

# PostScript

## MATTERS ARISING

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### On the origin of rice bodies with apatite crystals

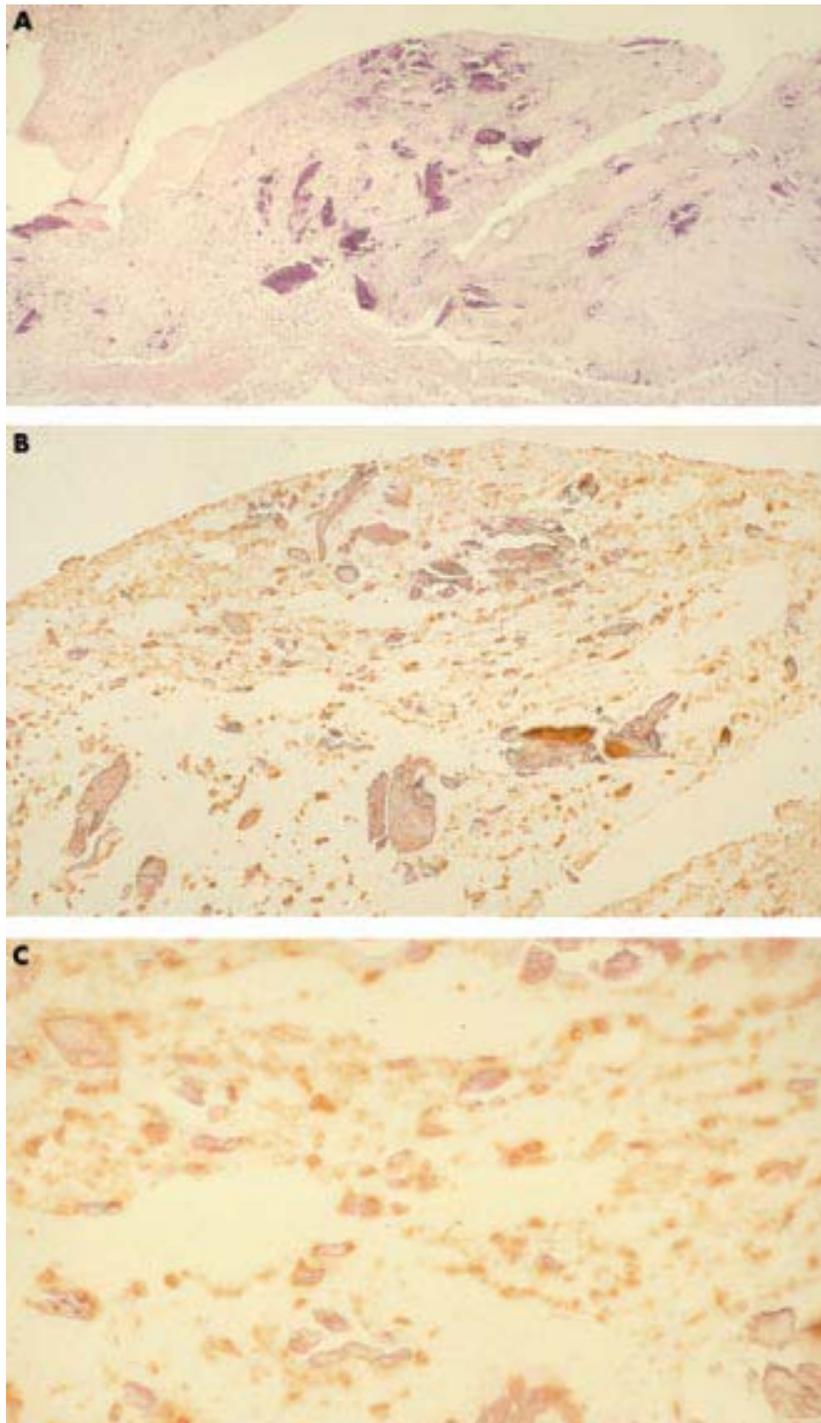
We read with interest the article of Li-Yu *et al* on synovial rice bodies containing calcium hydroxyapatite crystals.<sup>1</sup> From their findings the authors assume that the pathogenesis of this "apparently" rare coincidence of fibrin with bone-like apatite crystals remains unexplained.

A brief case report may give insight into the development of such a coincidence. A specimen taken at operation from the knee joint of a 55 year old woman with longstanding seropositive rheumatoid arthritis and rapid joint destruction owing to ischaemic bone necroses of the femoral and tibial compartment exhibited macroscopically a synovial membrane entirely covered with villous fibrin.<sup>2</sup> Light microscopy showed villi of older fibrin including a lot of tissue fragments (fig 1A). Sections stained with haematoxylin and eosin showed that these particles consisted of irregular shaped bone sequesters and basophilic granules as well as shreds of hyaline cartilage. In alizarin red stained sections the bone fragments were usually faintly stained (fig 1B). However, a multitude of tiny granules were characterised by a strong stainability with this "calcium dye" (fig 1C).<sup>3</sup>

From this observation it can be deduced that bone debris from osteonecrotic areas gained access to the synovial membrane via the synovial fluid. The shreds of bone debris induced a preferentially "fibrinous inflammation", leading to villi with entrapped cartilage and bone fragments of different size as well as tiny bone particles appearing as alizarin red granules.

