

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.

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- 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.

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- 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-