Annals of the

RHEUMATIC DISEASES

Leaders

Methotrexate in rheumatoid arthritis

It is unusual in the conservative world of rheumatology for a treatment to be widely hailed as a therapeutic 'advance'. Examples might include the introduction of non-steroidal anti-inflammatory drugs and, more recently, the use of pulse intravenous cyclophosphamide regimens in vasculitis.

One that must surely qualify for consideration, however, is the use of low dose methotrexate in inflammatory arthritis—a treatment being assessed world wide.

Although methotrexate has been in use in psoriasis for many years, its success in rheumatoid arthritis has only recently been emphasised. Perhaps rheumatologists are making up for lost time—in 1980 there was one paper on the subject, in 1988 over 120 were published—surprisingly few from the United Kingdom.

In October 1989 a symposium held at St Thomas's Hospital in London sought to redress the balance and brought together many with extensive experience of the drug, including Dr Michael Weinblatt, who reviewed his own and other large series, and Dr Andrew Griffiths, who presented a dermatologist's viewpoint.

Consensus has been reached on a number of issues.¹ The drug is often dramatically and quickly (sometimes in under four weeks) effective, even in doses as low as 7.5 mg weekly. Some patients require temporary or more prolonged higher doses, such as 15–25 mg weekly, or intramuscular injection if a suspicion of impaired bioavailability is present. Improvement occurs in all indices, many patients being able to relinquish steroids totally. Renal clearance of the drug is important—indeed the importance of impaired renal function in drug dosing with methotrexate may well have been understressed.

Most studies show a far higher patient acceptance with methotrexate than other second line agents. In a recent life table analysis of 6688 patients, for example, treatment termination at five years was significantly less ($p < 0.0001$) for methotrexate than for other antirheumatic drugs.²

The negative aspects are well known. The drug is contraindicated in pregnancy. Any drug which affects cell division raises fears of long term oncogenicity, though so far no greater incidence of malignancy has been seen in patients with rheumatic disease receiving methotrexate. Many

patients suffer severe flares on stopping the drug. Interactions with other protein binding drugs occur, as well as with other agents with anti-folate activity. (Recently some debate has centred on possible benefits of adding folinic acid.)

The most well known side effect is hepatotoxicity. Serious liver damage certainly seems to be less common than with earlier studies in psoriasis. Routine liver biopsy at the onset of treatment is no longer regarded as mandatory, though our as-yet limited experience with methotrexate demands that the risk of liver damage remains under constant re-evaluation. In practical terms, excess alcohol intake is a contraindication and transient interruption of treatment is normally advised if liver function tests rise to twice normal (some would suggest three times normal).

One of the most worrying side effects is lung hypersensitivity—at its mildest an irritating dry cough, but at its other extreme, as in one of the cases presented at the St Thomas's symposium, an acute life threatening allergic alveolitis. Oddly, this side effect was rarely seen in the older psoriasis studies and just may, in part, be related to an underlying propensity to pulmonary involvement in rheumatoid arthritis.

There is always a danger of overenthusiasm, especially with an agent with therapeutic potential in diseases as diverse as asthma and Crohn's disease. Nevertheless, methotrexate is clearly and dramatically improving the lot of many patients with inflammatory arthritis. It is also toxic and, compared with the lifespan of rheumatoid arthritis, still quite new.

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1 Weinblatt M E, Kremer J M. Methotrexate in rheumatoid arthritis. *J Am Acad Dermatol* 1988; 1: 126–8.

2 Duncan I J S, Hurst N P. A multiple life table analysis comparing anti-rheumatic drugs: Is methotrexate the anti-rheumatic drug of first choice? [Abstract]. *Br J Rheumatol* 1989; 28: 118–9.