With respect to the development of rice bodies of fibrin with enclosed "apatite crystals" it may be assumed that parts of the villous fibrin with bone particles can become detached from their synovial adherence and "reappear" in the synovial fluid with the formation of rice bodies.

The morphological findings described in the case report are an unusual major form of fibrinous debris synovitis due to large bone necroses. However, minor forms of this synovial reaction, originally described by Freund in 1927,<sup>4</sup> are not rare, and histological investigations on synovial membranes from



**Figure 1** Fibrinous debris synovitis due to bone fragments. Staining: (A) haematoxylin and eosin; (B, C) alizarin red S. (A) Synovial villus of older fibrin containing a multitude of basophilic bone particles. Magnification  $\times 30$ . (B) In the identical villus faintly stained bone fragments and strong stained granules. Magnification  $\times 70$ . (C) A section of (B) taken from about the middle of the figure showing a multitude of calcium containing granules derived from bone fragments. Magnification  $\times 180$ .

patients with advanced rheumatoid arthritis disclosed intrasynovial bone and cartilage fragments in about 50% of patients.<sup>5</sup> A fibrinous debris synovitis also often occurs in

osteoarthritis.<sup>6</sup> This may indicate that the opportunity for the appearance of rice bodies with bone derived apatite crystals owing to bone "abrasion" in advanced osteoarthritis or

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"<sup>1</sup> is supported.

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## References

- 1 Li-Yu J, Clayburne GM, Sieck MS, Walker SE, Athreya BH, DeHoratius RJ, *et al*. Calcium apatite crystals in synovial fluid rice bodies. *Ann Rheum Dis* 2002;61:387-90.
- 2 Mohr W. "Schneeweisse" Synovialmembran als Folge einer fibrinösen Knochendritusynovialitis. ["Snow-white" synovial membrane caused by bone debris synovitis.] *Aktuel Rheumatol* 2002;27:264-6.
- 3 Puchler H, Melan SN, Terry MS. On the history and mechanism of alizarin and alizarin red S stains for calcium. *J Histochem Cytochem* 1969;17:110-24.
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- 5 Menninger H, Stiegler A, Mohr W, Wessinghage D. Detritusynovialitis bei chronischer Polyarthrit: eine klinische und operationshistologische Auswertung. [Debris-synovitis in rheumatoid arthritis: clinical and histological findings.] *Z Rheumatol* 1989;48:89-94.
- 6 Mohr W. Morphogenesis of osteoarthritis. In: Giffka J, Ogilvie-Harris DJ, eds. *Osteoarthritis. Fundamentals and strategies for joint-preserving treatment*. Berlin, Heidelberg: Springer, 2000:23-35.

## 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).<sup>1</sup> 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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## Reference

- 1 Gravallese EM, Pettit AR, Lee R, Madore R, Manning C, Tsay A, *et al*. Angiopietin-1 is expressed in the synovium of patients with rheumatoid arthritis and is induced by tumour necrosis factor  $\alpha$ . *Ann Rheum Dis* 2003;62:100-7.

## 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  $\alpha$  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 paper<sup>1</sup> 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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## Reference

- 1 Gravallese EM, Pettit AR, Lee R, Madore R, Manning C, Tsay A, *et al*. Angiopietin-1 is expressed in the synovium of patients with rheumatoid arthritis and is induced by tumour necrosis factor  $\alpha$ . *Ann Rheum Dis* 2003;62:100-7.

## 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,<sup>1</sup> 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.<sup>2</sup>

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  $1\alpha$  and tumour necrosis factor  $\alpha$  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.<sup>3,4</sup>

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 skillful 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

molecular interpretations and another dimension of authenticity would have been added had clinical data been provided about the donors of the specimens. This work will assume a place of honour on my bookshelf.

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#### References

- 1 **Müller-Ladner U**, Gay S. MMPs and rheumatoid synovial fibroblasts: Siamese twins in joint destruction? *Ann Rheum Dis* 2002;61:957-9.
- 2 **Fassbender HG**, Simmling-Annefeld M. The potential aggressiveness of synovial tissue in rheumatoid arthritis. *J Pathol* 1983;139:399-406.
- 3 **Bresnihan B**, Tak PP, Emery P, Klareskog L, Breedveld F. Synovial biopsy in arthritis research: five years of concerted European collaboration. *Ann Rheum Dis* 2000;59:506-11.
- 4 **Cunnane G**, Madigan A, Murphy E, FitzGerald O, Bresnihan B. The effects of treatment with interleukin-1 receptor antagonist on the inflamed synovial membrane in rheumatoid arthritis. *Rheumatology (Oxford)* 2001;40:62-9.

### CORRECTION

**Analgesic action of acetaminophen and rofecoxib on knee pain and function** (*Ann Rheum Dis* 2003;62(suppl I):484 (ABO435).)

