and high blood pressure values were found for the first time. After four months of persistently moderate hypertension she was admitted to our clinic in November 1991. On admission her blood pressure was 160/110 mmHg. Physical and funduscopic examination, electrocardiography, and chest roentgenogram did not show any abnormalities. Laboratory studies showed thrombocytopenia ($110 \times 10^9/l$), positive VDRL with negative TPHA and FTA, positive antinuclear antibodies (1/40) with a homogeneous immunofluorescence pattern, low concentrations of C4 (90 mg/l and 70 mg/l on further measurement), low to normal values of C3 (770 mg/l and 740 mg/l on further measurement). Both IgG and IgM anticardiolipin antibodies estimated by enzyme linked immunosorbent assay (ELISA)³ were positive: 110 GPL U/ml and 50 MPL U/ml. A lupus anticoagulant test, performed by kaolin clotting time,⁴ a Coombs' test, rheumatoid factor, antibodies to double stranded DNA, antibodies to extractable nuclear antigens, antimitochondrial and antithyroid antibodies were all negative. No other abnormality emerged from routine blood and urine laboratory tests.

A captopril test disclosed peripheral plasma renin activity (PRA; SORIN kit) rising from 1.3 to 8.6 ng/ml/h. Differential renal vein renin determinations showed: inferior vena caval PRA: 4 ng/ml/h, right renal vein PRA 3.95 ng/ml/h, left renal vein PRA 7.9 ng/ml/h. Aortography and selective renal arteriography showed a 70% stenosis in the middle portion of the left renal artery (figure). Transluminal angioplasty was not performed because of the potential danger of inducing thrombosis.

Before drug treatment, blood pressure ranged from 150/100 to 190/120 mmHg. In December 1991 enalapril 10 mg/day was given and blood pressure quickly fell to 130/80 mmHg. Since dismissal her blood pressure has never exceeded 135/85 mmHg.

Two other cases of renovascular hypertension associated with antiphospholipid antibodies have been reported.^{1,2} One patient with a diagnosis of primary antiphospholipid syndrome presented an angiographic appearance of unilateral renal artery stenosis attributed to recanalisation of a thrombus of the renal artery.¹ No documentation was shown, however, so a 'pure' renal artery stenosis cannot be excluded. The other patient, a 13 year old girl with clinical features resembling systemic lupus erythematosus and very high levels of serum antiphospholipid antibodies, presented marked stenosis of both renal arteries, associated with filling defects extending from the left renal artery into its

branches, appropriately interpreted as revascularised thrombosis.²

In our patient hypertension due to renal artery stenosis was associated with laboratory features of antiphospholipid syndrome. False positive VDRL, high IgG and IgM anticardiolipin antibodies, positive antinuclear antibodies, a low C4 concentration, and slight thrombocytopenia were the main features. No evidence of venous or arterial thrombosis was present.

The few reported cases of association between renal artery stenosis and antiphospholipid syndrome do not allow obvious inferences. Nevertheless, the two conditions might be related for various reasons. The hypothesis of thrombosis of the main renal artery, followed by a recanalisation resembling renal artery stenosis, seems the least tenable, given the available angiographic images. Rather one might speculate that renal artery stenosis can favour local thrombosis in patients prone to vascular thrombosis, such as those with antiphospholipid syndrome. This vascular complication might worsen hypertension, or even elicit a hypertensive state in subjects previously normotensive despite renal artery stenosis, so causing an association between the two conditions. Lastly, one cannot exclude a causal relationship between antiphospholipid antibodies and some types of 'fibromuscular dysplasia' of the renal arteries. The two conditions both have similar female sex preponderance and similar age of presentation. In some forms of immune mediated vasculitis, antiphospholipid syndrome might sometimes be responsible for renal artery lesions producing stenosis.

The possible link between these conditions nevertheless deserves further investigation, particularly a systematic assessment of antiphospholipid antibodies in young patients with renovascular hypertension.

