LETTERS TO THE EDITOR

Adhesion of peripheral blood lymphocytes to high endothelial venules of gut mucosa

Sir: We would like to respond to the rapid report by Kadioglu and Sheldon in a spirit of constructive criticism.

1 To achieve a purity of 'greater than 90% lymphocytes' after a single step gradient centrifugation is remarkable. The purity of the starting cell population is of more than academic interest as monocytes as well as neutrophils bind to endothelium.

2 How well documented is the statement that non-inflamed high endothelial venules are present in the porcine gut sections?

3 What is the behaviour of lymphocytes from other peripheral sites of inflammation, such as the pleural and peritoneal cavities?

4 Do activated, as distinct from resting, peripheral blood lymphocytes show increased adhesion to high endothelial venules of gut mucosa? This is crucial to their hypothesis as activated lymphocytes, particularly of the CD45RO 'memory' phenotype, show high adhesive ability to endothelial cells,² no matter what the source of the lymphocytes. Synovial cells are more than 90% CD45RO and more than 60% DR+ (activated) unlike those from the blood.

The concept that cells causing disease, not only lymphocytes but also antigen presenting cells carrying aetiologically important gut antigens, may home to the rheumatoid joint is interesting, but we feel that hard evidence in its support is still somewhat weak.

G S PANAYI
G H KINGSLEY
Rheumatology Unit
Division of Medicine
Guy's and St Thomas's
Medical and Dental School
London SE1 9RT
United Kingdom

C PITZALIS
St Helier Hospital
Surrey
United Kingdom

- 1 Kadioglu A, Sheldon P. Adhesion of rheumatoid peripheral blood and synovial fluid mononuclear cells to high endothelial venules of gut mucosa. *Ann Rheum Dis* 1992; 51: 126-7.
- 2 Pitzalis C, Kingsley G, Haskard D, Panayi G S. The preferential accumulation of helper-inducer T lymphocytes in inflammatory lesions: evidence for regulation by selective endothelial and homotypic adhesion. *Eur J Immunol* 1988; 18: 1397-404.

Authors' reply

Sir: We are happy to reply to the specific points raised by Professor Panayi and colleagues.

1 The purity of our lymphocyte populations, as assessed by Leishman's stain after gradient centrifugation, has been checked, and we abide by our original statement.

2 The statement that non-inflamed high endothelial venules are present in the Peyer's patches of porcine gut was based on the assumption that the tissues were physiologically normal. The intestines were obtained from

inspected healthy animals on all occasions. We therefore assume they were 'normal'. It has furthermore been shown recently that inducible cell adhesion molecule 110 (INCAM-110), which was present on postcapillary venules of actively inflamed endothelium (acute appendicitis, granulomatous lymphadenitis, and chronic rheumatoid synovitis), was not present on Peyer's patch endothelium, though it was found on follicular dendritic cells.¹

3 We have not, as yet, tested lymphocytes from other peripheral sites of inflammation, such as pleural or peritoneal cells. Binding of such cells would not necessarily imply inflammation as these sites are also regarded as 'mucosal'. Perhaps a more stringent test would be to compare binding of lymphocytes from inflamed and non-inflamed peripheral lymph nodes. This we hope to do. (On this point, it is interesting to ponder why in patients with active rheumatoid arthritis, regional lymphadenopathy is the exception rather than the rule.)

4 The question of cell activation is, we agree, of crucial importance. Preliminary work, using lymphocytes obtained from rheumatoid synovial membrane, has been carried out to establish the HLA-DR status of adherent cells. About 75% were DR+ (presumed activated T cells) and 25% negative. By this criterion, therefore, a quarter of bound cells did not possess this marker of activation. If, as Panayi *et al* say, 90% of synovial cells are CD45RO and show high adhesive ability to endothelial cells, why did such cells in our hands show far less binding to porcine lymph node high endothelial venules than to lamina propria endothelium (see below)?²

Thus activation itself is not the sole reason for the adhesion of cells as they still showed organ specificity.

A further point has come to light since the paper appeared. The sites of binding to high endothelial venules were thought to represent Peyer's patch high endothelial venules, but in fact would appear from the work of Jeurissen *et al*² to be lamina propria endothelium, which lacks the 'high' morphology of high endothelial venules, yet stains positively with MECA 325, a monoclonal antibody to Peyer's patch high endothelial venules. The sites we counted as 'poor in high endothelial venules' were in fact the areas within the Peyer's patches where the high endothelial venules are present. Thus our term 'relative binding' means binding to lamina propria high endothelial venule compared with Peyer's patch high endothelial venule. From this, therefore, it seems that, in rheumatoid arthritis, a greater proportion of synovial fluid lymphocytes bind to lamina propria endothelium than do peripheral blood lymphocytes, and so do lymphocytes released from porcine Peyer's patches compared with porcine peripheral lymph node or porcine peripheral blood.

