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ferent patient selection. We selected patients with RA who had taken at least one conventional 2nd line agent previously. The mean number of 2nd line agents per patient was 3, and only a minority had taken azathioprine and methotrexate (in 1990 in The Netherlands these were still 2nd line agents "at the top of the pyramid") or used corticosteroids at the start of the study. This might indicate a patient group with relatively mild disease compared to the patient group in Flipo and Reigneau's study. In our opinion, patients with milder disease have less chance of developing unacceptable nephrotoxicity and/or hypertension, and these adverse events seriously influenced the discontinuation rate in Flipo and Reigneau's study.

It is therefore questionable whether it is wise to limit the use of CyA only to patients with failure of most conventional 2nd line agents (including methotrexate), as has been ordered by registration authorities in a number of countries. We feel that CyA is safe in patients with RA provided that renal function and blood pressure are closely monitored and dose titrations according to the guidelines are immediately implemented. Such meticulous followup should include a kidney biopsy in case of progressive increase of serum creatinine in the long term, especially if continuation of CyA is considered clinically desirable.

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### Evaluation of Disease Activity in Rheumatoid Arthritis and Other Arthritides Using <sup>99m</sup>Tc Labeled Nonspecific Human Immunoglobulin

To the Editor:

We read with interest the article by Jamar, *et al*. The scintigrams 6 h after intravenous (iv) injection of 555 mBq <sup>99m</sup>Tc IgG were subjectively scored on a 0–3 scale where 0 = no uptake; 1 = faint uptake; 2 = definite uptake, and 3 = marked uptake. The scores of synovial uptake correlated significantly with systemic variables of inflammation<sup>1</sup>. The authors maintain that methods commonly used to assess joint inflammation are rather subjective and observer-dependent and that no available radiopharmaceutical has proven entirely satisfactory to evaluate synovitis. They claim that <sup>99m</sup>Tc-IgG scintigrams can objectively determine joint activity. However their scintigrams are scores on an arbitrary scale and therefore this method is subjective.

In their discussion the authors mentioned that the use of a semiquantitative index for assessing joint activity appeared technically unpractical (background subtraction, large vessel capacity, small size of some joints, and limited spatial resolution of the gamma camera). <sup>99m</sup>Tc-pertechnetate (<sup>99m</sup>TcO<sub>4</sub>) uptake in the joint after iv injection of <sup>99m</sup>TcO<sub>4</sub> (7 MBq) has been found to be a valuable objective variable of joint inflammation<sup>2–5</sup>. In this method a simple collimated sodium-iodide crystal (probe) is used. An excellent to good correlation was found between the results of the <sup>99m</sup>Tc-pertechnetate uptake and different clinical variables of joint inflammation. Reproducibility was good. Radiopharmaceutical uptake in the joint can be measured shortly after the iv injection<sup>1</sup>. The <sup>99m</sup>TcO<sub>4</sub> uptake technique has proven to be useful in the diagnosis of doubtful arthritis and for evaluation of the effect of local and systemic therapy in inflammatory activity of the joint<sup>6</sup>.

Radiodiagnostic methods to assess synovial inflammation most likely determine all the vascular changes (vascular proliferation, vasodilatation, vascular congestion, and endothelial lesions) induced by inflammation. The main advantage of external direct counting of joints in comparison with <sup>99m</sup>Tc-IgG scintigraphy of the joints is the lower dosage of <sup>99m</sup>Tc. In addition objective quantitation may be less difficult, the method is faster, relatively

simple, and inexpensive. The distribution of the radiopharmaceutical in the joint recorded on the scintigraph can give local information, but this is not relevant for measuring the severity of the disease activity.

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### Drs. Jamar and Manicourt reply

To the Editor:

We thank Dr. Boerbooms and Buijs for their comments on our paper<sup>1</sup>. It was not our aim to quantify local synovitis, for several, mainly practical reasons. The word "activity" in our title should be understood widely as both extent and severity. We agree with Boerbooms and Buijs that, for assessing the activity of knee joints, the simple collimated sodium iodide crystal probe is more objective than our visual scoring system<sup>2</sup>. However, this statement calls for further comment. (1) Although we use such a probe on a regular basis, (especially for hematological studies), this equipment is not available in the majority of nuclear medicine centers. Thus, this procedure is limited to certain centers, whereas ours requires basic nuclear medicine equipment, i.e., a gamma camera which is widely available. (2) As each probe has its own physical characteristics, (especially with regard to geometry), normal quantitative values have to be established in each center. (3) Although the radiation to patients using 7.4 mBq (200 μCi) <sup>99m</sup>Tc-pertechnetate is much less than with 555 mBq <sup>99m</sup>Tc-human immunoglobulin, such a small dose does not allow whole body scanning and is unpractical for assessing the extent of arthritides such as in rheumatoid arthritis. (4) Boerbooms, *et al* have rightly restricted use of their method to the study of the knee, i.e., a large peripheral joint. It is indeed unlikely their probe method can accurately explore synovitis either in small peripheral joints, such as the hands, or in large and more axial joints, such as hips and shoulders. In contrast, human immunoglobulin scintigraphy can readily and accurately detect synovitis in small peripheral joints and in large axial joints as well. Further we believe that the method proposed by Boerbooms and Buijs is perfectly suitable to assess the effect of local therapy, which was not the aim of our study.

