The Influence of Treatment on the Natural History of Rheumatoid Disease

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In the few decades that have passed since Lord Horder described the rheumatic diseases as the Cinderella of medicine they have generated an almost explosive interest among clinicians and research workers. Despite such interest, much industry and a wealth of information, the cause of rheumatoid disease remains unknown and knowledge of its natural history is still imperfect.

Thoughts concerning the cause of the disease fluctuate in emphasis rather than undergo fundamental change. Search for a causative organism is reminiscent of that for the Holy Grail, but pursuit of a single outside insult responsible for the development of the disease may be a mistaken policy. There is sufficient difference in the clinical state of patients in whom the diagnosis of rheumatoid disease is made to allow the possibility that they suffer from a variety of disorders with different initiating and perpetuating mechanisms. To use the term rheumatoid disease acknowledges that involvement of joints is neither the only, nor necessarily the most important, feature of the condition but there could be greater merit in using the term rheumatoid syndrome.

At regular intervals for many years, organisms of different kinds have been isolated from involved joints but these appear to be witnesses to the accident rather than responsible for it. Similarly, various methods of study have failed to establish a viral aetiology. Nevertheless, the hypothesis of an initiating infection remains attractive and is supported by a good deal of circumstantial evidence (Denman, 1975).

The soil is likely to be as important as the seed. In mice, genetic factors influence the control of immune responses to virus infections and it is reasonable to suppose that such factors can be of importance in man. There is clear evidence of an association between HL-A antigens and polyarthritis occurring in relation to bacterial infections, but in rheumatoid disease such a relationship appears to exist only in Finland.

One of the many difficulties in the study of this disease has been lack of a naturally occurring, or induced, similar disorder in animals. A recent observation of potential importance is that the feeding of young pigs on a diet that includes a large amount of dried fish meal results in an enormous increase of *Clostridium perfringens* in the intestine, followed by the development of an inflammatory
polyarthritis that clinically and histologically resembles that of human rheumatoid disease. Whether or not, from the point of view of such things as tissue typing, all pigs are equal, or some more equal than others, is unknown, but the observation provokes interest, as in about 60 per cent of patients suffering from rheumatoid disease there are large numbers of a special type of Clostridium perfringens present in the stools.

A major advance was made by Glynn (1975) who succeeded in producing an animal model in which the arthritis is self-perpetuating and appears to be an autoimmune process. Study of this model provides the possibility of better understanding of the mechanisms involved in naturally occurring chronic arthritis and the opportunity for better assessment of drugs used in the treatment of rheumatoid disease.

None would dispute the contention that the natural history of rheumatoid disease is very variable; the disease is one that fluctuates in its activity but is progressive and usually lasts for a lifetime. We know little of the factors concerned with its exacerbation or remission, and information concerning the long-term effects of the disease is more a matter of impression than fact. Studies over a period of about ten years have been in rough agreement that the order of 10 to 15 per cent of patients become severely incapacitated and that about 50 per cent have either gone into clinical remission or have continued with problems that do not impair the quality of life.

Only a small proportion of those patients suffering from rheumatoid disease will eventually succumb to the disease itself but the disease does shorten life expectancy (Bywaters et al., 1961). Causes of death in these patients are not substantially different from those found in the general population; death just occurs at an earlier age. Some senior rheumatologists have suspected that the disease has become less severe, an impression not confirmed by Valkenburg (1975) who concluded that the disease has not changed but is less crippling because of improved care.

Despite having some idea of what might happen on a percentage basis we are unable to give an accurate prognosis for the individual patient. In general, the presence of nodules, rheumatoid factors in higher titre and evidence of vasculitis tend to be associated with more severe disease and overt involvement of other systems. Such clinical clues are of limited value since it is not rare to meet patients over 70 years old who are in relatively good health despite the presence of nodules for many years; nor is it rare to meet the patient with gross joint damage without nodules and persistently negative results in tests for rheumatoid factor.

Thus, we have the problem of a disease, or possibly a group of diseases, of unknown cause and variable prognosis, together with a very limited ability to forecast the pattern of illness in an individual. In such circumstances it is near to impossible to be sure whether the natural history of the disease can be influenced by treatment, and we enter into the dangerous realm of clinical impression and support our arguments by the authority of experience.
MANAGEMENT OF PATIENTS SUFFERING FROM RHEUMATOID DISEASE

Apart from drugs, most measures relevant to good patient care are directed toward dealing with the effects of the disease rather than influencing the disease process (Table 1).