Based on these findings, we feel that joint fluid mononuclear cells in rheumatoid arthritis may be a population of cells from Peyer's patches en route to lamina propria, for some reason diverted into joints. This might be due to the rheumatoid process affecting Peyer's patch lymphocytes, causing them to express a synovium specific addressin, or, alternatively, the rheumatoid process might cause the synovial high endothelial venules to express lamina propria-like ligand.

Like our colleagues, we find the concept of gut lymphocytes homing to rheumatoid joints interesting. We are beginning to accumulate evidence to support this notion,

though obviously more work needs to be carried out in this area.

PETER SHELDON
ARAS KADIOGLU
Department of Microbiology
Medical Sciences Building
University Road
Leicester LE1 9HN
United Kingdom

- 1 Rice E G, Munro J M, Corless C, Bevilacqua M P. Vascular and nonvascular expression of INCAM-110. A target for mononuclear leukocyte adhesion in normal and inflamed human tissues. *Am J Pathol* 1991; 138: 385-93.
- 2 Jeurissen S H M, Duijvestijn A M, Sontag Y, Kraal G. Lymphocyte migration into the lamina propria of the gut is mediated by specialized HEV-like blood vessels. *Immunology* 1987; 62: 273-7.

Potential for drug interactions in elderly patients with arthritis

Sir: I read with interest the paper by Buchan and Bird on drug interactions in arthritic patients.¹ They reported a potential drug interaction in 55 of 100 consecutive new patients admitted to a regional rheumatology centre. Eleven of the patients displayed clinical manifestations of a drug interaction.

I reviewed the admissions of 53 consecutive patients (45 female, eight male) over the age of 60 admitted to the arthritis service at the Holy Family Hospital, Vancouver, Canada. Their mean age was 72 years (range 60-90). The mean number of diagnoses was 2.6 (range 1-6). The commonest musculoskeletal diagnoses were rheumatoid arthritis (in 26), osteoarthritis of the peripheral joints (14), and osteoarthritis of the spine (eight). The commonest non-musculoskeletal diagnoses were hypertension (16), ischaemic heart disease (nine), obesity (eight), depression (five), prior peptic ulcer disease (three), bronchial asthma (three), and renal insufficiency (three).

The mean number of drugs being taken by each patient was 2.9 (range 0-6). The commonest drugs being used were non-steroidal anti-inflammatory drugs (NSAIDs) in 33, diuretics in 18, prednisone in 12, ranitidine in seven, calcium channel blockers in six, digoxin in six, cimetidine in five, amitriptyline in four, and β blockers in two. The potential for drug interactions was assessed with *Drug Interaction Facts*,² each drug interaction being assigned a significance rating from (1) major severity—the effects being potentially life threatening or capable of causing permanent damage and the interaction being well documented; (2) moderate severity—the effects may cause deterioration in a patient's clinical status. Additional treatment, admission to hospital, or extension of hospital stay may be necessary, and the interaction is established or probable; (3) minor severity—the effects are mild and the consequences may be bothersome or unnoticed and the interaction is well documented or probable; (4) major or moderate severity but the data documenting the interaction are limited; (5) minor severity—the documentation of the interaction is limited.

The commonest potential drug interaction seen in 11 patients was between NSAIDs and diuretics, which is assigned a significance rating of five. The combinations of digoxin with a diuretic and digoxin with a calcium channel blocker were each seen in three patients. These combinations have a signifi-

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.

T HUNTER
Holy Family Hospital
Vancouver, Canada

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.

HOWARD BIRD
Clinical Pharmacology Unit
University of Leeds
Royal Bath Hospital
Cornwall Road
Harrogate HG1 2PS

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.

D R PORTER
Centre for Rheumatic Diseases
Royal Infirmary
Glasgow G4 0SF
United Kingdom

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.

B GODEAU
C CORMIER
C J MENKES
Department of Rheumatology
Cochin Hospital
75674 Paris Cedex 14
France

1 Perez T, Dansin E, Wallaert E, Tonnel A B. Manifestations pleuro pulmonaires de la polyarthrite rhumatoïde. *Rev Med 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.