MATTERS ARISING

Pigmented villonodular synovitis

I write with regard to the paper by Zuber and colleagues that purports to demonstrate a case of pigmented villonodular synovitis (PVNS).¹

The pathology material presented by the authors, however, is not diagnostic of PVNS, in that the cellular infiltrate did not demonstrate the large polyhedral cells—usually dubbed histiocytes—that are requisite for the diagnosis of PVNS. Villi, nodules, giant cells, and haemosiderin are not specific, and may be seen in a variety of conditions other than PVNS. It is the histiocyte that renders the pathology of PVNS unique and diagnostic. Indeed, Lichtenstein has described PVNS as a 'histiocytosis' of the synovial membrane.²

In addition, the authors suggest that in their patient PVNS was found to affect the second to fifth MCP joints. However, the diffuse form of PVNS is nearly always monarticular; documented cases of polyarticular (usually biarticular) involvement by PVNS are exceptionally rare, and probably number less than half a dozen in the medical literature.

The patient under discussion—who presented with progressive, bilateral ulnar deviation at the MCPs—most probably had rheumatoid disease, not PVNS. If there is a 'lesson' to this case, it is that the correct diagnosis of an unusual condition such as PVNS requires awareness of the characteristic clinical presentation of the disease and attentiveness to its diagnostic histopathology.

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Author's reply

Dr Docken expresses the opinion that the patient under discussion did not suffer from pigmented villonodular synovitis (PVNS) but from rheumatoid arthritis. Although I do agree that rheumatoid arthritis has to be considered as a differential diagnosis, the described patient did not fulfil the 1987 revised criteria for the classification of rheumatoid arthritis.¹ The patient did not suffer from morning stiffness in and around joints. She did have swellings of the MCP joints that were asymmetrical—that is, far more prominent on her left side; no signs of arthritis in these joints were present, however. The symptoms were not symmetrical. The patient did not have subcutaneous nodules, no rheumatoid factor was present in her serum, x rays of hands and feet did not show any erosions.

The patient presented in the department of traumatology, hand and reconstructive surgery with a fixed flexion deformity of her

left MCP joints, which caused inability to open her hand properly. She did not present with typical symptoms of rheumatoid arthritis such as morning stiffness, tenderness or pain. Synovectomy of the second to fifth MCP joints and reconstruction of the extensor hood of the left hand was performed. The right hand showed discrete thickening of the MCP joints. No need for surgery was discovered there. After surgery the patient was referred to rheumatology. Here the discrepancy between the lack of typical symptoms and signs of rheumatoid arthritis and the severe and asymmetric ulnar deviation, both of which is very unusual, was noted. Because of this discrepancy it was decided to ask for the routinely performed histological evaluation of the operation specimen, which clearly stated that PVNS was present.

The second point Dr Docken raises is the evaluation and interpretation of the histological specimen. His concern is that there might have been no histiocytes present in the specimen. Jaffe, Lichtenstein, and Sutro described in 1941² the salient histological features of PVNS, which are deposition of haemosiderin and infiltration of histiocytes and giant cells in a fibrous stroma within the synovium of tendon sheaths and large joints. I agree that it is the fibrohistiocytic proliferation that is characteristic for the pathology of the PVNS. Lipid filled histiocytes, also called foam cells, are depicted in figure 2 of the paper together with giant cells and scattered lymphocytes.

The third issue Dr Docken discusses is the fact that diffuse PVNS tends to occur monarticular. The knee is the most frequent joint involved, followed by the hip and ankle. Infrequently, the diffuse form will present in the hand, shoulder, wrist, and vertebral. Bilateral forms do occur occasionally³ and polyarticular forms are rare.⁴ Recently an unusual case of multiple site involvement of PVNS in a child has been reported.⁵ The case presented in our paper belongs to the rare polyarticular forms of diffuse PVNS.

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Combination DMARD therapy for rheumatoid arthritis. Full or low DMARD doses?

We read with great interest the paper by O'Dell.¹ We would like to offer some comments on it. Although we strongly believe in the rationale of the author, we feel that as clinicians our options should be based on clear cut data when treating patients with erosive progressive rheumatoid disease. In

our clinical practice, in active and severe diseases, we try to optimise any treatment by using the highest doses of both non-steroidal anti-inflammatory drugs and disease modifying antirheumatic drugs (DMARDs), compatible with an acceptable risk of toxicity. According to the medical literature, in rheumatoid arthritis (RA) the highest doses of OH-chloroquine (OH-C) are 6 mg/kg/day, of methotrexate (MTX) 17.5-20 mg/week, and of sulphasalazine 3 g/day.²⁻⁴ Poor or inadequate responses can be assessed only when these amounts are reached. In the study by O'Dell,⁵ three groups of patients were studied, one receiving full doses of MTX, one a combination of full doses of OH-C and 1 g/day sulphasalazine, and the third a combination of the three. To our knowledge no data exist suggesting that the combination of full doses of OH-C plus 1 g/day of sulphasalazine is any better than OH-C alone. It might well be that an additive effect is reached by such a combination, but this has never been proved. In addition no proof exists that 1 g/day sulphasalazine from the beginning, is clinically of any value in the long term treatment of RA.

