Current Practice

CLINICAL PROGRESS

Rheumatoid Arthritis

Aetiology

A. M. DENMAN,* M.B., B.S., M.R.C.P.

British Medical Journal, 1970, 4, 601-602

Two fundamental questions about rheumatoid arthritis have yet to be answered. What is the nature of the stimulus which initiates inflammation of the joints? What are the factors which lead to its chronicity?

Role of Infection

Recently interest has revived in the possible role of micro-organisms in rheumatoid arthritis and, indeed, in many other forms of chronic inflammatory disease accompanied by intense immunological activity.¹ This revival is due to two main developments. Firstly, we now know that many forms of virus infection may not give rise to obvious signs.² Secondly, many apparently autoimmune phenomena are found in chronic inflammatory diseases known to be provoked by micro-organisms. Furthermore, there have been an increasing number of reports incriminating infective agents in human inflammatory diseases of unknown aetiology and of analogous diseases in animals.

It is difficult to assess the significance of the reported isolations of micro-organisms from the joints of patients with rheumatoid arthritis. Since a true analogue of this disease does not occur in other species, it is not feasible to try to produce it by injecting material isolated from inflamed joints into animals. It has been claimed³ that chronic polyarthritis can be regularly transmitted to newborn mice by injecting extracts from the synovial membrane of patients with rheumatoid arthritis, and that the disease is congenitally transmitted in the recipient through three generations. Great caution is needed, however, in interpreting histological appearances in rodents after injecting fairly crude material, and these experiments need to be rigorously controlled.

Particular attention must be given to the techniques employed in culturing material from inflamed joints. There is a risk of introducing from other sources precisely those organisms whose isolation has been most frequently claimed. One report stated that diphtheroid bacilli were isolated from 21 of 78 synovial membranes and from 12 of 126 specimens of synovial fluid obtained from patients with rheumatoid arthritis.⁴ On the other hand, there were few isolations from the joints of patients with other diseases. In contrast, a technique in which the specimens were washed initially and then inoculated under germ-free conditions greatly reduced the frequency with which diphtheroid bacilli were isolated.⁵

Recovery of Mycoplasma

There have been numerous reports—both positive and negative—about the recovery of mycoplasma from the joints of patients with rheumatoid arthritis. The chances of contaminating cultures with mycoplasma from the laboratory environ-

ment are high,⁶ and tissue culture cell lines used for inoculation may already carry this kind of organism. Despite these reservations, however, reports of mycoplasma infection in rheumatoid arthritis should not be dismissed simply on the grounds of probable contamination. Collateral evidence that patients from whose joints organisms were recovered have some form of specific immunological response to the same organisms would indicate that mycoplasmas are a genuine cause of infection. In general, antibodies to diphtheroids⁴ or mycoplasma⁸ have not been detected more frequently or in higher titre in patients with rheumatoid arthritis than in other conditions or in controls.

In a recent study *Mycoplasma fermentans* was cultured from 31 of 79 synovial fluids taken from patients with rheumatoid arthritis, compared with 3 of 37 fluids from patients with other conditions.⁸ In vitro techniques showed that 67% of 43 patients with rheumatoid arthritis had delayed hypersensitivity to *Mycoplasma fermentans*, a form of immunological reactivity not shown by control subjects. Probably delayed hypersensitivity is important in the pathogenesis of rheumatoid arthritis,⁹ perhaps synergistically with circulating antibody.¹⁰

Another finding has been that fibroblasts derived from the synovial membranes of patients with rheumatoid arthritis are resistant to infection with rubella virus.¹¹ This suggests that these cells are already colonized by some form of intracellular organism. Clearly, these observations need extensive confirmation since most attempts at demonstrating mycoplasmal or viral infection by direct culture as well as more complex techniques have given negative results.^{4, 12} Furthermore, the finding that a joint is infected by a particular micro-organism does not prove that this has a primary aetiological role. The hypervascular synovial membrane with its rich content of macrophages is an obvious nidus for secondary infection, and septic arthritis is a recognized complication of the disease even in patients who are not receiving corticosteroids.¹³

Nevertheless, if similar organisms are repeatedly isolated in different parts of the world by reasonably standardized techniques the significance of such findings will be greatly increased—particularly if the patients are also shown to have definite immunological reactions. Isolations of infective agents would be particularly convincing if they were made early in the course of the disease, preferably from patients with acute undiagnosed polyarthritis, before the issue was obscured by the secondary effects of chronic disease and its treatment. In many forms of experimental virus arthritis the agent can be recovered only in the early stages of the infection.¹⁴

Host Responses

The suspicion that patients with rheumatoid arthritis suffer from some form of peculiar tissue response to antigens in

* Member of M.R.C. Scientific Staff, Clinical Research Centre, Harrow, Middlesex.

