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.

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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.

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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