15 Bennett W M, Strong D. Arthralgia after high-dose steroids. *Lancet* 1975; i: 332.
16 Kurki P. The effects of "pulse" corticosteroid therapy on the immuno system. *Scand J Rheumatol [Suppl]* 1983; 54: 13–16.
17 Silverman E D, Myones B L, Miller J J. Lymphocyte subpopulation alterations by intravenous megadose pulse methylprednisolone. *J Rheumatol* 1984; 11: 287–90.
18 Newmark K J, Mitra S, Berman L B. Acute arthralgia following high-dose intravenous methylprednisolone therapy. *Lancet* 1974; ii: 229.
19 Tvede N, Nielsen L P, Andersen V. Bradycardia after high-dose intravenous methylprednisolone therapy. *Scand J Rheumatol* 1986; 15: 302–4.
20 Kirk A P, Pitt P I, Kenny D, Berry H. Methylprednisolone infusion in rheumatoid arthritis. *Br J Rheumatol* 1985; 24: 119.

Cyclosporin in Wegener's granulomatosis with renal failure

Sir: In 1987 we presented in this journal the case history of a patient with Wegener's granulomatosis, in whom remission of the disease was achieved with cyclosporin.[1] Now, after more than three years' treatment with this immunosuppressive drug no further activity of the disease has occurred. Although we stated that cyclophosphamide is still the drug of first choice in the treatment of Wegener's granulomatosis, this positive experience persuaded us to start cyclosporin treatment in another patient with Wegener's granulomatosis resistant to conventional treatment. As the effect of cyclosporin in this patient was even more impressive than it had been in the previous subject we feel it is worth reporting this case history.

In 1982 a 72 year old women was admitted to our hospital for evaluation of cough, rhinorrhoea, fever, and fatigue. Laboratory tests showed a raised erythrocyte sedimentation rate (ESR) of 122 mm/h, thrombocytosis (platelets 625×10^9/l), and normal renal function. An *x* ray examination of the chest and sinus showed no abnormalities. Histopathological examination of a biopsy specimen of the nasopharynx, however, showed destructive granulomatous reaction with necrotising vasculitis, characteristic of Wegener's granulomatosis. Consequently, treatment with cyclophosphamide (100 mg/day) and prednisone (30 mg/day) was started. Six weeks later her clinical condition and laboratory indices had normalised. During the following months the doses of both drugs were tapered slowly, with success.

Unfortunately she withdrew from further outpatient clinic control until she was admitted to hospital again in 1986 because of severe fatigue and depression. By that time she had stopped taking prednisone but continued with cyclophosphamide 100 mg/day. Laboratory examination showed a raised ESR (83 mm/h), anaemia (haemoglobin 93 g/l), low platelet count (78×10^9/l), increased serum creatinine (156 μmol/l), and haematuria (15–30 erythrocytes in the urinary sediment); testing for the presence of antineutrophil cytoplasmic antibodies was not done at that time. Her raised ESR and renal failure were considered as markers of activity of Wegener's granulomatosis; anaemia and low platelet count were thought to be manifestations of bone marrow depression due to cyclophosphamide. The administration of cyclophosphamide was stopped and prednisone 30 mg/day was given. Nevertheless, her clinical condition deteriorated and serum creatinine rose to 365 μmol/l. The corticosteroid regimen was changed to methylprednisolone 1500 mg every other day intravenously for 10 days and the addition of azathioprine 25 mg every eight hours, but this did not prevent further progression of renal failure and further rise of serum creatinine to 516 μmol/l.

As Wegener's granulomatosis seemed to be progressive despite intensive treatment we decided—after informed consent of the patient—to start treatment with cyclosporin 5 mg/kg body weight a day and prednisone 40 mg/day. Trough concentrations of cyclosporin (by radioimmunoassay and measured in whole blood) ranged from 405 ng/ml to 780 ng/ml. One month later her condition had clearly improved, with decreased values of ESR (48 mm/h) and serum creatinine (213 μmol/l). During the following period cyclosporin trough concentrations were kept at about 600 ng/ml, and prednisone was tapered slowly. More than two years after the initiation of cyclosporin this patient, who at that time was aged 79, is doing very well with stabilised serum creatinine concentrations of 190–210 μmol/l and no antineutrophil cytoplasmic antibodies.

In this case of Wegener's granulomatosis cyclosporin seems to have been effective. Interestingly, improvement of renal function was achieved by treatment with an immunosuppressive drug for which nephrotoxicity is the most prominent side effect. This observation fits with another case report showing the beneficial influence of cyclosporin in a patient with Wegener's granulomatosis with renal failure.[2] Obviously, cyclosporin is an alternative to cyclophosphamide in treatment of patients with Wegener's granulomatosis. Additional studies are necessary to confirm the precise role of cyclosporin in the treatment of this disease.

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1 Borleffs J C C, Derksen R H W M, Hené R J. Treatment of Wegener's granulomatosis with cyclosporin. *Ann Rheum Dis* 1987; 46: 175.
2 Gremmel F, Druml W, Schmidt P, *et al.* Cyclosporin in Wegener's granulomatosis. *Ann Intern Med* 1988; 108: 491.