microbial agents has stimulated an intensive study of the factors which influence host responses in chronic inflammation.¹⁵ Population studies have mostly shown only minor differences in the incidence of rheumatoid arthritis in various regions and have not produced any clues to its aetiology. Again, though seropositive rheumatoid arthritis may have a familial aggregation,¹⁶ no simple genetic mechanism can explain its incidence and distribution.¹⁷ Rheumatoid arthritis seems likely to be a syndrome with differing forms of clinical expression, representing either diseases of different aetiology or a wide spectrum of response to a single agent. Epidemiological studies in Western Nigeria suggest that the incidence and expression of polyarthritis may be strikingly modified by immunological factors. The incidence of rheumatoid arthritis there was low judged by hospital data and population surveys,¹⁸ while its clinical and serological features differed from those in Caucasians,¹⁹ possibly reflecting the effects of chronic parasitic infection in the Nigerian patients.²⁰

Rheumatoid Factor

The role of rheumatoid factor in the pathogenesis of rheumatoid arthritis is still controversial, though it is known to be an antibody against some antigen present in the serum immunoglobulin G (IgG).²¹ Rheumatoid factor is found in a variety of diseases characterized by prolonged antigenic stimulation, including chronic parasitic and bacterial infections²² and in patients who have had transplants.²³ Titres diminish after successful treatment of infections. Nevertheless, rheumatoid factor is found more commonly and in higher titre in rheumatoid arthritis than in other conditions, and apparently healthy persons with rheumatoid factor in high titre have a greater than average chance of developing rheumatoid arthritis.²⁴ There is a recognized correlation between vasculitis and other extra-articular features of rheumatoid arthritis and the presence of a high titre of rheumatoid factor.²⁵ In synovial effusions aggregated IgG and globulin could combine with rheumatoid factor and form soluble complexes.²⁶ Possibly these complexes fix complement,²⁷ and this would explain the reduced concentration of complement observed in synovial effusions²⁸ and the rapid flux of polymorphonuclear leucocytes through synovial effusions.

Factors in Chronicity

The mechanisms concerned in continued inflammation are better understood than the factors which initiate the process.

Lysosomal enzymes released from polymorphs and from macrophages in the hyperplastic synovial membrane probably account for much of the progressive erosion of the articular surfaces.²⁹ Nevertheless, it is unlikely that the primary defect in rheumatoid arthritis is an abnormal leakiness of lysosomes³⁰ in the synovial membranes, whose enzymes then provoke an inflammatory reaction. The functions of rheumatoid factor may be primarily protective by regulating antibody production³¹ or helping the clearance of antigen-antibody complexes from the blood.²⁷ Rheumatoid factor neutralizes infectious virus-antibody complexes in the presence of complement,³² while serum hepatitis antigen has been identified in the lesions of some patients with diffuse vasculitis.³³ Clearly, rheumatoid factor may have many roles in the pathogenesis of rheumatoid arthritis, but their relative importance is still unknown.

This description of the immunopathological processes concerned still fails to explain why rheumatoid arthritis is a chronic disease. Experiments in animals have suggested several possibilities including sensitization of the products of inflammation with a resulting autoimmune phase,^{15 34} or a similar response to a virus antigen. There is little convincing evidence that analogous processes are operating in the human disease. No characteristic pattern of response or immunological aberration has consistently been shown in patients with rheumatoid arthritis, whether in the form of increased or reduced responsiveness to antigenic challenge. It is attractive to postulate that rheumatoid arthritis is initiated by delayed hypersensitivity to micro-organisms replicating within macrophages in the synovial membrane. If these widely distributed micro-organisms do initiate this chronic destructive process host factors must also play a major part in determining why only a small percentage of the population develop the disease. Similarly, only a minority of people exposed to Group A streptococci develop rheumatic fever. Though the belief that rheumatoid arthritis is primarily an autoimmune disease has lost ground in recent years, many would agree that patients with this disorder may have an immunological defect as a result of which short-lived stimuli induce a persisting response, either to microbial antigens or cross-reacting tissue antigens.

Possibly several micro-organisms provoke a pattern of immunological response in patients with rheumatoid arthritis which is qualitatively or quantitatively abnormal. This could involve cellular or antibody mediated immunity. The attraction of this concept is that it offers a variety of experimental approaches.

Medical Management

R. BLUESTONE,* M.R.C.P.

British Medical Journal, 1970, 4, 602-604

The medical management of patients with rheumatoid arthritis has not benefited from any recent dramatic advances in therapy and is still governed by one major consideration. This is that the disease may be life-long and is characterized by spontaneous remissions and relapses. Inflamed joints may become so disorganized and stiff that considerable disability may continue long after the active synovial inflammation has regressed. The management must therefore concern the general well-being of the patient as a whole within his or her daily environment. Therapeutic guidelines are necessary for the immediate and long-term care of the patient. These guidelines must be flexible, designed to cope with relapses, and practicable to allow a relatively normal life.

* Registrar and Tutor in Medicine, Department of Medicine, Royal Postgraduate Medical School, London, W.12.

General Care

Rest

Patients with painful polyarthritis, often accompanied by malaise, benefit greatly from a spell of rest in bed, which may be best achieved within hospital. After ambulation, rest-periods during the day and early bed-times are advisable. The use of mild sedatives at night is useful but drugs of addiction should be avoided because of the risks entailed in their persistent use.

Diet

No special dietary measures are indicated for rheumatoid arthritis. Nevertheless, it is worth stressing the wisdom of a well-balanced diet containing adequate iron, folate, and