rheumatoid patients as had been suggested by others.¹⁻⁴ Our assessment methods were chosen for the purpose of answering a particular question and in the event, gave an unequivocal, albeit negative, result.

The information about osteoporosis was, in a sense, incidental, but nevertheless we believe valid. Our data clearly showed that a significant number of cases with rheumatoid arthritis and osteoarthritis had a trabecular bone volume (TBV) of less than 11%, the vertebral fracture threshold suggested as one method of defining osteoporosis.⁵ When this threshold was applied 13 osteoarthritic and 15 rheumatoid patients had osteoporosis. Thirteen biopsy specimens from rheumatoid patients and twelve from osteoarthritics were unsuitable for morphometry but were examined histologically by an experienced bone pathologist. Twelve out of 42 rheumatoid patients and 11 out of 40 osteoarthritic patients were judged to have osteoporosis. The pathologist's own threshold on this assessment corresponds to a TBV of around 9%. Our results, therefore, represent a conservative estimate of osteoporosis in these populations of arthritic patients, and the margin of error would allow for the 30% difference between samples and sites for trabecular bone volume found by Dequeker,⁶ though we would also point out that other investigators do not agree that there is such a large variability.⁷⁻¹¹

We are not able to respond to the point about the influence of skeletal size or our failure to discriminate between primary and secondary osteoarthritis except to state that the female and male patients with each type of joint disease were of comparable height. A good age match was also clearly achieved and was necessary because we believed that if we were considering such environmental factors as physical activity, sunlight exposure, and diet, it was important to have two closely comparable groups.

We do not wish to comment on the suggestion that osteoarthritis increases skeletal size, except to state that to the best of our knowledge this is applicable to generalised osteoarthritis and is not a factor in other forms of disease.

We are in no doubt that osteoarthritis and osteoporosis are separate entities and are aware of the evidence cited by Dequeker and others.¹²⁻¹⁴ One group¹⁴ reported increased bone density in generalised osteoarthritis but found no such change in other forms of osteoarthritis. Dequeker and colleagues¹² noted differences between women with osteoporosis and those with generalised osteoarthritis. Height was decreased compared with arm span in the former due to vertebral collapse. A similar, though lesser, reduction in height was present in generalised osteoarthritis but considered to be due to aging. We did not have the generalised disease in mind when referring to osteoarthritis and osteoporosis, neither do we believe that this is what is meant by those believing that the two diseases do not occur together. One study clearly shows both conditions occurring in the same patient and contains the clear statement that 'half of the subjects examined had radiological evidence of both osteoarthritis and osteoporosis of the hip and pelvis simultaneously'.¹³ Finally we were surprised to find osteoporosis in osteoarthritic patients as frequently as in those with rheumatoid arthritis. The fact that this was the case in a study which did not set out to look for

osteoporosis, and therefore was less likely to be biased, is, we feel, good evidence for our statement that osteoarthritis and osteoporosis are not mutually exclusive.

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Use of D-penicillamine in osteoarthrosis

SIR, Because osteoarthrosis is considered by some authorities to be an inflammatory disease and because cysteine, a compound of similar chemical structure, inhibits latent collagenase in synovial fibroblast culture, we have compared D-penicillamine with placebo in a small pilot study in osteoarthrosis.

Thirty patients with generalised osteoarthrosis (all with osteoarthrosis localised to the hips and knees, all with adequate radiological criteria, were allocated at random to D-penicillamine in a dose increasing to 500 mg daily

week 8 or to a matched placebo in addition to their existing analgesic or non-steroidal anti-inflammatory regimen. Treatment was continued for a six-month period with monthly assessments. We found no improvement in the clinical parameters measured (night pain, early morning stiffness, articular index, functional impairment, pain on walking, pain at rest, or range of movement) in the penicillamine-treated group compared with the placebo group. Eight of these patients (four on active treatment and four on placebo) had raised erythrocyte sedimentation rates (ESRs) at the start of the study, and no improvement was seen in the ESR in either group. Three patients withdrew from the penicillamine-treated group because of accepted side effects from this drug. Blind analysis of x-rays taken at the start and end of the study showed no serial improvement for either group over this six-month period. Although the number of patients studied was extremely small, we found no evidence from this pilot study that penicillamine might be worthy of larger and more labour-intensive trials in osteoarthritis.