Anaerobic bacteria in rheumatoid arthritis

Sir: In past years some rheumatologists have thought that anaerobic bacteria have a role in the pathology of rheumatoid arthritis.[1]

We considered that if anaerobic bacteria were essential to metabolism in the diseased joint then it should be possible to measure substantial amounts of their metabolic products—short chain fatty acids—in the synovial fluid.

We used a modification of McArthur's gas chromatographic method[2] to examine 11 normal synovial fluids obtained during negative explorations on knees for meniscal disease and 15 fluids taken from the knees of patients with classical or definite rheumatoid arthritis. The synovial fluid samples were treated with hyaluronidase, then the short chain fatty acids were extracted with ether and freeze dried at −80°C. Before injection into the gas chromatograph the freeze dried material was redissolved in 8 M formic acid. 2-Ethylbutyric acid was used as an internal standard.

The mean concentrations (range) of short chain fatty acids in normal fluid were found to be: acetic acid 102 (54–149) μmol/l; propionic acid 13 (0–31) μmol/l; n-butyric acid 3·4 (0–9) μmol/l; n-valeric acid 3·6 (0–18) μmol/l. There were no significant differences between normal and rheumatoid synovial fluids.

Thus it seems that the direct action of anerobic bacteria—for example, *Clostridium perfringens* and others, which produce short chain fatty acids, is excluded.

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2 McArthur B, Sarnaik A P, Mitchell R A. Short-chain fatty acids and encephalopathy of Reye's syndrome. *Neurology* 1984; 34: 831–4.

Treatment of polymyalgia rheumatica and giant cell arteritis

Sir: We read with interest Kyle and Hazleman's article on the treatment of polymalgia rheumatica and giant cell arteritis,[1] which sheds some light on the problems of treatment in these two conditions. We would support their views that the lowest doses of steroid possible should be used both in the initial and maintenance treatment, but would like to draw attention to the possible dangers of undertreatment of the ophthalmic manifestations of giant cell arteritis.

Although doses may indeed be to some extent based on tradition and anecdote, in such a capricious and visually devastating condition it is anecdotal exceptions to which attention must be directed if the opportunity to prevent visual loss is to be taken.

The fact that the 'high dose' group had fewer episodes of relapse than the 'low dose' group, but still suffered a significant therapeutic failure rate, implies that even higher dose regimens should be considered. Ophthalmologists usually use much higher doses of steroid, at least initially, when treating patients who present with the visual sequelae of giant cell arteritis.[2] Although quite probably most cases of giant cell arteritis might be managed with a lower dose even than 40 mg prednisolone initially, success in the majority is not the ultimate aim of treatment, when the fate of the rest may be irreversible visual loss.

Sadly, the acute ischaemic optic neuropathy resulting from giant cell arteritis is often bilateral, with the second eye being affected very shortly after the first. A recent review of 50 cases of anterior ischaemic optic neuropathy related to giant cell arteritis[3] found that when large doses of steroid (80–120 mg prednisolone initially, followed by the same dose for several days after) were used 95% of patients were protected from disease in the

second eye, and when a similar regimen was used to treat giant cell arteritis without ocular involvement, all patients were protected from developing ischaemic optic neuropathy.

Furthermore, giant cell arteritis can actually be precipitated by inadequate treatment of polymyalgia rheumatica.[4] It is our standard practice to treat patients with giant cell arteritis with an initial dose of 4 mg of dexamethasone intravenously immediately, followed by 4 mg dexamethasone intramuscularly four times a day for two days, and at the same time to start treatment with 80 mg prednisolone a day orally, gradually reducing the dose of oral prednisolone as the symptoms resolve. We would wholeheartedly concur with the view expressed by Kyle, Cawston, and Hazleman in the follow paper[5] that neither erythrocyte sedimentation rate nor C reactive protein concentration is a reliable monitor of the state of the disease, and we would base dose reductions on the clinical features and symptoms. It may well be that giant cell arteritis leading to ocular involvement represents a different spectrum of disease than that represented in their paper. We would recommend, however, that any potential visual involvement be treated aggressively.

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1 Kyle V, Hazleman B L. Treatment of polymyalgia rheumatica and giant cell arteritis. I. Steroid regimens in the first two months. *Ann Rheum Dis* 1989; **48**: 658–61.
2 Graham E, Holland A, Avery A, Russell R W R. Prognosis in giant cell arteritis. *Br Med J* 1981; **282**: 269–71.
3 Beri M, Klugman M R, Kohler J A, Hayreh S S. Anterior ischaemic optic neuropathy. VII. Incidence of bilaterality and various influencing factors. *Ophthalmology* 1987; **94**: 1020–8.
4 Reilly P A, Maddison P J. Giant cell arteritis precipitated by a diagnostic trial of prednisolone in suspected polymyalgia rheumatica. *Clin Rheumatol* 1987; **6**: 270–2.
5 Kyle V, Cawston T E, Hazleman B L. Erythrocyte sedimentation rate and C reactive protein in the assessment of polymyalgia rheumatica/giant cell arteritis on presentation and during follow up. *Ann Rheum Dis* 1989; **48**: 667–71.

