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.

Clinical trials on the prophylactic role of either folic or folic acid are limited and should be interpreted cautiously. The statement of Morgan et al that, in general, folic acid lessens toxicity without altering efficacy is incorrect. This is illustrated by the studies of Tisch and Buckley. 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 folic or folic 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 folic acid on the course of rheumatoid arthritis patients treated with MTX, as well as the role of the relative dose of folic acid compared with the dose of MTX.

**Bone mineral density and osteoarthritis**

Sir: Knight, Ring, and Bhalla in their leader 'Bone mineral density and osteoarthritis' 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, 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 and an increase in osteocalcin concentration in the bone matrix.

Furthermore, there are alterations in the mineralisation profile of bone in patients with generalised osteoarthritis. 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 antagonises 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.

**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, he was not the 'first' to report a case of postpartum autologous transfusion in a patient with RA. In 1987 our group reported the same procedure and extensively reviewed published reports. Unlike Dr Scoville's patient, ours did not respond so we did not pursue this approach further.

**The antiquity of rheumatoid arthritis**

Sir: The antiquity of rheumatoid arthritis is still a controversial issue. The pictures of Siebenbruns Sixtius presented by Dequequer are impressive but not fully convincing. Other arthritides may result in hand deformations 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 XVIII century, perhaps as a result of a virus.

**Letters to the editor**

**Autologous pregnancy plasma transfusion in RA**

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


**The antiquity of rheumatoid arthritis**

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

The antiquity of rheumatoid arthritis.

M F Kahn

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