Menstrual arthritis

Sir: I read with interest the article by McDonagh *et al* on menstrual arthritis.[1] I also recently saw a patient with episodic inflammatory monarthritis directly related to the menstrual cycle.

A 39 year old woman presented in May 1992 with three episodes of painful swelling in the left knee. The attacks occurred spontaneously mid-way between menstrual losses and lasted for three or four days. On examination during an attack there was a warm effusion of the right knee with no other physical signs. Aspiration of synovial fluid showed a high white cell count with no evidence of crystals or bacteria. Radiographs of the knees were normal. Full blood count, erythrocyte sedimentation rate, C reactive protein, rheumatoid factor, antinuclear antibody titre, and HLA-B27 status were all normal. Since then she has had an exacerbation in the right knee for a few days during each menstrual cycle, though the severity of each attack has varied and attacks could be significantly reduced by non-steroidal drugs taken for a few days mid-cycle.

I was intrigued at the putative mechanism described in the article suggesting an anti-inflammatory effect around ovulation. The patient described in McDonagh's article fulfils this theory, whereas results in the patient I described suggest the reverse. I would be interested to know if others have had similar patients and readers' comments as to possible mechanism.

PAUL W THOMPSON
Poole Hospital
Poole
Dorset BH15 2JB
United Kingdom

1 McDonagh J E, Singh M M, Griffiths I D. Menstrual arthritis. *Ann Rheum Dis* 1993; **52:** 65–6.

Folate supplementation and methotrexate

Sir: We would like to share our concerns about points raised in the article 'Does folate supplementation make sense in patients with rheumatoid arthritis treated with methotrexate?' by Stenger *et al.*[1]

Although the authors refer to a lack of data supporting the possible immunosuppressive action of methotrexate (MTX), we and others have shown that the administration of MTX to patients with rheumatoid arthritis (RA) is accompanied by decreased serum levels of IgM and IgA rheumatoid factors and decreased in vitro synthesis of IgM rheumatoid factor.[2 3] We have also shown that the mitogen induced proliferative response of peripheral blood mononuclear cells from patients with RA treated with MTX is impaired. The proliferative response is artificially normalised if the experiments are conducted in folate-rich culture medium and if the folate dependent conversion of uridylate to thymidylate is bypassed by the use of preformed thymidine.[4] Lack of attention to these sources of error may explain the fact that inhibition of cell proliferation could not be shown previously.[5]

The authors state that although the mechanism of action of MTX in RA is unknown, depletion of intracellular folates by inhibition of dihydrofolate reductase is likely to alter 'inflammation and proliferation in arthritis target tissues'. This is an oversimplified statement that attributes all the effects of MTX to the inhibition of dihydrofolate reductase. Upon entry into cells, MTX is converted to poly-γ-glutamyl derivatives that have inhibitory activities not found in unmodified MTX. Inhibition of 'distal' enzymes, such as thymidylate synthase or phosphoribosyl-amino-imidazole-carboxamide - ribotide - formyl - transferase, by polyglutamates of MTX may be as important or more important in altering the rheumatic process than inhibition of dihydrofolate reductase.[6] The fact that fully oxidised folic acid lessens the toxicity while efficacy is maintained indicates that inhibition of dihydrofolate reductase is not complete, and such inhibition may not be essential to obtain a therapeutic response in RA.[7 8] This is further indicated by the fact that the administration of small doses of folinic acid, a carbon substituted, reduced folate that does not require reduction by dihydrofolate reductase, seems to lessen toxicity without altering efficacy.[9] Conversely, excessive doses of folinic acid, which could effectively compete with MTX and prevent its polyglutamylation, eliminate both its toxicity and its efficacy.[10]

In their review the authors cite our work[7] and that of Stewart *et al*[8] regarding folic acid supplementation, as well as the experience with folinic acid,[9] as the basis for suggesting that a reduction in the dose of MTX makes more sense than the concomitant administration of MTX with folates. The authors state that with the exception of Stewart's work the others studies were short term with small numbers of patients. They also state that an assay of folate status, such as the C_1 index, was not done. Some clarifications are in order.

