LETTERS TO THE EDITOR

Methotrexate, pneumonitis, and infection

Sir: In a recent issue of this journal Cook and Carroll¹ reported on two patients with rheumatoid arthritis (RA) in whom it was possible to reintroduce methotrexate after a presumed methotrexate related pneumonitis. At the time these cases occurred (in 1985 and 1986) opportunistic infections were not considered to be important in the treatment of RA with methotrexate, so it is understandable that their report made no mention of specific investigations in that direction. Nowadays it is agreed that opportunistic infections, especially *Pneumocystis carinii*, must be excluded in the evaluation of pneumonitis in patients treated with methotrexate for RA.² In the cases presented this type of pneumonitis could not be fully excluded, especially not in the patient who was also treated with co-trimoxazole.

We report the case of a patient who had two episodes of methotrexate related pneumonitis, in which opportunistic infections could be sufficiently excluded. This case history further emphasises that caution is needed when reintroduction of methotrexate after an episode of pneumonitis is considered.

A 61 year old man had had erosive, rheumatoid factor positive RA since 1985, previously treated with hydroxychloroquine, sulphasalazine, aurothioglucose, and azathioprine. Chest radiography showed slight reticular changes in the basal segments in August 1987. On pulmonary function testing a restriction (total lung capacity 5.1 litres (normal 6.1)) and a decreased carbon monoxide diffusing capacity (carbon monoxide transfer factor) (0.93 mmol.min⁻¹.kPa⁻¹.l⁻¹ (normal 1.40-1.60)) were found. In November 1987 methotrexate 7.5 mg orally weekly, increasing to 15 mg weekly over two months, was started. Ten months later, at a cumulative methotrexate dose of 540 mg, dyspnoea on effort and a non-productive cough without fever developed, together with mouth ulcers. Chest radiography showed progression of reticular changes, and the carbon monoxide transfer factor had decreased to 0.79. In the absence of sputum production no cultures could be done. Methotrexate was stopped, and low dose prednisone treatment (7.5 mg daily) started. Two weeks later pulmonary complaints and mouth ulcers had disappeared. Control chest radiographs and pulmonary function testing returned to pretreatment values. D-Penicillamine was given for active RA but proved ineffective.

In October 1989 methotrexate, 7.5 mg orally weekly, increasing to 10 mg weekly over three months, was restarted, with a sufficient response of the RA. In April 1991 the methotrexate dosage was increased to 12.5 mg weekly because of reactivation of RA. One week later, at a cumulative methotrexate dose of 600 mg in this second episode, acute dyspnoea with a non-productive cough without fever developed. There was no response to amoxycillin. Methotrexate was stopped immediately.

On admission pulmonary complaints had already improved. The respiratory rate was 24/min and bibasilar crackles were heard over

the lungs. Skin lesions on both legs, suspected to be due to vasculitis, were seen. Laboratory data were as follows: erythrocyte sedimentation rate 95 mm/hour, white cell count $9.7 \times 10^9/l$, no eosinophilia, arterial blood gas tensions were: P_{O_2} 8.9 kPa, PCO_2 5.0 kPa on room air. Extension of bilateral reticular changes on chest radiographs and deterioration of pulmonary restriction (total lung capacity 4.6 litres) were found. The carbon monoxide transfer factor had not changed. Microbiological evaluation, including bronchoalveolar lavage and open lung biopsy, remained negative. The lung biopsy specimen showed interstitial pneumonitis with lymphocytic infiltrate, bronchiolitis, and multinucleated giant cells, without signs of vasculitis. Light microscopy of skin lesions showed allergic vasculitis. The patient's pulmonary condition rapidly improved after discontinuation of methotrexate, but the RA flared. Azathioprine was given, resulting in gradual improvement of both polyarthritis and skin lesions. Pulmonary complaints did not recur.

