cance rating of one. The combinations of NSAIDs with a β blocker, quinidine with cimetidine, and glibenclamide with a thiazide diuretic each occurred in one patient. These combinations have a significance rating of two. The combinations of NSAIDs with methotrexate, salicylates with enalapril, and digoxin with hydroxychloroquine each occurred in two patients. These combinations have a significance rating of four.

None of the patients had reported a drug interaction before admission. The mean duration of admission was 39 days (range 7–84), during which time the only adverse reactions were diarrhoea secondary to auranofin in one patient and a skin rash secondary to sodium aurothiomalate in one patient. This small study supports previous studies illustrating the potential for drug interactions in patients with arthritis and emphasises the need for continued vigilance. Most potential drug interactions involve NSAIDs.¹ The absence of significant clinical drug interactions might be attributed to the judicious use of NSAIDs. They were reserved for the management of definite inflammation, and of the 33 patients receiving NSAIDs, 22 were receiving half the maximum recommended dose.

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1 Buchan I E, Bird H A. Drug interactions in arthritic patients. *Ann Rheum Dis* 1991; 50: 680–1.

2 Tatro D S. *Drug interaction facts*. St Louis: Lippincott, 1990.

Author's reply

Sir: Dr Hunter's findings from Canada are of interest and broadly reflect our own, though the factors contributing to the incidence of drug interactions are diverse, including the drugs available, local prescribing practices, and the national threshold for defining the severity of interaction. Nevertheless, the potential interaction between NSAIDs and diuretics, in particular, comes through strongly, as in our own series and Dr Hunter's counsel to use NSAIDs in the lowest effective dose provides sound advice world wide.

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Bronchiolitis obliterans in systemic lupus erythematosus

Sir: I was interested to read the recent case report 'Bronchiolitis obliterans in systemic lupus erythematosus: beneficial effect of intravenous cyclophosphamide'.¹ However, caution is required before accepting the authors' interpretation. It would be useful to have additional information about the patient's pulmonary function tests—typically, in obliterative bronchiolitis there is severe airways obstruction (reduced forced expiratory volume in one second/vital capacity, air trapping but not hyperinflation, reduced forced expiratory flow (FEF) 25–75%), associated with reduced diffusing capacity, but relatively normal trans-

fer coefficient. A 'mild restrictive defect' is most unusual; the reduced FEF, 25–75% in the case reported, is in keeping with small airways obstruction, but values for the residual lung volume and total lung volume are needed for full interpretation of the results.

The authors state that abnormal radiographs are common in obliterative bronchiolitis, but this is not the case in obliterative bronchiolitis associated with rheumatoid arthritis, when the radiograph is usually normal. The radiograph is often abnormal in obliterative bronchiolitis and organising pneumonia, which seems to be a quite distinct entity from obliterative bronchiolitis seen in association with connective tissue disease. The two radiographs shown are not comparable because of considerable differences in penetration of the films. They further state that obliterative bronchiolitis associated with rheumatoid arthritis occurs 'mainly in association with penicillamine treatment'. This is not true—the role of penicillamine in obliterative bronchiolitis remains an unproved hypothesis with little foundation—in the original case series only three of the six patients had ever been treated with penicillamine.²

The authors report that after treatment intravenously with cyclophosphamide the patient 'dramatically improved', but in fact there was minimal improvement in pulmonary function—the vital capacity improved only from 1.84 litres to 1.89 litres, PaO₂ from 9.2 to 10 kPa, and there was no improvement in the transfer factor at all. Indeed, a more reasonable conclusion from the data presented is that one month's cyclophosphamide treatment made no appreciable difference to the patient's lung function.

This case is of a patient with active systemic lupus erythematosus, with evidence of multi-organ involvement (leucopenia, membranous glomerulonephritis, hypocomplementaemia), who might or might not have had obliterative bronchiolitis. Intravenous cyclophosphamide was used with little evidence of benefit.

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1 Godeau B, Cormier C, Menkes C. Bronchiolitis obliterans in systemic lupus erythematosus: beneficial effect of intravenous cyclophosphamide. *Ann Rheum Dis* 1991; 50: 956–8.