Until we have more effective drugs, appropriate use of these measures is as important as choice of drug regime.

Table 1. Management of patients suffering from rheumatoid disease.

| 1. GENERAL | 4. SURGERY |
|------------|------------|
| explanation | soft tissue |
| rest and activity | synovectomy |
| diet | reconstructive |

| 2. NON-SURGICAL LOCAL MEASURES | 5. REHABILITATION AND SOCIO-ECONOMIC MEASURES |
|-------------------------------|-----------------------------------------------|
| splintage | soft tissue |
| injection (including 'chemical synovectomy') | synovectomy |
| | reconstructive |

| 3. DRUGS | |
|-------------------|---|
| salicylates | salvage |
| other non-steroid anti-inflammatory drugs | other measures |
| gold | |
| penicillamine | |
| steroids and ACTH | |
| cytostatic drugs | |

DRUG THERAPY

Many kinds of drug are prescribed for patients suffering from rheumatoid disease. The situation seems similar to that in the treatment of syphilis at the beginning of the century when specific treatments abounded and ranged from sarsaparilla and sassafras to gold and mercury. It is possible that by the end of the century some of the present so-called anti-rheumatic drugs will be judged to have been the therapeutic equivalent of sarsaparilla for syphilis.

For many patients the activity of the disease is such that they can achieve a comfortable life by use of simple non-steroid anti-inflammatory drugs such as salicylates and indomethacin. For others, this is not so and these drugs need to be supplemented by, or replaced by, others. Figure 1 represents the majority view with respect to the therapeutic ladder in relation to available drugs. Some drugs are not included in this scheme and, since it is capable of favourably influencing the various clinical and laboratory indices of disease activity, chloroquine is probably the most important of these. Those who consider that the merits of chloroquine outweigh the risk of its adverse effects would probably consider using it before gold or penicillamine. Some physicians prefer to use at an early stage a small supplementary dose of steroids rather than embark on gold therapy or the
like but, in general, the disposition to use steroids seems to bear inverse relationship to the experience of the physician.

**Non-steroid Anti-inflammatory Drugs**

With the exception of salicylates, the non-steroid anti-inflammatory drugs are often referred to as anti-rheumatic drugs. This has the disadvantage of suggesting some sort of specific action they may not possess and also obscures the fact that they may influence inflammatory reaction occurring in sites other than the joints. Although the situation has not yet been recognised as occurring, it is possible that a drug most effective in suppressing inflammation, but devoid of influence on the provoking stimulus, could do much more harm than good.

Information concerning the mechanism of action of these drugs is limited. It is probable that they do not all act in the same way and that they affect in varying degree the different components of the inflammatory reaction; nevertheless, attempts have been made to provide some common denominator of action. McArthur and his colleagues (1971) have suggested that drugs clinically effective in the treatment of rheumatoid disease act by displacement of protein-bound peptides possessing anti-inflammatory action. Measurement of plasma L-tryptophan provides an index of such displacement and is useful in the assessment of such drugs, but the hypothesis does not provide a satisfactory and complete answer to the problem.

Many enzymes are known to exist within cell lysosomes; some of these enzymes, when extruded into the cytoplasm or the extracellular space, can damage cartilage and bone and promote further inflammatory reaction. Ability to stabilise the lysosome membrane, or in other ways influence the release of lysosome enzymes, appears to be an important attribute of some of the commonly used drugs, including such widely differing substances as benorylate and steroids.

Prostaglandins play an important role in the inflammatory reaction and it has been suggested that inhibition of prostaglandin synthetase is the main action of many anti-inflammatory drugs. The fact that mars the beauty of this hypothesis is that steroids, the most potent of anti-inflammatory drugs, do not possess this action.
McConkey and his colleagues (1972, 1973) have demonstrated the value of serial estimation of the serum acute phase proteins as a method of assessing disease activity and its response to treatment. Drugs such as salicylates, indomethacin and ibuprofen do not influence the acute phase proteins and therefore, although capable of giving symptomatic relief, cannot be expected to alter the course of the disease, whereas such drugs as gold, penicillamine and steroids inhibit the acute phase response and exert prolonged influence on the binding of tryptophan to the plasma proteins, which suggests action more fundamental than mere suppression of clinical signs and symptoms, and allows the hope of some beneficial effect upon the disease process itself. Not all of the non-steroid anti-inflammatory drugs have been thoroughly assessed in this way but, of those that have, alclofenac has been shown to have some actions of this kind (Aylward et al., 1975). Such action on the results of laboratory tests offers no explanation of any favourable effect upon the disease that might occur; nevertheless, a classification of drugs of this kind according to their influence upon such things as acute phase reaction could be a useful advance.

