our report.¹ We agree that opportunistic infection was not ruled out and that the recovery after treatment with co-trimoxazole increases the likelihood of pneumocystis pneumonia. No sputum was obtained at any stage in the course of our patient's illness and bronchoalveolar lavage was not performed.

We note with interest the frequency with which leucopenia and perhaps lymphopenia has been present in reported cases of *P carinii* infection complicating methotrexate treatment in rheumatoid and psoriatic arthritis.²⁻⁴ Examination of serial blood samples before the respiratory illness in patient 1 showed a steady reduction in the lymphocyte count ($1.79 \times 10^9/l$ in September 1984, $1.77 \times 10^9/l$ in December 1984, $1.21 \times 10^9/l$ in February 1985, and $0.96 \times 10^9/l$ just before presentation). After methotrexate was stopped the lymphocyte count rose to $1.10 \times 10^9/l$ in May 1985 and to $2.64 \times 10^9/l$ in June 1985. These results add weight to the proposition that opportunistic infection was responsible for the respiratory illness. In the light of these observations it is possible that both of the patients described in our report subsequently tolerated methotrexate because infection was in fact responsible for the pneumonitis rather than hypersensitivity or some other form of drug toxicity, such as accumulation of methotrexate in pulmonary tissue.

Clearly, it is important to diagnose opportunistic infection not only in order to institute appropriate treatment but also because it may be possible to use methotrexate again if the evidence favours infection rather than a drug reaction. Furthermore, titrating the dose of methotrexate against peripheral blood lymphocyte counts may allow the drug to be used more safely in the treatment of rheumatic diseases.

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The antiphospholipid syndrome: a syndrome in evolution

Sir: I read with interest the leader by Asherson and Cervera¹ and agree that disease conditions other than deep vein thrombosis, recurrent fetal loss, or stroke may occur, not only in association with defined systemic lupus erythematosus (SLE) or 'lupus-like' disease, but also with 'primary' antiphospholipid syndrome (APS). The authors included Sneddon's syndrome (cerebrovascular disease with livedo reticularis) in the category of 'primary' APS.

Sneddon's syndrome comprises about 0.26% of total cerebrovascular cases.²

Clearly, no immunological testing to detect antiphospholipid antibodies in Sneddon's original patients was undertaken.³ However, pathogenesis of Sneddon's syndrome remains unclear. Sneddon speculated that skin biopsies in future cases would show endarteritis obliterans in dermal arterioles. It was thought that intravascular pathology of a similar nature was responsible for cerebrovascular accidents. There is no serological evidence of SLE or other systemic disorders in most reported cases of classical Sneddon's syndrome.²⁻⁴⁻⁸ None of these studies, however, included specific tests for antiphospholipid antibodies or lupus anticoagulant.

A recent study of 10 cases of cerebrovascular disease, in association with livedo reticularis in six cases, showed seven had SLE.⁹ Five were positive for the Venereal Disease Research Laboratory (VDRL) test, and were positive for lupus anticoagulant. All had cutaneous vascular disease in the form of digital gangrene, cutaneous ulcer, and superficial thrombophlebitis; two had pulmonary embolism. There is little doubt that these cases belong to the category of 'primary' APS, with or without SLE.

A case of Sneddon's syndrome in association with deep vein thrombosis and pulmonary embolism is presented here; repeated search for antiphospholipid antibodies and lupus anticoagulant proved negative.

In October 1990 a 45 year old man presented with a history of sudden onset of left sided hemiparesis (MRC grade 4) and hemianaesthesia. He had had deep vein thrombosis and pulmonary embolism in 1971. A chronic ulcer appeared on the front of his right leg in 1974. Apart from his neurological signs, he had left leg deep vein thrombosis, left sided pleural rub, and a chronic 'venous' ulcer on the front of his right leg with surrounding pigmentation. Additionally, he had acrocyanosis of his toes and both dorsalis pedis pulsations were absent. No skin rash or nodules were present. He was in sinus rhythm and normotensive, with no heart murmur or carotid bruit. Body temperature was normal.

Laboratory investigations showed an erythrocyte sedimentation rate of 70 mm/h (normal <10), plasma viscosity 2.08 mPa.s at 25°C (normal ± 0.05), C reactive protein 16 mg/l (normal <10); antinuclear factor was positive at a titre of > 1/1024 (homogeneous pattern), with DNA binding of 13% (normal 0-5). Chest radiography showed peripheral consolidation in the left mid-zone, and a venogram of his left leg showed extensive thrombus in the deep venous system. A computed tomographic scan of his brain showed a large wedge-shaped, well defined, hypodense lesion in the right parietal lobe.

Results of the following investigations were either normal or negative: haemoglobin, white cell count, platelets, packed cell volume, automated serum chemistry, including cholesterol and triglycerides; prothrombin time, kaolin cephalin coagulation time; plasminogen, protein S, protein C, and antithrombin III levels; lupus anticoagulant, IgG and IgM anticardiolipin antibodies (reference laboratory—Hammersmith Hospital, London); VDRL tests, antineutrophilic cytoplasmic antibody, cryoglobulins, rheumatoid factor latex test, direct Coombs' test, hepatitis B surface antigen, serum protein electrophoretic pattern, and urine microscopy. A duplex scan of the carotid arteries, a two dimensional echocardiogram, and the electrocardiogram were all normal.

About two weeks after his initial presentation the patient developed generalised livedo reticularis affecting trunk and extremities. Eighteen months later he still has left sided hemiparesis (MRC grade 4) and hemianaesthesia. His skin rash persists. Multiple biopsy specimens of unaffected skin¹⁰ show essentially normal histology. The patient's most recent erythrocyte sedimentation rate is normal, but his antinuclear factor remains positive with a low titre of 1/10 (homogeneous pattern). Double stranded DNA antibody is, however, negative. Repeat testing for anticardiolipin antibodies failed to show any abnormalities. In view of his proneness to recurrent thromboembolism, long term anticoagulation treatment with warfarin has been continued.

This case further illustrates that Sneddon's syndrome may also exist as a distinct entity whose pathogenesis remains to be elucidated.

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Anticardiolipin antibodies and renovascular hypertension

Sir: Two cases of renovascular hypertension associated with antiphospholipid syndrome have been reported recently.^{1,2} We report a case of renovascular hypertension, without angiographic appearance of thrombosis, associated with laboratory features found in primary antiphospholipid syndrome.

A 30 year old woman was admitted to our clinic for hypertension evaluation. At the age of 14 a positive Venereal Disease Research Laboratory (VDRL) test with negative fluorescein treponemal antibody (FTA) and negative *Treponema pallidum* haemagglutination antibody (TPHA) absorption was detected. She had had only one pregnancy at the age of 21 with a normal delivery. Since the age of 22 she had been using an intrauterine device. At 29 she began to complain of frequent headaches,

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 fundoscopic 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.