SPECIFIC THERAPY FOR RHEUMATOID ARTHRITIS

The term 'specific' is used to describe the effects of drugs like gold and penicillamine in rheumatoid arthritis. This type of action is to be distinguished from the effects of 'non-specific' or symptomatic therapy, for example with analgesic and anti-inflammatory drugs.

In rheumatoid arthritis, specific drugs act not only on pain and inflammatory manifestations like swelling and stiffness, but also on extra-articular features of the disease such as nodules. Their action is slow, taking several months to reach a maximum, and is accompanied by reduction in ESR, rheumatoid factor and immunoglobulins. There is evidence that some of these drugs alter the outcome of the disease: for example cyclophosphamide has been shown to slow the rate of radiological deterioration (Cooperating Clinics Committee of the American Rheumatism Association, 1970). By contrast, non-specific therapy will relieve pain and manifestations of inflammation but does not alter extra-articular features of the disease, ESR, rheumatoid factor, immunoglobulins or the outcome of the disease.

The action of non-specific drugs is not dependent on the nature of the underlying disease—anti-inflammatory drugs are likely to be effective in any inflammatory arthropathy but 'specific' therapy implies an action dependent on the underlying disease. Penicillamine is effective in rheumatoid arthritis but not in inflammatory arthritis as a whole. Unfortunately formal trials of many specific drugs have not been carried out in conditions other than rheumatoid arthritis. Certainly some are effective in other conditions, for example, immunosuppressives may be useful in psoriatic arthropathy. For this reason, the term specific can be criticized. More appropriate nomenclature may become available when there is greater understanding of the mode of action of the drugs.

One problem, which has delayed studies of the mode of action, has been the lack of animal models. Many of these compounds are not active in conventional models of inflammation such as carrageenan oedema and adjuvant arthritis. Perhaps the most promising model to demonstrate their effects is pertussis vaccine oedema (Arrigoni-Martelli et al., 1976) or pertussis vaccine pleurisy (Dieppe et al., 1976). This model, mediated by delayed hypersensitivity, distinguishes at least certain of the specific agents from anti-inflammatory drugs; the former enhance the inflammatory reaction and the latter suppress it. Not all of the specific agents have this effect, and it is unlikely that they all act in the same way.

The mode of action of the drugs in man cannot easily be deduced. These compounds have been shown to exert many different actions, some of which must be irrelevant. The actions of penicillamine, for example, include chelation of copper, inhibition of polio virus and a lathyritic effect which does not appear to be important (Lovell et al., 1976). The importance of one of these mechanisms might be inferred from finding a correlation between it and changes in the disease. Such a correlation does not necessarily imply a causal relationship: changes in laboratory parameters such as immunoglobulins may be secondary to changes in the disease and show a correlation for this reason. Support for a mechanism of action would also come from the finding of a common action of two or more drugs which were known to have the same effect on the disease. It is therefore of interest that levamisole has been shown to have a specific action in rheumatoid arthritis similar to that of D-penicillamine (Huskisson et al., 1976) and that both these compounds have in common the ability to enhance a cell-
mediated inflammatory reaction, pertussis vaccine oedema (Arrigoni-Martelli et al., 1976; Dieppe et al., 1976). Levamisole does not chelate copper and penicillamine is not anthelmintic. If more compounds are found to have these actions in common, it would support the view that the effect of one type of specific compound is mediated by immune stimulation. Immune stimulation is a broad term, and is used in this context only to imply a common action in an in vivo experimental model.

Therapeutic efforts in recent years have been directed at immune suppression rather than stimulation but it is not impossible to explain how both suppression and stimulation could exert similar clinical effects (Willoughby and Huskisson, 1976). Gold is unlikely to fit into either of these categories and further work is likely to lead to further subdivision of this class of drugs.

Gold is the oldest of this type of compound (Empire Rheumatism Council, 1961). Similar properties have subsequently been demonstrated by chloroquine (Popert et al., 1961), d-penicillamine (Jaffe, 1970), levamisole (Huskisson et al., 1976) and a number of immunosuppressive drugs (Currey, 1976). Perhaps clotrimazole has this type of action (Wyburn Mason, 1974). Aylward (1975) himself expressed surprise that a non-steroidal anti-inflammatory agent, alclofenac, would have an additional specific action and his findings await confirmation. McConkey (1976) has put forward evidence that Dapsone has some features of this type of action though without reduction in rheumatoid factor. This is further evidence for the view that a specific type of action may be produced in several different ways.

The importance of these drugs lies in their ability to modify the course of rheumatoid arthritis. Gibson et al. (1976) put forward evidence that the outcome of rheumatoid arthritis is more favourable in patients able to continue taking d-penicillamine. The toxicity of these drugs is such that only a proportion of patients are able to continue treatment and a number of serious side-effects have appeared which demand that drugs like penicillamine be reserved for patients with severe or progressive disease. The potential of specific therapy is clearly considerable and it is to be hoped that some of the drugs now being developed will be capable of controlling the disease in a higher proportion of patients without the risks of currently available compounds.

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References


