Thus suggested that the relation between the complex of immunoglobulin A and alp-1-antitrypsin and the acute phase response as measured by C-reactive protein in rheumatoid arthritis treated with gold or D-penicillamine. Br J Rheumatol 1987; 26: 351–2.


AUTHORS’ REPLY We were interested to read Dr Stanworth’s letter, in which he recalled his thoughts in the 1970s about the mechanism of action of D-penicillamine and his more recent experiments on the IgG-α1-antitrypsin complex. Dr Israel Jaffe, very reasonably, had suggested to us that his studies of periarthritis injection of penicillin, that this drug degraded IgM rheumatoid factor (IgM RF) by sulphydryl reduction of the IgM RF molecule is uncertain and that this was the mechanism because we reasoned that the therapeutic effect should occur more rapidly than the several months required if a simple chemical reduction of IgM RF took place. It seemed to us that it was more likely that the delayed onset of clinical improvement was associated with a gradual change in the cellular immune response in the synovial membrane due, perhaps, to a progressive inactivation of a cytotoxic antibody playing a part in this response. We reasoned that this should be reflected in a gradual fall in the titre of rheumatoid factor. The fall in titre might not necessarily be the reason for the joint improvement but, rather, an associated change.

It was for this reason that we decided to measure the titres of IgM RF over time in patients receiving penicillin. It turned out that the titre gradually fell over a period of months. As pointed out by Dr Stanworth, in subsequent experiments carried out in collaboration with Dr Jaffe, our laboratory showed that there was no correlation between RF titre and clinical improvement in patients treated with penicillin.1 Similar results have been reported by several other groups. In later experiments carried out in Dallas Olsen et al noted a correlation between spontaneous synthesis of IgM RF by peripheral blood mononuclear cells and disease activity in patients treated with penicillin.2 This result suggested that penicillin suppressed the release of cells producing RF into the circulation, possibly from the inflamed synovium itself. Thus this observation was also compatible with a cellular mechanism. Lipsky and Ziff have, in fact, shown that penicillin inhibits helper T cell function in the presence of copper.3

We are aware of the observations that the complex of immunoglobulin A and α1 antitrypsin is reduced by gold and D-penicillamine. Recently, however, that the levels of serum IgA-α1 antitrypsin complex might be a predictive indicator of erosions in early rheumatoid arthritis are of interest. Undoubtedly, further studies would tell us if this is the only predictor. If indeed α-penicillamine can reduce this complex, then we would expect erosions to heal, or perhaps not occur, if the complex level is reduced by treatment. We are not aware that studies to date have provided overwhelming evidence for such a role for D-penicillamine.

Fortunately, many treatments introduced into medicine for the wrong reason have still been effective and have stimulated subsequent excellent research.

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