levels reflect not only vascular injury but the activity of the fundamental disease process of giant cell arteritis. It also supports the argument that steroid treatment, although mitigating vascular injury progressing to thrombotic/embolic occlusion, has little effect on the underlying disease. In this study 'nine of 63 patients still receiving corticosteroids had a ... vascular occlusive episode'. Moreover, the use of vWF as a marker obscures its pathogenic potential via its main function, the initiation of platelet adhesion. vWF release at the site of vascular injury is the vital first step in the thrombotic cascade, which even when it does not lead to occlusion will perpetuate vascular pathology by the release of derived vasoactive substances and growth factors. There is a strong correlation between vWF levels and such growth factors after myocardial infarction.23 Of further pathogenic relevance is the close relationship between vWF release and expression of the endothelial cell polyamine adhesion molecule GMP-140, which occurs because both are stored in Weibel-Palade bodies. Thus the principal implication is that in relapsing cases or those unresponsive to steroids there should be a low threshold for using agents which could modulate or modify either vascular injury or the disease process and that vWF responses might provide clues to the most effective drugs and their optimal usage. von Willebrand factor responses may also help to identify new immunomodulators. Indeed, given that vWF release is Ca2+ dependent, it is tempting to speculate about the therapeutic effect of calcium channel blockers in giant cell arteritis and other vasculitides.

Renal cell carcinoma with acute monanthritis

SIR: We read with interest the report of two cases of renal cell carcinoma presenting with acute monanarthritits.1 We would like to report a similar case. A 55 year old woman presented in June 1988 with a painful left knee after a walking holiday. Although arthroscopy was carried out on her knee in May 1989, showing normal joint surfaces and an inflamed synovium which bled easily, no biopsy sample or radiograph was taken. When seen by us in April 1990, there was considerable tender, warm swelling. Radiography showed a large osteolytic lesion in the lower left femur with a pathological fracture and a surrounding soft tissue mass (figure). Histology showed that there was an invading clear cell tumour. Further investigations to find the primary tumour disclosed a second metastatic deposit in the right shoulder and two small metastatic nodules in the lung. Abdominal computed tomography showed a large mass arising from the right kidney. Treatment proceeded to nephrectomy, which confirmed a poorly differentiated clear cell tumour with invasion into the cavity of the renal vein. She received radiotherapy to the femur, and the left knee was reconstructed successfully. Interferon was given, but the patient died early in August 1990. Metastatic bone disease is found in 49% of patients with renal cell carcinoma.2 Interestingly, it is reported3 that bony metastases are usually ipsilateral to the primary tumour and rarely affect peripheral bones. This is thought to be because the paravertebral veins form a rich plexus extending from the skull to the knees and elbows by way of its connections with the vasa vasoorum. Frequent connections between the renal vein and the paravertebral plexus occur directly on the left but indirectly on the right. Of the 40 patients discussed with bony metastases, 10 had axial involvement alone (three right sided primary tumours, seven left sided) and a further 15 also had
Letters to the editor

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Authors' reply

We would like to thank Dr Pal for his reaction. We completely agree with his statements and in fact we did send in our article for the title 'Mastocytosis and sicca syndrome'. However, this was changed by the editor to 'mastocytosis and Sjögren's syndrome'. Obviously, there is still some debate about which criteria are to be applied to patients diagnosed as having Sjögren's syndrome. If Sjögren's syndrome is regarded as an autoimmune disorder with specific histology and serological abnormalities then we should restrict this term to those patients who meet all criteria. We might then probably consider this also as Sjögren's disease.

It was our intention to describe a patient with the sicca syndrome caused by mast cell infiltration of the salivary glands, which was not reported before. Together with haemosiderosis, sarcoidosis, and amyloidosis mastocytosis should also be considered as a non-Sjögren cause of the sicca syndrome.

Rheumatic problem such as rheumatoid arthritis or lupus.

It is important that Sjögren's syndrome is diagnosed only when patients meet the necessary diagnostic criteria of objective keratoconjunctivitis sicca and xerostomia in the presence of some serological markers of autoimmune dysfunction such as antinuclear factors but more characteristically the antibodies to extractable nuclear antigens—namely, Ro and La. In many cases a lower lip biopsy for histopathological evidence of the typical lymphocytic infiltration in the accessory salivary tissue is necessary to confirm the diagnosis. Patients with keratoconjunctivitis sicca and xerostomia due to other causes, such as sarcoidosis, should perhaps be more specifically called non-Sjögren sicca syndrome.

Letters to the editor

Radiograph of the knees showing a large lytic lesion in the left femur, with surrounding soft tissue mass.

peripheral bones affected. Most axial lesions occurred in the T12 and L5 vertebrae. Thirty patients had peripheral bones affected, 19 unilaterally and 11 bilaterally. Fifteen of the unilateral metastases were ipsilateral to the primary tumour (eight right side, seven left side) and four contralateral (three right side, one left side). Of the 11 with bilateral metastases eight were right sided primary tumours and three left sided. Seventeen of the 40 (43%) had presented with symptoms related to their bone lesions. Thus right sided primary tumours are more likely to have either contralateral or bilateral bony metastases, which is supported by the recent report1 and our case.

Fixation, possibly with radiotherapy and cryotherapy, is recommended for a lytic lesion in a weightbearing bone if the life expectancy is greater than three or four months.

Metastases to periarticular foci are not uncommon, especially in the hip, shoulder, and knee, and the synovial reaction is either non-neoplastic or due to extension through the subchondral bone plate to affect the synovial membrane secondarily.2 There is nothing to suggest in the cases presented that there was primary involvement of the synovium, and we would thus suggest that what has been described is not rare but certainly might have been underreported recently.

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Systemic mastocytosis and Sjögren's syndrome

Sir: I wish to comment on the case report by Bac and van Marwijk Kooy1 of a patient with systemic mastocytosis labelled as having Sjögren's syndrome. There is obviously some problem here with semantics and nomenclature. The patient described by the authors had features of systemic mastocytosis together with dry eyes and mouth; the latter manifestations apparently resulted from mast cell infiltration of the secretory glands as shown by the biopsy findings of the minor salivary glands. The authors do not mention any lymphocytic infiltration of the salivary tissues characteristic of Sjögren's syndrome, and I presume there was none.2 Nor was there any serological evidence of Sjögren's syndrome, such as the presence of antinuclear factors and specifically the Ro and La antibodies which are found frequently in this disorder.3 On the basis of the authors' findings, therefore, I do not believe that their patient fulfills the required diagnostic criteria for Sjögren's syndrome as described by Fox et al4 or, indeed, by others.5

In my opinion this patient with mastocytosis developed features of sicca syndrome (and not Sjögren's syndrome) because of lachrymal and salivary gland compromise due to heavy mast cell infiltration. Keratoconjunctivitis and xerostomia of this nature have been previously documented in other conditions where the secretory glands are infiltrated by various agents—for example, amyloid, haemosiderin6 and sarcoid granuloma.7 A sicca syndrome associated with idiopathic haemochromatosis has also been reported.8 These heterogeneous groups of ailments are not examples of Sjögren's syndrome (although sometimes misdiagnosed as such, as in the present case) but simply illustrations of glandular impairment clinically manifesting in the sicca syndrome.

Conversely, however, it has to be borne in mind that an occasional patient with primary Sjögren's syndrome may masquerade and be misdiagnosed as sarcoidosis,9 or indeed another