Gold
For almost fifty years gold has been used in the treatment of patients suffering from rheumatoid disease and although during this time enthusiasm for its use has waxed, waned and waxed again, its use has never been abandoned. On the basis of clinical and laboratory criteria, gold can favourably influence the course of the disease in the majority of patients (Empire Rheumatism Council, 1960, 1961). There is no certain way of forecasting the response that may occur in the individual patient and any beneficial effect is delayed by some weeks, or possibly a few months. The effect of gold therapy sometimes appears to outlast the period of its administration but the situation is confused by the variable persistence of the drug in the body and its variable concentration in different tissues. Gold exerts a favourable influence on acute phase proteins and on plasma tryptophan levels. It seems likely that it has some effect upon the unknown insult that results in inflammation and that one of its major actions may be stabilisation of lysosome membranes.

Penicillamine
D-penicillamine is a drug that has been shown to be superior to placebo (U.K. Multi-centre Trial Group, 1973) and, over a six-month period, appears to be as effective as gold (Huskisson et al., 1974). Judged by clinical criteria, effects on acute phase proteins and plasma tryptophan levels, penicillamine appears to suppress disease activity. Its adverse effects are common, their reported incidence being as high as 60 per cent and in about half of affected patients they have been serious enough to warrant withdrawal of the drug. With use of a dose much lower than that used in earlier trials clinical response is still satisfactory but attended by considerable reduction in the incidence of adverse effects (Hill and Hill, 1975).
Despite the adverse effects, there is probably little to choose between penicillamine and gold (Huskinson et al., 1974).

**Steroids**
Most of the potential benefits and hazards of steroid therapy are so well known that they do not require discussion. A passionate affair was followed by a marriage of convenience that now survives against a background of extramarital relationship with any drug that appears capable of influencing the symptoms of the disease. No analogy should be pushed too far but it is possible that the non-steroid mistress of unknown personality might sometimes involve greater risk.

Sound clinical trials have shown that patients on steroids fare better than those on salicylates but that their advantage diminishes with time (M.R.C. and Nuffield Foundation, 1959). Despite the problems that their use involves, steroids can provide a valuable contribution to the care of many patients. Inappropriate use, or dosage, of steroids provides the real difficulty, and most of the hazards of treatment with these drugs relate more closely to the prescriber than to the drugs themselves.

**Cytostatic drugs**
On occasion, rheumatoid disease may threaten life and its activity may fail to be suppressed by large doses of steroids. In such desperate circumstances cytostatic drugs are sometimes used and sometimes appear to inhibit disease activity. Only two drugs, the alkylating drug cyclophosphamide and the anti-metabolite drug azothiaprin, have been used to any appreciable extent. Most trials of these drugs have been short term and few have been controlled. There is no correlation between their clinical effect in this disease and their inhibitory effect on the immune apparatus, and a non-specific inflammatory action seems possible. It has been suggested that they may delay joint damage but there is no evidence that they provide anything that approaches a cure. Use of these drugs provides risk to life and, in the absence of clear evidence that they have merit outweighing their risks, they seem destined to continue in the role of providing a small hope in a situation of despair.

**CONCLUSION**
The phenomenon of cause and cure unknown is one that encourages prayer but that this is not enough was well recognised by Hippocrates who stated ‘Prayer indeed is good but, while calling on the gods, a man should himself lend a hand’.

With respect to rheumatoid disease his advice has been well taken and the ability to lend a hand in its management is considerable. Despite the imperfections of available drugs they offer symptomatic relief of a fairly high order and, when combined with other measures such as surgery, improved techniques of rehabilitation and improved social and economic care, they help to provide expectation of a relatively normal life for the majority of those afflicted by this disease.
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