Sir: We agree that threatened visual loss should be treated aggressively. The results of our study indicate that a high initial dose of prednisolone is necessary in treating giant cell arteritis followed by a slow carefully monitored reduction to achieve the lowest dose consistent with controlled symptoms and avoidance of side effects. Four of the 20 patients on the high dose regimen relapsed on reduction and required a higher dose of prednisolone. It was the rate of reduction that was too rapid rather than the initial dose of prednisolone that was too low. Seventy per cent of relapses occurred when the dose was reduced to 20 mg prednisolone a day in the first month or to 20 mg prednisolone a day or less in the second month.

Six of the 39 patients with polymyalgia rheumatica developed giant cell arteritis during the first two months of treatment, but provided that patients are monitored it should not be necessary to use high doses of prednisolone for all patients with polymyalgia rheumatica. Frequent and careful follow up is necessary.

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Synovial fluid fibronectin concentrations in chronic arthritis: influence of intra-articular steroids or oral non-steroidal anti-inflammatory drugs

Sir: Goebel and Storck showed that the intra-articular administration of the antioxidant enzyme orgotein significantly reduced the synovial fluid fibronectin concentration in patients with rheumatoid arthritis.[1] Do other treatments influence synovial fluid fibronectin concentrations?

Fibronectin concentrations are significantly increased in synovial fluid from patients with rheumatoid arthritis, but, characteristically, plasma fibronectin concentrations do not vary greatly.[2] In contrast, it has been shown that plasma concentrations correlate with disease activity in systemic lupus erythematosus.[3] Fibronectin also provides a useful biochemical marker in experimental arthritis and concentrations reflect the inflammatory activity.[4] As an extracellular product of mesenchymal cells, fibronectin is a marker for proliferation of synovial connective tissue, a process which may be central to the pathogenesis of chronic synovitis.[5 6] An increase in fibronectin concentration in synovial fluid may reflect increased connective tissue proliferation; similarly, a decrease in fibronectin may be a response by local tissue to treatment.

To study the hypothesis further we measured fibronectin concentrations in synovial fluid before and after treatment of chronic arthritis of the knee with either oral non-steroidal anti-inflammatory drugs or intra-articular steroids. Sixteen patients with chronic arthritis of the knee were admitted to the study, which was approved by the local ethical committee. Ten were treated with oral azapropazone (600 mg twice daily) and six with one intra-articular injection of triamcinolone (25–50 mg). Synovial fluid was aspirated from the affected knee joint of patients before treatment and four weeks later. The fibronectin concentration in the synovial fluid was measured by an enzyme linked immunosorbent assay (ELISA) method.[7]

Mean initial fibronectin concentrations in synovial fluid were 0·64 (SD 0·11) μg/ml for the azapropazone group and 0·55 (0·12) μg/ml for the steroid group. Neither drug had a significant effect on the synovial fluid fibronectin concentration measured four weeks later: azapropazone 0·59 (0·16) μg/ml; triamcinolone 0·55 (0·11) μg/ml.

Although our results were negative, they are important in relation to previous studies which showed a significant reduction in synovial fluid fibronectin concentrations after treatment.[1] Our data indicate that the short term treatment of arthritis by steroids or non-steroidal anti-inflammatory drugs does not cause significant changes in fibronectin concentrations in synovial fluid. Our results imply that local steroids and oral non-steroidal anti-inflammatory drugs do not affect synovial connective tissue proliferation and therefore have no influence on proliferative disease processes.

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1 Goebel K M, Storck U. Effect of intra-articular orgotein versus a corticosteroid on rheumatoid arthritis of the knees. *Am J Med* 1983; **74**: 124–8.
2 Carsons S, Mosesson M W, Diamond H S. Detection and quantitation of fibronectin in synovial fluid from patients with rheumatic disease. *Arthritis Rheum* 1981; **24**: 1261–7.
3 Carsons S, Parenti D, Lavietes B, Diamond H S, Singer A, Boxer M. Plasma fibronectin in systemic lupus erythematosus: relationship to clinical activity, DNA binding and acute phase proteins. *J Rheumatol* 1985; **12**: 1088–92.
4 Stecher V J, Kaplan J E, Connolly K, Mielens Z, Saelens J K. Fibronectin in acute and chronic inflammation. *Arthritis Rheum* 1986; **29**: 394–9.
5 Fassbender H G. *The pathology of rheumatic disease*. Berlin: Springer, 1975.
6 Williams J D, Scott D L, DeBrito F B, Willoughby D A, Huskisson E C. Rheumatoid inflammation and joint destruction: Cause and effect or parallel phenomena? *Agents Actions* 1986; **18**: 538–43.
7 Herbert K E, Coppock J S, Griffiths A M, Williams A, Robinson M W, Scott D L. Fibronectin and immune complexes in rheumatic diseases. *Ann Rheum Dis* 1987; **46**: 734–40.