Firstly, our study included 32 patients in accordance with an a priori established sample size necessary to detect differences in the toxicity between folic acid supplemented and non-supplemented patients. Secondly, the mean percentage decrease in the C_1 index over six months was significantly greater in the placebo supplemented than in the folic acid supplemented MTX treated patients. Finally, the data reported by Stewart *et al* need to be more carefully scrutinised.[8] Strictly speaking, what they reported is not a clinical trial, but rather a retrospective analysis of data on their patients. Furthermore, they did not include a true control group, since all their patients were supplemented with folic acid. These methodological problems raise questions about the conclusions reached by these investigators.

In summary, as a result of our previous and continuing work we strongly believe that folic acid supplementation has a role in the treatment of patients with RA receiving MTX. Although reducing the dose of MTX may appear to be more rational and may achieve similar results with regards to the toxicity of MTX, there are no data to validate such a practice in terms of MTX efficacy. The article by Stenger *et al* may give the *Annals* readership the sense that folic acid supplementation in MTX treated patients with RA should not be used. Our interpretation of the reports published is quite different.

SARAH L MORGAN
JOSEPH E BAGGOTT
WILLIAM J KOOPMAN
CARLOS L KRUMDIECK
GRACIELA S ALARCÓN
Departments of Nutrition Sciences and Medicine (Division of Clinical Immunology and Rheumatology)
University of Alabama at Birmingham
Birmingham AL 35294
USA

1 Stenger A A M E, Hourtman P M, Bruyn G A W. Does folate supplementation make sense in patients with rheumatoid arthritis treated with methotrexate? *Ann Rheum Dis* 1992; **51:** 1019–20.
2 Alarcón G S, Schrohenloher R E, Bartolucci A A, Ward J R, Williams H J, Koopman W J. Suppression of rheumatoid factor production by methotrexate in patients with rheumatoid arthritis. Evidence for differential influences of therapy and clinical status on IgM and IgA rheumatoid factor expression. *Arthritis Rheum* 1990; **33:** 1156–61.
3 Olsen N J, Callahan L F, Pincus T. Immunologic studies of rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum* 1987; **30:** 481–8.
4 Hine R J, Everson M P, Hardin J M, *et al.* Confounding effects of folic acid and thymidine on proliferation of mononuclear cells of methotrexate treated RA patients. *Rheumatol Int* 1990; **10:** 165–9.
5 Anderson P A, West S G, O'Dell J R, Via C S, Claypool R G, Kotzin B L. Weekly pulse methotrexate in rheumatoid arthritis: chemical and immunological effects in a randomized double-blind study. *Ann Intern Med* 1985; **103:** 489–96.
6 Baggott J E, Vaughn W H, Hudson B B. Inhibition of 5-aminoimidazole-4-carboxamide ribotide transformylase, adenosine deaminase and 5'-adenylate deaminase by polyglutamates of methotrexate and oxidized folates and by 5-aminoimidazole-4-carboxamide riboside and ribotide. *Biochem J* 1986; **236:** 193–200.
7 Morgan S L, Baggott J E, Vaughn W H, *et al.* The effect of folic acid supplementation on the toxicity of low-dose methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 1990; **33:** 9–18.
8 Stewart K A, Mackenzie A H, Clough J D, Wilke W S. Folate supplementation in methotrexate-treated rheumatoid arthritis patients. *Semin Arthritis Rheum* 1991; **20:** 332–8.
9 Hanrahan P S, Russell A S. Concurrent use of folinic acid and methotrexate in RA. *J Rheumatol* 1988; **15:** 1078–80.
10 Tishler M, Caspi D, Fishel B, Yaron M. The effects of leucovorin (folinic acid) on methotrexate therapy in rheumatoid arthritis patients. *Arthritis Rheum* 1988; **31:** 906–8.

AUTHORS' REPLY We thank Morgan *et al* for their remarks on our article,[1] especially those on the proposed mechanism of action of methotrexate (MTX).

We agree that the data on the immunosuppressive action of MTX are conflicting. In vitro changes of immune variables are mostly referred to in published reports.

When commenting on our statement that inhibition of the enzyme dihydrofolate reductase is by far the most relevant action of MTX, Morgan *et al* remark that inhibition of other cell enzymes by MTX polyglutamates such as thymidylate synthetase or the phorphoribosyl - amino - imidazole - carbox - amide-ribotide-formyl-transferase may be more important. It is well established, however, that enzymes such as this transformylase and thymidylate synthetase are equally dependent on the availability of coenzyme forms of folic acid.[2] For example, deoxythymidylic acid is formed from deoxyuridylic acid by thymidylate synthetase, which is a methylation requiring the participation of the folic acid coenzyme, *N*5,*N*10-methylenetetrahydrofolate as methyl donor. *N*5,*N*10-methylenetetrahydrofolate is merely one of many coenzyme forms of tetrahydrofolic acid, all functioning in a large number

of enzymatic reactions in which one-carbon groups are transferred from one metabolite to another.