When examining the combination studies that have been published on MTX and OH-C, we found no evidence of a statistically significant clinical or biological additive or synergistic effect of the two drugs. Therefore either the addition of low doses sulphasalazine to the two drugs exerts some peculiar, beneficial synergistic effect, still to be unequivocally proved, or the study lacks the data of a fourth group combining MTX plus 1 g/day sulphasalazine. Possible support for the additive effect, comes from a previously published open study using a combination of lower doses of MTX (mean dose throughout the study: 8.3 mg/week) plus full doses of sulphasalazine (2-3 g/day). The study showed that the association was more beneficial than the monotherapy with MTX alone.⁶ In fact while mean values of disease activity score (DAS) decreased by 26% in monotherapy, a mean decrease of 49% was seen in combination therapy. As the initial values of DAS were 5 or more, the results at the sixth month were certainly statistically significant, although of uncertain clinical importance. In contrast, in the O'Dell study⁵ the difference between groups, arose only after the 8-10th month of treatment with the multiple combination.

Therefore the real part in clinical practice, played by several combinations with low or full doses of each molecule, needs to be unequivocally confirmed.

Few studies have used full doses of single drugs or of various drugs in combination for long periods of time. Some negative results, at least, could have resulted from low doses or the results with single drug therapy could have been improved by using full doses of the drug.

As clearly hypothesised by O'Dell, by using full doses of the available drugs, the results should be even better either in terms of time lapse before the appearance of the response or of the degree of the response. We also need a clear distinction among the patients, between those who improve in a clinically meaningful manner (50% or more) and those who survive while receiving treatment without such a significant clinical benefit. For example, in our own experience with MTX, only 37% of 159 patients with active, erosive RA, followed up for three years, had a clinically important response,⁷ even though 83% were still receiving the drug (Ferraccioli

G F and colleagues, submitted data). As far as the per cent of patients obtaining a clear improvement is concerned, our results with MTX fully agree with those by O'Dell in his two year study.

In conclusion, in our view, when establishing a combination therapy to improve the clinical results in severe, active RA, full doses of each drug should be tried, and only clinically meaningful outcomes should be taken into consideration.

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Author's reply

I would like to thank Dr Ferraccioli and colleagues for their thoughtful letter on my leader.¹ I certainly agree with their main points: in combination studies (and other studies as well) full dose DMARDs should be used and success should be based on a meaningful degree of response (we chose 50% improvement of composite criteria). Clearly we believe that one of the main reasons that some combination DMARD studies have not shown differences has been that the DMARD dose in the combination arms have been low.

In our study we used what we considered at the time to be full dose methotrexate (17.5 mg/wk) and full dose hydroxychloroquine (400 mg/day).² We did, however, use low dose sulphasalazine (1 g/day) because of the concern about possible toxicity with the methotrexate-sulphasalazine combination. In our study the combination of methotrexate-sulphasalazine-hydroxychloroquine was clearly superior to methotrexate alone ($p < 0.001$); as pointed out by Dr Ferraccioli and colleagues it is unclear whether this increased efficacy resulted from the hydroxychloroquine, the sulphasalazine, or a combination of the two. We have a study in progress that we hope will

answer this question and in our current study the dose of sulphasalazine is increased to 2 g/day.

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Tissue crosslinks concentrations in normal joints and chronic articular diseases

We read with interest the recent paper by Takahashi *et al*¹ concerning joint tissue concentrations of collagen crosslinks (Pyr, Dpyr) in patients with osteoarthritis (OA) and rheumatoid arthritis (RA). The main discovery of this study was the presence of Dpyr also in extra-osseous tissues, namely cartilage and synovium in patients with joint disorders and in the synovium of non-arthritic controls. These data suggest that extra-skeletal sources may contribute to the increased urinary excretion of the two crosslinks in joint disorders, as several observers have reported in recent years.²⁻⁴

We recently performed a similar study on samples of subchondral bone, cartilage, and synovium of six patients with OA (mean (SD) age 58.1 (10.7)) and six patients with RA (age 61.1 (18.1)) who underwent total hip arthroplasty. In contrast with the study by Takahashi, as a control group we studied joints from six young patients (aged 37.5 (13.5)) who underwent surgical amputation of an extremity for malignant osteosarcoma. All patients were physically active before sur-

gery, permitting the sampling of normal 'healthy' joint tissues.

Briefly, tissue specimens of articular cartilage, subchondral bone, and synovium were collected, cleaned, dried, and immediately weighed and stored at -80°C . The assay of their crosslinks content was performed by high performance liquid chromatography according to a published method⁵ after an overnight hydrolysis.