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Antibodies to peptidoglycan in spondylarthritis?

SIR, We read with interest the study of Park *et al.*¹ showing some association between serum antibody to bacterial peptidoglycan (PG) and both ankylosing spondylitis (AS) and Reiter's syndrome (RS), but surprisingly no such association with rheumatoid arthritis (RA). Antibody levels were measured by enzyme-linked immunosorbent assay (ELISA) with a synthetic PG as antigen, which consisted of PG-precursor pentapeptides (L-Ala-γ-D-Gln-L-Lys-D-Ala-D-Ala) covalently linked to a random polypeptide. This pentapeptide is similar to that found commonly in PG of Gram-positive bacteria, whereas the PG of Gram-negative bacteria has a different structure containing diaminopimelic acid (DAP) in a peptide (L-Ala-γ-D-Gln-meso-DAP-D-Ala-D-Ala) or similar peptide sequence together with different cross linking. Furthermore, PG is not such a prominent antigen in Gram-negative organisms as is the case for Gram-positive bacteria. For example, we find that rabbit antisera raised against isolated Gram-positive PG react only poorly or not at all with most Gram-negative bacteria, including klebsiella, unlike their consistently strong reaction with most Gram-positive bacteria.

An ELISA has been developed in this laboratory for antibodies reactive with peptidoglycan-polysaccharide polymers (PG-PS) isolated from Gram-positive group A *Streptococcus pyogenes* cell walls.² A significantly increased prevalence ($p < 0.005$) of serum anti-PG-PS antibody was found in juvenile chronic arthritis (70% of

patients had anti-PG-PS levels above the upper limit of the normal range), seropositive RA (46%), and seronegative RA (50%), compared with AS, systemic lupus erythematosus, myeloma, and healthy controls.² In a separate study, in collaboration with Dr A. Ebringer, it was found that only 6% of patients with either active ($n=40$) or inactive ($n=50$) AS had anti-PG-PS serum antibody levels raised above normal limits (unpublished data).

We suggest that the weak associations between anti-PG antibody levels and both AS and RS observed by Park *et al.*¹ may be due to unrelated infections with Gram-positive bacteria and that these data provide no relevant information on immunity to Gram-negative bacteria, such as klebsiella, shigella, and yersinia.

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SIR, We thank Evans *et al.* for their letter and the editor for giving us the opportunity to respond. Their suggestion that the weak associations between anti-PG antibody levels and both AS and RS may be due to 'unrelated infections' with Gram-positive bacteria may or may not be correct. The cause(s) of the rheumatic diseases, such as AS, RS, and RA, is not known. Moreover, the antibodies that we measured¹ could have developed from an immune response to Gram-positive (or even possibly Gram-negative) bacteria at various sites, including normal flora. Our recent report² of soluble forms of PG present in the urine samples of healthy volunteers who had taken an oral dose of penicillin suggests that the bacteria responsible for the PG-like antigen in humans may not necessarily be engaged in infections.

The discrepancies that exist in the literature on the association of anti-PG antibodies with several diseases (some of which were mentioned in the Discussion¹), may have arisen from differences in populations studied (bacterial colonisation and genetic make up), treatments administered (antibiotics), and assays employed. The antibodies measured in our study¹ were specifically directed against the major determinant of the PG, the D-Ala-D-Ala sequence, because we used a synthetic PG precursor pentapeptide (Ala-γ-D-Glu-Lys-D-Ala-D-Ala) as the antigen and a synthetic tripeptide (α-Boc-Lys-D-Ala-D-Ala) as a specific antibody inhibitor.¹ The antibodies measured by Johnson *et al.*³ had a different and more complex specificity. Their anti-PG-PS antibodies found in RA sera were not significantly inhibited by two tripeptides