2 Geddes D, Corrin B, Brewerton D, et al. Progressive airways obliteration in adults, and its association with rheumatoid disease. *Q J Med* 1977; 46: 427–44.

Authors' reply

Sir: We did not distinguish in the reported case between pure bronchiolitis obliterans and bronchiolitis obliterans with organising pneumonia.

Indeed, we had noticed, associated with a severe and sudden dyspnoea, a slight basal interstitial shadowing and a mixed functional syndrome with a striking improvement after treatment.

The forced expiratory flow from 25 to 75% of forced vital capacity increased from 40 to 60% of the predicted value.

In May 1987 the total lung volume was 3458 ml (72% of the predicted 4783) and the residual lung volume was 1757 ml (110% of the 1587 predicted value).

In June 1987 total lung volume was 3350

ml (77% of predicted 4348 ml) and residual lung volume was 1419 ml (88% of the 1605 ml predicted value).

The effect of D-penicillamine in this kind of lesion in rheumatoid arthritis (RA) has been recognised since 1985, and 30 cases have been published.¹

It is of course also possible that D-penicillamine has only an aggravating role on pre-existent lesions induced by rheumatoid arthritis.

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1 Perez T, Dansin E, Wallaert E, Tonnel A B. Manifestations pleuro pulmonaires de la polyarthrite rhumatoïde. *Rev Mal Respir* 1991; 8: 169–89.

Pamidronate associated hallucinations

Sir: Gallacher *et al* reported the effectiveness of intravenous (IV) pamidronate (Aredia, Ciba Geigy Pharmaceuticals) in treating Paget's disease of bone while commenting that optimum dose regimens have yet to be defined.¹ While pamidronate has an established role in the treatment of hypercalcaemia associated with malignancy,² it has no licence for the treatment of Paget's disease, though it has been widely used and found effective for most such patients. Parenteral therapy is more effective than oral treatment,³ with a recent report suggesting that a single IV infusion may be successful in many patients.⁴ Intravenous doses used have been up to 180 mg/day, given as a progressive, dose increasing regimen.⁵ We report here a case of vivid visual hallucinations after a single IV infusion of 90 mg pamidronate, which suggests that caution is required in giving high dose IV treatment in some patients.

A 75 year old man (weight 86 kg) with diffuse Paget's disease complained of progressively increasing pain in his right proximal femur of five years' duration. Alkaline phosphatase was only marginally raised at 320 IU/l (normal 130–300 IU/l). He had had 12 monthly injections of 100 IU calcitonin and a four day course of oral etidronate (1200 mg/day) in the previous 16 months, neither of which had resulted in a significant reduction in his pain. Renal function was slightly impaired (creatinine 152 μ mol/l, urea 9.0 mmol/l) with normocalcaemia (corrected serum calcium 2.57 mmol/l) (normal 2.20–2.65) before treatment with pamidronate.

He received a single IV infusion of 90 mg pamidronate (1 mg/kg) in 1 litre of 0.8% sodium chloride over 24 hours. Within two hours of completing the infusion he developed palpitations, followed by visual hallucinations. Initially, these were of houses, people, and fantasy scenes. Over a period of 10 days the visual hallucinations changed and became gradually more frequent and upsetting, and he seriously contemplated suicide. He had no auditory hallucinations nor any past psychiatric history.

He was admitted for evaluation of his hallucinations three months after the infusion. There were no diurnal variations in mood, difficulty in sleeping, problems with concentration, or weight loss, though he became clinically depressed after admission to hospital.

Corrected serum calcium and full blood count remained normal. A drug induced central nervous system toxicity syndrome was diagnosed by a psychiatrist, and thioridazine reduced the frequency and disturbing effect of the hallucinations. A brain computed tomographic scan was normal.