In our opinion both episodes of pulmonary complaints in our patient can be attributed to methotrexate treatment. Microbiological causes, including opportunistic infections, were sufficiently excluded during the second episode. Pathology of the lung biopsiespecimen, and the clinical course after discontinuation of methotrexate are compatible with methotrexate induced pneumonitis. Investigations of the first episode were less extensive, and, in particular, microbiological causes were not fully excluded, but the response to methotrexate withdrawal, without antimicrobial treatment, strongly supports a relationship with methotrexate treatment. As far as we know, no correlation between cumulative methotrexate dose and pneumonitis has been reported. In our patient the cumulative methotrexate dosage of each treatment period at the time pneumonitis developed was in the same range (540 mg and 600 mg respectively). From the report of Cook and Carroll¹ it can be estimated that in at least one of their patients the cumulative methotrexate dose after reintroduction of the drug exceeded that of the first episode. In our patient reintroduction of methotrexate after methotrexate pneumonitis seemed to be successful until the dose was increased to about 80% of that at which the first episode of pneumonitis had developed. Both patients reported by Cook and Carroll were rechallenged at doses clearly below the initial dose (50% in patient 1; 66% in patient 2).

The pathophysiology of methotrexate related pneumonitis remains unknown. Reports of the successful reintroduction of methotrexate seem not to be consistent with a hypersensitivity reaction that has often been suggested. Our case suggests that at least in some patients a direct toxicity with a threshold may be responsible for the development of methotrexate related pneumonitis. At present no risk factors for the development of methotrexate pneumonitis or a recidivism upon rechallenge are known. Whenever a rechallenge cannot be avoided, reintroduction of methotrexate at a much lower dose seems to be advisable.

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- 1 Cook N J, Carroll G J. Successful reintroduction of methotrexate after pneumonitis in two patients with rheumatoid arthritis. *Ann Rheum Dis* 1992; 51: 272-4.
- 2 Cannon G W, Williams H J. Pulmonary toxicity of methotrexate. In: Wilke W S, ed. *Methotrexate therapy in rheumatic diseases*. New York: Marcel Dekker, 1989: 243-60.

Sir: We read with interest the article on the successful reintroduction of methotrexate after pneumonitis in two patients with rheumatoid arthritis.¹ In this article two patients were described, of whom the first was classified as having definite methotrexate pneumonitis and the second probable methotrexate pneumonitis, though the authors conceded that pulmonary infection might have been responsible in the last case.

We feel that in the first case also a pulmonary infection might have been responsible—namely, *Pneumocystis carinii* pneumonia. In our opinion this possibility was not sufficiently ruled out.

Since 1983 there have been several reports on *P carinii* pneumonia complicating low dose methotrexate treatment. Methotrexate pneumonitis and *P carinii* pneumonia have the same clinical presentation and can produce grossly the same abnormalities on the chest radiograph.² Furthermore, the course of the illness in the first patient is also suggestive of *P carinii* pneumonia because improvement only started after institution of co-trimoxazole (beside other antibiotics), an agent to which *P carinii* responds particularly well.

P carinii is infrequently present in sputum, and serological detection lacks sufficient sensitivity and specificity. The most commonly used procedure to diagnose *P carinii* pneumonia is bronchoalveolar lavage, followed by Grocott staining.³ The severity of *P carinii* pneumonia justifies in our opinion this invasive procedure on every patient who is treated with low dose methotrexate and who presents with acute pulmonary disease. Thus we fully agree with Lang and colleagues who stated that opportunistic infections like *P carinii* pneumonia should be considered, and ruled out, before a definite diagnosis of methotrexate pneumonitis is made.⁴ In any case this limitation should be made if the diagnostic criteria advocated by Searles and McKendry are used.⁴

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- 1 Cook N J, Carroll G J. Successful reintroduction of methotrexate after pneumonitis in two patients with rheumatoid arthritis. *Ann Rheum Dis* 1992; 51: 272-4.
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AUTHORS' REPLY We thank Drs Stenger and Houtman for prompting us to reconsider pulmonary infection and, in particular, *Pneumocystis carinii* infection in patient 1 in

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 hemianesthesia. 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 hemianesthesia. 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,