Data are expressed in nmol of crosslinks/gram of fresh tissue. Our data confirm the presence of both crosslinks in cartilage and in synovial samples from all the groups tested. The mean ratio Pyr/Dpyr was 30:1 in cartilage and 17:1 in synovium and was similar in the three groups. In both controls and in patients, cartilage was the tissue with the highest content of Pyr (table 1). Looking at the differences in tissue levels among groups (fig 1), we observed a sharp reduction of both crosslinks in both bone and in cartilage in patients with joint diseases compared with healthy controls. In contrast, mean levels of crosslinks found in synovium remained relatively constant. These results can be interpreted as a true 'escape' of crosslinks from subchondral bone and articular cartilage in the terminal phases of joint disorders and are in contrast with previous results by Takahashi *et al*¹ who performed a quantitative analysis of Pyr in articular cartilage of patients with different bone and joint disorders and concluded that cartilage Pyr content was not affected by articular diseases. This last study lacks a control group and a true comparison with healthy joints was not available. Moreover, changes in crosslinks tissue levels may be more representative of the true collagen content when data are expressed as absolute values (nmol/g of fresh tissue) rather than after normalisation for collagen moles. Our finding of a reduced Pyr content in articular tissues in joint disorders is in agreement with recently published experimental data demonstrating that a decrease in collagen crosslinks content is associated with a reduced bone strength.⁷ Finally, the lack of significant difference in synovial content of collagen crosslinks

Table 1 Mean (SEM) concentrations of collagen crosslinks (nmol/g of fresh tissue) in articular tissue of healthy controls and in patients with osteoarthritis (OA) and rheumatoid arthritis (RA)

	n=6	Pyr	Dpyr	Pyr/Dpyr
Subchondral bone	Controls	1313 (366)	164 (20)	8 (2.6)
	OA	221 (92)	24 (4)	8 (4.5)
	RA	139 (7)	26 (2)	6 (1.4)
Articular cartilage	Controls	2150 (241)	88 (8)	25 (1.7)
	OA	1570 (266)	63 (15)	36 (7.7)
	RA	1166 (342)	40 (5)	29 (8.8)
Synovium	Controls	360 (50)	32 (3)	12 (1.2)
	OA	405 (81)	25 (7)	20 (5.2)
	RA	384 (101)	20 (4)	18 (2.3)

Figure 1 Mean concentrations (SEM) of Pyr and DPYR in subchondral bone and cartilage in patients with osteoarthritis, rheumatoid arthritis, and in healthy controls.

between controls and patients, which has been reported also by Takahashi *et al.*⁶ makes unlikely the contributory role of synovial membrane to urinary excretion of crosslinks in chronic joint diseases, which seems to be related to subchondral bone and articular cartilage increased turnover. This hypothesis is consistent with data from our previous study⁸ demonstrating that crosslinks concentrations in synovial fluid are similar in two conditions with a highly different metabolic turnover of synovial membrane such as OA and RA.

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Authors' reply

As stated by Sinigaglia *et al.* both pyridinoline (Pyr) and deoxypyridinoline (Dpyr) have been recently found in more various tissues than previously expected.^{1,2} I would like to offer the following comments.

Firstly, the usefulness of a biochemical marker does not need to be related to change of the concentrations of materials for marker in tissues. For instance both of the above crosslinks in urine have been established as bone resorption markers.³ The urinary crosslinks considerably increase in metabolic bone diseases, however they do not increase in bone, but an increase in the bone resorption (bone turnover) leads to an increase of crosslinks in urine. For a biochemical marker reflecting tissue turnover, if the content of a marker material does not change in disease, change in urinary excretion of the marker reflects the net turnover of its distributed tissue. Therefore, the authors conclusion that no change in concentration of crosslinks in synovium does not contribute to urinary crosslinks excretion is not correct.

Secondly, Pyr and Dpyr are physiological crosslinks to maintain the structure of collagen fibril. Therefore, their reduction is expected to be responsible for the degeneration of collagen and also the fragility of extracellular matrix. Our paper did not concentrate on this issue, so does not give the solution because of the absence of normal control in the study for bone and cartilage. Our previous study showed that Pyr did not change in cartilage in OA and RA compared with that in osteoporosis where a significant degeneration of cartilage is not involved.⁴

There are two problems in methodology in the comments made by Sinigaglia *et al.* One is that the concentrations of crosslinks were expressed per gram of fresh weight. The authors maintain that crosslinks tissue levels per weight is more representative of the true collagen content, which however implies that content of collagen changes but not crosslinks in collagen. The other is that the control group is considerably younger than the OA and RA groups. I do not claim, however, that the crosslinks are constant among OA, RA, and normal groups. A reduction of crosslinks in cartilage in OA and RA seen by Sinigaglia *et al.* may explain the degenerative change of cartilage in those diseases. However, the concentrations of Pyr and Dpyr in bone were considerably lower in OA and RA compared with the control group. In contrast, but in agreement with what I have previously mentioned, as Pyr and Dpyr are physiological crosslinks, the considerable change of these crosslinks induces diseases such as lathyrism. Therefore, the extreme reduction of crosslinks in bone is unlikely. The ideal way to solve this problem is to study the degenerated lesion and intact lesion of tissues mostly in cartilage in the same subjects, although I understand that it is difficult to critically distinguish those two lesions.

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