Studies of patients with Paget's disease treated with pamidronate have consistently shown a transient fall in serum calcium and phosphate, which are seldom of clinical significance and are associated with a decline in urinary calcium excretion and an increase in plasma parathyroid hormone levels.⁶ Transient haematological changes and fevers have also been reported⁴ after both oral and IV pamidronate, possibly mediated through direct or indirect effects on mononuclear phagocytes, resulting in the activation of cytokines.³ The mechanism underlying hallucinations in this patient is unknown but is considered unlikely to be due to alterations in serum calcium concentrations.

Adverse psychiatric reactions to biphosphonates appear to be rare, although etidronate has previously been reported to cause confusion (Committee on Safety of Medicines, personal communication). It is recommended that the mental state of patients given high dose infusions of pamidronate for Paget's disease should be monitored closely after their treatment.

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1 Gallacher S J, Boyce B F, Patel U, Jenkins A, Ralston S H, Boyle I T. Clinical experience with pamidronate in the treatment of Paget's disease of bone. *Ann Rheum Dis* 1991; 50: 930-3.

- 2 Morton A R, Cantrill J A, Tracy A E, Howell A, Davies M, Anderson D C. Comparison of single dose versus daily intravenous amino hydroxypropylidene-1,1 biphosphonate (APD) for the management of the hypercalcaemia of malignancy. *BMJ* 1988; 296: 390-1.
- 3 Harinck H I J, Papapoulos G E, Blanksma H J, Moolenaar A J, Vermey P, Byvoet O L M. Paget's disease of bone: early and late responses to three different modes of treatment with aminohydroxypropylidene biphosphonate (APD). *BMJ* 1987; 295: 1301-5.
- 4 Thiebaud D, Jaeger P, Gobelet C, Jacquet A F. A single infusion of biphosphonate AH Pr BP (APD) as treatment of Paget's disease of bone. *Am J Med* 1988; 85: 207-12.
- 5 Cantrill J A, Anderson D C. Treatment of Paget's disease of bone. *Clin Endocrinol* 1990; 32: 507-18.
- 6 Thiebaud D, Jaeger D, Burckhardt P. Paget's disease of bone treated in five days with AHPBP (APD) per os. *J Bone Min Res* 1987; 2: 45-52.

Correction

Sir: We are writing to correct an inadvertent error in our manuscript entitled 'Detection of antineutrophil cytoplasmic antibody in a patient with L-tryptophan induced eosinophilia-myalgia syndrome', which appeared in volume 50 of the *Annals* last year.¹ The caption of fig 1, on page 817, stated that the antineutrophil cytoplasmic antibody stain shown was demonstrated on ethanol fixed human neutrophils. This photomicrograph was actually of the antineutrophil cytoplasmic antibody indirect immunofluorescence on formalin-acetone fixed human neutrophils. This is of importance because the antineutrophil cytoplasmic antibody (ANCA) specificity documented by enzyme immunoassay was for myeloperoxidase, which typically produces a perinuclear/nuclear staining pattern on ethanol fixed neutrophils rather than the granular cytoplasmic staining which is depicted. This

pattern on ethanol fixed neutrophils is associated with antiproteinase 3 specificity in about 85-90% of cases. An assay for antiproteinase 3 was negative in our patient, who also had a high titre of antinuclear antibody present at the time the ANCA was detected. Myeloperoxidase ANCA are difficult to detect on ethanol fixed neutrophils in the presence of antinuclear antibodies; therefore, we used the formalin-acetone fixation technique, which prevents the translocation of myeloperoxidase from the primary granules in the neutrophil cytoplasm to the nucleus when the nuclear membrane is lysed. When this technique is used, both types of ANCA demonstrate the staining pattern shown. In the absence of antinuclear antibodies ethanol fixed neutrophils are then used to rescreen the patient's serum and if the pattern converts to a perinuclear/nuclear one, myeloperoxidase specificity is present in 90% of cases. When antinuclear antibodies obscure the ANCA pattern a secondary assay such as the enzyme linked immunosorbent assay (ELISA) we used must be employed to identify the specificity of the ANCA present.

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1 Cilursu A M, Goeken J, Olson R R. Detection of antineutrophil cytoplasmic antibody in a patient with L-tryptophan induced eosinophilia-myalgia syndrome. *Ann Rheum Dis* 1991; 50: 817-9.