Furthermore, polyglutamation of MTX is not only important for inhibition of the coenzymes mentioned above but also allows accumulation of free intracellular drug far above the concentrations of the parent compound that would otherwise stay in equilibrium with extracellular MTX. Free MTX and MTX polyglutamates have at least equal affinity to dihydrofolate reductase, but MTX polyglutamates dissociate much more slowly. Finally, the most striking property of polyglutamates is their ability to remain within the cell, even in the absence of an extracellular drug concentration; this is in contrast with free MTX, which freely diffuses in and out the cell, depending on the concentration gradient.[2]

Clinical trials on the prophylactic role of either folic or folinic acid are limited and should be interpreted cautiously. The statement of Morgan *et al* that, in general, folinic acid lessens toxicity without altering efficacy is incorrect. This is illustrated by the studies of Hanrahan,[3] Tishler,[4] and Buckley.[5]

Although the study of Morgan *et al* is methodologically correct, these authors use a toxicity score which leads one to wonder whether some side effects might have influenced the overall result more than others. Their study is a short term follow up (24 weeks) and lacks 'hard' outcome measures, such as progression of joint erosions. It is feasible that supplementation with folic acid causes a more rapid deterioration of radiological abnormalities. Furthermore, to our knowledge there are no data as to folate or folinic acid supplementation reducing serious side effects, such as haematological or hepatic toxicity or opportunistic infections, which tend to occur after a prolonged period of time.

Future long term prospective studies are needed to investigate the effect of folate supplementation on the course of rheumatoid arthritis in patients treated with MTX, as well as the role of the relative dose of folate or folinic acid compared with the dose of MTX.

ANNEMIEK A M E STENGER
PIETERNELLA M HOUTMAN
GEORGE A W BRUYN
Department of Rheumatology
Medical Centre of Leeuwarden
Henri Dunantweg 2
8934 AD Leeuwarden
The Netherlands

1 Stenger A A M E, Houtman P M, Bruyn G A W. Does folate supplementation make sense in patients with rheumatoid arthritis treated with methotrexate? *Ann Rheum Dis* 1992; **51:** 1019–20.
2 Jolivet J J, Cowan K H, Curt G A, Clendeninn N J, Chabner B A. The pharmacology and clinical use of methotrexate. *N Engl J Med* 1983; **309:** 1094–104.
3 Hanrahan P S, Russell A S. Concurrent use of folinic acid and methotrexate in RA. *J Rheumatol* 1988; **15:** 1078–80.
4 Tishler M, Caspi D, Fishel B, Yaron M. The effects of leucovorin (folinic acid) on methotrexate therapy in rheumatoid arthritis patients. *Arthritis Rheum* 1988; **31:** 906–8.
5 Buckley L M, Vacek P M, Cooper S M. Administration of folinic acid after low dose MTX in patients with RA. *J Rheumatol* 1990; **17:** 1158–62.

Bone mineral density and osteoarthritis

Sir: Knight, Ring, and Bhalla in their leader 'Bone mineral density and osteoarthritis'[1] call attention to the role subchondral bone density might play in the pathogenesis of osteoarthritis. In their summary they state that 'there is no convincing evidence that patients with osteoarthritis have a generalised increase in bone mineral density'.

In an earlier publication,[2] however, we clearly showed that at the iliac crest in women aged 60–75 years there is a significantly increased amount of cortical and trabecular bone mass in those with osteoarthritis of the hands. Bone mass was evaluated by three different methods: dual photon absorptiometry, physical assessment according to Archimedes' principle, and histomorphometry. This increased bone mass in osteoarthritis is associated with an increase in biomechanical properties of bone as stiffness and compressive strength[3] and an increase in osteocalcin concentration in the bone matrix.[4]

Furthermore, there are alterations in the mineralisation profile of bone in patients with generalised osteoarthritis.[5] Using a density fractionation technique, we found a significant shift to higher densities in the patients with osteoarthritis compared with young adults and controls matched for age and sex.

