


**COMBINATION CHEMOTHERAPY IN RHEUMATOID ARTHRITIS**

Pharmacological purists recommend that we should use one drug for one disease but it is seldom possible in rheumatoid arthritis. Many patients take and appear to need and benefit from combinations of analgesic, anti-inflammatory and long-term suppressive agents. Even the pragmatic rheumatologist will try to manage his patient with one drug of each type but he may be missing potentially useful combinations of drugs. In the treatment of some types of malignant disease, combination chemotherapy is well established. Rheumatoid arthritis is not a malignant disease but it is often very nasty.

Various combinations have been used. Martin *et al.* [1] were enthusiastic about combinations of penicillamine and hydroxychloroquine but Bunch *et al.* [2] found penicillamine alone rather better than the combinations; Gibson *et al.* report a study in this issue of the Journal which confirms their view [3]. Combination therapy with chloroquine and penicillamine was no more effective than penicillamine alone. Bitter [4] tried combinations of gold with either penicillamine, levamisole or chlorambucil, and penicillamine with levamisole or chlorambucil, looking for remissions or cures in patients with progressive disease. The number of such successes was disappointingly small but they appeared to be more frequent with combinations than with single drug therapy; gold and penicillamine produced the best results but the numbers were small and this experience needs confirmation in a longer study. Taggart *et al.* [5] showed that the combination of penicillamine and sulphasalazine was superior to sulphasalazine alone but did not compare the combination with penicillamine alone. Combinations of cytotoxic drugs may offer the best prospect to a patient with severe and unresponsive rheumatoid arthritis. Butler and Tiliakos [6] found the combination of methotrexate and cyclophosphamide in low doses superior to methotrexate alone or continued treatment with drugs like gold and penicillamine in a small group of patients with intractable arthritis. Particularly impressive was the healing of erosions
in four of five patients, compared to continuing radiological deterioration in the other groups. Csuka et al. [7] used a combination of cyclophosphamide, azathioprine and hydroxychloroquine in patients whose rheumatoid arthritis had failed to respond to conventional therapy. Despite the uncontrolled nature of the study, the results were impressive, 16 of 31 patients achieving complete remission, seven 'near remission' and seven partial suppression of disease. There was only one patient in whom the treatment was regarded as a complete failure.

It is fear of toxicity which limits the use of combinations. Berry and Huskisson [8] abandoned the use of penicillamine and azathioprine because of an unacceptable incidence of side-effects despite striking efficacy. Only six of the 31 patients treated so successfully with combinations of cyclophosphamide, azathioprine and hydroxychloroquine developed no adverse reactions. Amongst the remainder there were three cancers, a case of erythroleukaemia, thrombocytopenia and the usual non-life-threatening complications like stomatitis. Adverse effects of methotrexate/cyclophosphamide combinations were relatively minor. Not surprisingly, the combination of penicillamine and sulphasalazine produced more side-effects than sulphasalazine alone [5]. The addition of hydroxychloroquine or chloroquine to penicillamine did not increase the incidence of side-effects and the combinations of gold with penicillamine used by Bitter were at least as well tolerated as the individual drugs alone. One should however be cautious in drawing conclusions about side-effects of drugs like penicillamine in small groups of patients. Reported studies have shown a wide variation in the incidence of adverse reactions like proteinuria and blood disorders emphasizing their idiosyncratic and unpredictable nature.

The number of steps on the ladder of treatment for rheumatoid arthritis is increasing with the addition of new drugs like methotrexate and sulphasalazine which have recently been found to have a long-term suppressive action. Two extra steps are supplied by combination therapy. First, in the patient who has responded to a drug alone, an extra step is supplied by combination therapy. The addition of chloroquine or hydroxychloroquine is unlikely to be helpful. As with any other type of combination therapy, it is essential to document the response to both drugs, in order to demonstrate a worthwhile improvement with the first agent and a further worthwhile improvement with the second.

Patients with rheumatoid arthritis readily accumulate medicines which are not always needed. Second, in a patient with severe unremitting and progressive disease, it may be worth considering a combination of low-dose cytotoxic agents. The use of such combinations in the difficult case of rheumatoid arthritis, a not uncommon problem in large clinics, deserves further exploration. In the absence of knowledge about the mechanism of the disease and the mode of action of the drugs, the only way forward is by clinical trials of different combinations. With trial, there is always the risk of error.

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REFERENCES
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