Last, but not least, we are surprised by their choice of free <sup>99m</sup>Tc-pertechnetate as the tracer. Although this radiopharmaceutical offers several advantages, especially with regards to availability and simplicity of its use, it has not been used widely for imaging aseptic joint disorders. Indeed it has several drawbacks: (1) in contrast to <sup>99m</sup>Tc-human immunoglobulin, it is not an inflammatory agent and its use in arthritis is

purely empirical. (2) Normal synovium can be faintly visualized and the uptake by abnormal joints is less striking than the uptake of <sup>99m</sup>Tc-human immunoglobulin. (3) Accordingly, the interpretation of abnormal images requires much more experience than does imaging with <sup>99m</sup>Tc-human immunoglobulin.

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## Pancytopenia Related Eosinophilia in Rheumatoid Arthritis

To the Editor:

The case report by Bruyn, *et al*<sup>1</sup> states that eosinophilia has not been observed in other drug induced pancytopenias in patients with rheumatoid arthritis (RA). The authors further suggest that this could be a specific phenomenon associated only with methotrexate (MTX). Their references include mention of penicillamine as a drug not associated with eosinophilia in this context.

Apparently the authors overlooked an earlier paper describing 2 patients who developed neutrophilic agranulocytosis and eosinophilia during treatment with penicillamine<sup>2</sup>. In one case, eosinophilia was present only in the marrow, but in the 2nd case, there was eosinophilia in both marrow and peripheral blood, with values as high as 30% in the recovery phase. Because of this the term agranulocytosis was qualified as neutrophilic agranulocytosis, since the eosinophils were not only spared, but actually increased. There is nothing unique about the ability of MTX to induce this phenomenon.

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## Dr. Bruyn, et al reply

To the Editor:

We appreciate the interest shown in our paper<sup>1</sup>. In his letter, Jaffe mentions an article he and his colleagues published in 1964 on 2 patients with rheumatoid arthritis treated with D-penicillamine, who subsequently developed a neutrophilic agranulocytosis<sup>2</sup>. This article was not referenced because the Medline search covered the period 1966-1994. Jaffe's main point is that D-penicillamine may also cause agranulocytosis sparing the eosinophilic lineage.

While we acknowledge this possibility, we have several comments on the Jaffe, *et al* article. First, both his patients were receiving longterm cor-

ticosteroid medication, which was withdrawn shortly before occurrence of the agranulocytosis. The withdrawal could have induced adrenal cortex insufficiency, which can be accompanied by eosinophilia.

Second, both patients developed pruritus shortly after and the 2nd patient also developed a rash after commencing the D-penicillamine. In the 2nd patient the rash and eosinophilia appeared before agranulocytosis. These observations suggest drug hypersensitivity as cause of eosinophilia.

Third, the first patient showed no peripheral eosinophilia, while all our patients exhibited strong peripheral eosinophilia.

We do not know whether the pancytopenia associated with eosinophilia is a specific MTX related phenomenon. What we do know, however, is that MTX continues to be a drug with surprising clinical effects, as has been shown, for instance, in the case of digital nodulosis<sup>3</sup>.

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# Letters

## Photochemotherapy for Refractory Rheumatoid Arthritis

To the Editor:

We read with interest the editorial by Dr. Haberman<sup>1</sup> pointing out the use of photochemotherapy for the treatment of inflammatory arthritides, especially rheumatoid arthritis (RA). Extracorporeal photochemotherapy has been proposed in RA by Malawista<sup>2,3</sup> and ourselves<sup>4,5</sup>. Our procedure differs from that used by Malawista in that the enriched lymphocyte preparation is exposed *ex vivo* to 8-methoxypsoralen (8-MOP), in the presence of ultraviolet A (UVA). Oral ingestion of 8-MOP can be limited by the great variations of plasma final concentrations, and the total *ex vivo* procedure provides greater accuracy of lymphocyte irradiation. The technique reported by Laing, *et al*<sup>6</sup> is indicated for the local treatment of affected joints, and could be limited by the problems of requiring repeated arthroscopies and also the inherent local dangers of UVA overexposure.

The excellent tolerance and the possibility of prolonged positive effects make extracorporeal photochemotherapy a therapeutic option in refractory RA. Photophoresis may be considered as an immunomodulatory treatment to ensure better general control of the disease.

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