All our observations indicate that bone mineral density is indeed increased, not only around the affected joints but also generally in generalised osteoarthritis, and that this increase antedates the osteoarthritic degeneration. A change in bone mineral density is associated with a change in the mechanical properties of bone. These altered mechanical properties of the underlying subchondral bone may cause cartilage degeneration and affect the progress of osteoarthritis. Primary osteoarthritis is, in our opinion, part of a more generalised bone disease.

J DEQUEKER
J AERSSENS
Arthritis and Metabolic Bone Disease Research Unit
K U Leuven, U Z Pellenberg
B-3212 Pellenberg
Belgium

1 Knight S M, Ring E F J, Bhalla A K. Bone mineral density and osteoarthritis. *Ann Rheum Dis* 1992; **51:** 1025–6.
2 Gevers G, Dequeker J, Geusens P, Nyssen-Behets C, Dhem A. Physical and histomorphological characteristics of iliac crest bone differ according to grade of osteoarthritis at the hand. *Bone* 1989; **10:** 173–8.
3 Gevers G, Dequeker J, Martens M, Van Audekercke R. Biomechanical characteristics of iliac crest bone in elderly women, according to osteoarthritis grade at the hand joints. *J Rheumatol* 1989; **16:** 660–3.
4 Gevers G, Dequeker J. Collagen and non-collagenous protein content (osteocalcin, sialoprotein, proteoglycan) in the iliac crest bone and serum osteocalcin in women with and without hand osteoarthritis. *Coll Relat Res* 1987; **7:** 435–42.
5 Raymaekers G, Aerssens J, Van den Eynde R, *et al*. Alterations of the mineralization profile and osteocalcin concentration in osteoarthritic cortical iliac crest bone. *Calcif Tissue Int* 1992; **51:** 269–75.

Autologous pregnancy plasma transfusion in RA

I read the letter by Scoville on postpartum autologous plasma transfusion and its effect on rheumatoid arthritis (RA). Contrary to what was stated, his was not the 'first known report of a postpartum autologous transfusion in a patient with RA'. In 1987 our group reported the same procedure and extensively reviewed published reports.[2] Unlike Dr Scoville's patient, ours did not respond so we did not pursue this approach further.

DANIEL J WALLACE
Cedars-Sinai Medical Center
UCLA School of Medicine
Los Angeles, CA
USA

1 Scoville C D. Postpartum autologous plasma transfusion: effect on RA. *Ann Rheum Dis* 1992; **51:** 1342–3.
2 Wallace D J, Goldfinger D, Klinenberg J R. Use of autologous pregnancy plasma to treat a flare of juvenile rheumatoid arthritis: case report and literature review. *J Clin Apheresis* 1987; **3:** 216–8.

The antiquity of rheumatoid arthritis

Sir: The antiquity of rheumatoid arthritis is still a controversial issue. The pictures of Siebrandus Sixtius presented by Dequeker[1] are impressive but not fully convincing. Other arthritides may result in hand deformation resembling rheumatoid arthritis, including gout, psoriatic arthritis, and even systemic lupus with Jaccoud's deformation. The same problem occurs with every anecdotal case for which there are only pictures and vague history.

Some years ago I tried to carry out an epidemiological study of Flemish painting. In the works of Breughel the Elder hundreds of characters are painted with remarkable accuracy. It is possible to identify many pathological conditions, such as peripheral leg palsies and spine deformations. I studied reproductions of the hands of 1932 characters with a magnifying glass, but no typical hand deformations were seen.

The prevalence of rheumatoid arthritis is 0·5–1%, and even if, possibly, the reduced life span in Breughel's time prevented some people from reaching the age for rheumatoid arthritis, it is surprising that not a single case of this disease was found.

So far, I still consider that rheumatoid arthritis originated in France and England at the end of the XVIIIth century, perhaps as a result of a virus.[2]

MARCEL-FRANCIS KAHN
Médecin de l'Hôpital Bichat
46 rue Henri Huchard
75018 Paris
France

1 Dequeker J. Siebrandus Sixtius: evidence of rheumatoid arthritis of the robust reaction type in a seventeenth century Dutch priest. *Ann Rheum Dis* 1992; **51:** 561–2.
2 Kahn M F. L'agent étiologique de la polyarthrite rhumatoïde. Une hypothèse. *Rev Rhum Mal Ostéoart* 1979; **46:** 510–11.