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D-Penicillamine and rheumatoid factor

Sir: Having been fascinated for years by the possible role of D-penicillamine in the treatment of rheumatoid arthritis (RA), I read with considerable interest the recent article by Evelyn Hess and Morris Ziff,¹ entitled 'Effect

of penicillamine on the titre of the rheumatoid factor: a historical perspective'. It reminded me of past meetings of the 'Penicillamine Club', which Hugh Lyle (then of Eli Lilly) used to organise so successfully; these were structured on the assumption that an understanding of the mode of action of D-penicillamine could hold the key to the cause of RA.

Inevitably, a topic which was frequently discussed at such meetings was the effect of oral treatment with the drug on circulating rheumatoid factor levels. I remember, for instance, arguing with Dr Jaffe about this at a meeting in Spåtind (in Norway) in 1976; on which occasion I contested his claim that the efficacy of D-penicillamine in the treatment of RA could be attributed to such an effect because in our experience² there was no obvious relation between any resultant change in circulating rheumatoid factor level and improvement in clinical status, as measured by the usual indices. (More recently, Drs Jaffe and Ziff and colleagues³ have themselves concluded that changes in circulating levels of IgM rheumatoid factor brought about by penicillamine treatment show no correlation with disease activity in RA as measured by joint score over one year!)

Significantly, at that same meeting in Norway in 1976, Frank Wolheim and colleagues reported a correlation between clinical responsiveness to D-penicillamine treatment in RA and reduction in the circulating level of IgA- α_1 antitrypsin complex.⁴ In subsequent years we have confirmed and extended^{5,6} those observations, providing increasing evidence of a central immunopathological role for this covalently linked complex (unlike rheumatoid factor) in RA. Our findings seem to offer a plausible explanation of the mode of action of drugs like D-penicillamine and Myocrisin (sodium aurothiomalate) in the treatment of RA; such compounds supposedly forming mixed disulphides with thiol-active IgA, and thereby preventing it complexing with α_1 antitrypsin to form the deleterious IgA- α_1 antitrypsin complex. Furthermore, we have recently obtained evidence to suggest that measurement of the serum IgA- α_1 antitrypsin complex level provides a predictive indicator of the development of erosions in early RA.⁷

It seems likely, therefore, that D-penicillamine was chosen for the treatment of RA, as a consequence of the early studies of its effect on circulating rheumatoid factor level recalled by Drs Hess and Ziff,¹ for the wrong reasons!

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Selective angiography of the left renal artery, showing a short segmental narrowing in the middle portion of the main artery.

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AUTHORS' 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_1 antitrypsin complex. Dr Israeli Jaffe, very reasonably, had suggested, following his studies of intra-articular injection of penicillamine, that this drug degraded IgM rheumatoid factor (IgM RF) by sulphhydryl reduction of the IgM RF molecule. We were 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 critical cell population 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 the titre fell gradually 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.¹ 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.² This result suggested that penicillamine suppressed the release of cells producing RF into 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.³

We are aware of the observations that the complex of immunoglobulin A and α_1 antitrypsin is reduced by gold and D-penicillamine. Recent data suggesting that the levels of serum IgA- α_1 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 D-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 von Willebrand factor (vWF) and plasminogen activator inhibitor levels in a large cohort of patients with giant cell arteritis.¹ 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 persistent increase in vWF after successful corticosteroid treatment.²⁻⁴

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 in 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. von Willebrand factor 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 injury by the release of platelet derived vasoactive substances and growth factors. There is a strong correlation between vWF levels and such growth factors after myocardial infarction.⁵ Of further pathogenetic relevance is the close relation between vWF release and expression of the endothelial cell polymorph 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 Ca^{2+} dependent, it is tempting to speculate about the therapeutic effect of calcium channel blockers in giant cell arteritis and other vasculitides.

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Renal cell carcinoma with acute monarthritis

Sir: We read with interest the report of two cases of renal cell carcinoma presenting with acute monarthritis.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 November 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 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 capsule, ureter, and renal vein. She received radiotherapy to the femur, and the left knee was reconstructed successfully. Interferon was given, but the patient died in early 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 vasorum. 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