The last author was omitted from this abstract. The full author list should have been as follows:

H Sprott,<sup>1</sup> H Shen,<sup>1</sup> B A Michel,<sup>1</sup> D Uebelhart,<sup>1</sup> R E Gay,<sup>1</sup> S Gay,<sup>1</sup> H Sprott<sup>1</sup> *Rheumatology and Institute of Physical Medicine, University Hospital Zurich, Zurich, Switzerland*

### FORTHCOMING EVENTS

**25th Annual Meeting of the American Society for Bone and Mineral Research (ASBMR)**

19-23 September 2003; Minneapolis, Minnesota, USA  
Tel: +1 202 367 1161  
Fax: +1 202 367 2161  
Email: asbmr@dc.sba.com  
Website: www.asbmr.org

**10th European Pediatric Rheumatology Congress**

2-5 October 2003; Stresa, Italy  
*Contact:* Organising Secretariat, ECON srl, Via della Moscova 16, 20121 Milan, Italy  
Tel: +39 022 900 5745

Fax: +39 022 900 5790  
Email: econsrl@tin.it  
Website: www.pres.org.uk

**International Congress on Arthritis in the Elderly**

9-11 October 2003; Milan, Italy  
New perspectives in diagnosis and treatment  
*Contact:* Organising Secretariat: Elena Romero  
Tel: +39 02 65 71 200  
Fax: +39 02 65 71 270  
Email: eldrheum@oic.it

**7th EULAR Sonography Course**

9-12 October, 2003; Rome, Italy  
An introductory and practical course on musculoskeletal ultrasonography  
Scientific secretariat: Professor Guido Valesini  
Email: annamaria.iagrocco@uniroma1.it  
*Contact:* Organising secretariat: Michela Civelli, EDRA Spa, Medical Publishing and News Media, Viale Monza, 133 - 20125, Milan, Italy  
Tel: +39 (0)2 281 72300  
Fax: +39 (0)2 281 72399  
Email: edracongressi@dsmedigroup.com

**OARSI World Congress on Osteoarthritis**

12-15 October 2003; Berlin, Germany  
Tel: +1 202 367 1177  
Fax: +1 202 367 2177  
Email: oarsi@oarsi.org  
Website: www.oarsi.org

**American Back Society: Advanced Diagnosis and Treatment for Neck and Back Pain 2004**

11-15 November 2003; Las Vegas, Nevada  
24 CME category I units  
Tel: +1 510 536 9929  
Fax: +1 510 536 1812  
Email: info@americanbacksoc.org  
Website: http://www.americanbacksoc.org

**Fourth International Symposium on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis**

14-17 November 2003; Nice, France  
*Contact:* Organisation Secretariat, YP Communication, 108 boulevard G Kleyer, 4000 Liège, Belgium  
Tel: +32 (4) 254 12 25  
Fax: +32 (4) 254 12 90  
Email: yoland@piettecommunication.com  
Website: http://nice.piettecommunication.com

**2nd International Forum on Geronto-Rheumatology**

27-29 November 2003; Amsterdam, The Netherlands  
*Contact:* Erna Kleinjan, project manager Mark Two Communications, PO Box 358, 3830 AK Leusden  
Tel: +31 33 434 5730  
Fax: +31 33 434 5720  
Email: ekleinjan@marktwo.nl  
Website: www.marktwo.nl

**IOF World Congress on Osteoporosis**

14-18 May 2004; Rio de Janeiro, Brazil  
Abstract deadline 14 November 2003  
IOF awards are available for scientists:  
IOF Claus Christiansen Research Fellowship: €45 000  
IOF Servier Young Investigator Fellowship: €40 000  
*Contact:* Congress Secretariat at info@osteofound.org  
Website: www.osteofound.org

**XIth International Conference on Behçet's Disease**

27-31 October 2004; Antalya, Turkey  
*Contact:* Congress Secretariat, Figur Congress and Organization Services Ltd. STI, Ayazmaderesi Cad. Karadut Sok. No: 7 80888 Dikilitas, Istanbul, Turkey  
Tel: +90 (0212) 258 6020  
Fax: +90 (0212) 258 6078  
Email: behcet2004@figur.net  
Website: www.behcet2004.org

**4th International Congress on Autoimmunity**

3-7 November 2004, Budapest, Hungary  
Deadline for receipt of abstracts: 20 June 2004  
*Contact:* 4th International Congress on Autoimmunity, Kenes International—Global Congress Organisers and Association Management Services, 17 rue du Cendrier, PO Box 1726, CH-1211 Geneva 1, Switzerland  
Tel: +41 22 908 0488  
Fax: +41 22 732 2850  
Email: autoim04@kenes.com  
Website: www.kenes.com/autoim2004

**Future EULAR congresses**

9-12 June 2004; EULAR 2004; Berlin, Germany  
8-11 June 2005; EULAR 2005; Vienna, Austria  
21-24 June 2006; EULAR 2006; Amsterdam, The Netherlands

**Future ACR meetings**

24-28 October 2003; 67th Annual Scientific Meeting; Orlando, Florida  
16-21 October 2004; 68th Annual Scientific Meeting; San Antonio, Texas