bone infarcts is by no means unusual. Thus, the opinion of Li-Yu *et al* that "aggregates of apatites may be more common than previously recognised in rice bodies"¹ is supported.

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Angiopietin expression in synovial membranes from patients with RA

I should like to comment on a recent paper in the *Annals of the Rheumatic Diseases*, which demonstrates the expression of angiopoietin-1 in the synovium of patients with rheumatoid arthritis (RA).¹ Angiopietin-1 was demonstrated in most of the RA synovial membranes examined by immunohistochemistry, but there was a marked discrepancy in the amount and distribution of angiopoietin-1 at the mRNA level (as demonstrated by in situ hybridisation) compared with that seen at the protein level (as demonstrated by immunohistochemistry). This was not commented on by the authors of the paper but is rather surprising, particularly as such a discrepancy is not seen even with cytokine expression, which has a labile mRNA due to AUUUA-rich areas of the 3' untranslated region. It is not stated whether angiopoietin-1 mRNA has similar such regions and whether its mRNA is labile, but even this is unlikely to explain the discrepancy between the results of in situ hybridisation and immunohistochemistry for angiopoietin-1.

Using serial sections of RA synovial membranes, the authors stated that both CD68 positive macrophages and CD68 negative fibroblasts in the lining layer of the synovium contain angiopoietin-1, yet this is not very evident in the images displayed in fig 1. It surely would have been preferable to perform dual immunohistochemistry for CD68 and angiopoietin-1, or even to combine in situ hybridisation for angiopoietin-1 mRNA with immunohistochemistry for CD68 to demonstrate more definitively which cells in the RA synovial membrane are producing angiopoietin-1.

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Authors' reply

We thank Dr Smith for his interest in our study and for his comments about the differences between protein levels of angiopoietin-1 in RA synovium detected by immunohistochemistry and mRNA levels for angiopoietin-1 detected by in situ hybridisation. Immunohistochemical analysis frequently showed angiopoietin-1 protein in the synovial lining layer, as well as in cells within the sublining tissues, both in perivascular areas and in areas remote from vessels. Analysis of angiopoietin-1 mRNA expression by in situ hybridisation showed mRNA in these sites, but at low levels and with significantly less frequent detection of mRNA within the synovial lining layer. All the tissue samples evaluated by in situ hybridisation in this study, however, were paraffin embedded samples. It is known that during the processing of tissues into paraffin blocks, mRNA can be lost, even when care is taken to avoid RNase contamination. Owing to the limitations of this technique, we went on to examine both mRNA and protein expression in cultured synovial fibroblasts in vitro. We demonstrated angiopoietin-1 mRNA expression by northern blot analysis in unstimulated, as well as in tumour necrosis factor α stimulated, synovial fibroblasts, and confirmed the production of angiopoietin-1 protein by these cells using an enzyme linked immunosorbent assay (ELISA).

We believe that the serial sections in fig 1 of our previous paper¹ show that angiopoietin-1 protein is present in both CD68 expressing and non-expressing cells. Neither serial sections comparing angiopoietin-1 expression by in situ hybridisation and immunohistochemistry nor dual immunohistochemistry for CD68 and angiopoietin-1 is likely to yield new information.

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BOOK REVIEW

Pathology and pathobiology of rheumatic diseases. 2nd ed

H G Fassbender. (Pp503, 80.) Heidelberg: Springer, 2002. ISBN 3 540 62942 4.

Here is an impressive tour de force which could also be called "40 years' experience in microscopy of tissues from rheumatic disease patients". The author, born in 1929, has probably seen more joint specimens under his

microscope than anyone else and he is still head of a WHO centre of joint pathology in Mainz, Germany. This work is essentially based on his personal observations of histology and electron microscopy on biopsy, surgical, and perhaps postmortem material sent for diagnosis to his institution. It contains 31 chapters dealing with individual conditions and ends with a chapter called "Possibilities and limitations of synovial biopsy", which summarises Fassbender's legacy on three pages. Although the synovium is a loose tissue without definite structural components, it is possible to discern features distinguishing psoriatic arthritis and spondyloarthropathies from rheumatoid arthritis in its various stages and even to distinguish between osteoarthritis and "coxarthrosis". But it may take a lifetime to convince oneself, and even longer to convince the world, that this is indeed possible.

One hundred of the 500 pages are devoted to rheumatoid arthritis, and it is in this disease that the author has made his most significant contributions. He points out that cartilage destruction seems to be initiated by a transient tumour-like aggressive tissue, consisting of undifferentiated mesenchymal cells, which precedes pannus. Another observation of interest is the relative absence of osteoclasts. His hypothesis is that synovial fibroblasts are the dominating bone destructive cells. The hypothesis has gained support from experimental work in Dr Steffen Gay's laboratory in Zurich,¹ but it would be wrong to say that it has gained general acceptance. One explanation for Fassbender's relatively late recognition may be that most of his earlier work was published in German. The oldest English publication I could trace was from 1983.²

Fassbender is well aware of modern classics in the rheumatological literature and cites, for example, Dr Bywaters' paper on Jaccoud's deformity in the chapter on rheumatic fever. I believe, however, that most of us, including Eric Bywaters, now consider Jaccoud's deformity to be a manifestation of SLE. In synovial tissue obtained after joint replacement he finds giant cells as well as cement particles. Fibrin "exudation" (why not deposition?) is characteristic of rheumatoid joints and much less present in, for example, osteoarthritis or psoriatic arthritis. Some Germanisms can be found in the text. Interleukin 1 α and tumour necrosis factor α are proinflammatory and not pure inflammatory cytokines. Skeletal muscle changes are described in polymyalgia rheumatica, but unfortunately also in fibromyalgia, although the latter has been retracted and re-interpreted as normal. Of osteoarthritis we learn that "It is only with onset of secondary synovitis that osteoarthritis becomes apparent". It is stated (with no reference) that 70% of cases of gout start in the first metatarsophalangeal joint. These criticisms point to the sometimes superficial style of the book. It does not cover the current front line literature on pathophysiology, but then this may not have been its main mission. But I would have liked to read Fassbender's comments on recent development in semiquantitative assessment of synovitis.^{3,4}

This is a historical document and the enthusiastic foreword by J Claude Bennett phrases it well: "Although the illustrations and photomicrographs presented tell a convincing story, the real jewel of this volume is the skilful way in which the author has managed to integrate the pathogenic process in time, space, and molecular context". In my view, the illustrations take the lead over the