light microscopy to crystal identification are fully described in standard textbooks (Bunn 1961, Chamot & Mason 1958).

The finding of numerous crystals, many lying within leucocytes, in the fluid from an inflamed joint is characteristic of crystal synovitis. Table 1 indicates the points of differentiation between urate and CPPD. Fluid from chronically inflamed joints is often less informative, and the presence of very small numbers of crystals is of doubtful significance.

In general, polarized light microscopy provides a rapid and positive method of diagnosing crystal synovitis, and of differentiating between the two common types. It has undoubtedly added to the precision of diagnosis in rheumatology.

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The Role of Infection in the Causation of Rheumatoid Arthritis

Almost from the dawn of bacteriology until the mid-1930s the literature abounded with reports incriminating a variety of micro-organisms in the ætiology of rheumatoid arthritis. Interest in this approach seems to have waned not so much because a rival theory had arisen, autoimmunity being still a concept largely of the future, but because people became weary of work which always fell short of a final conclusion. The revived interest of the past few years has brought fresh but still only circumstantial evidence to support the theory of infection.

Evidence bearing on the role of infection can be assembled from consideration of the nature of the disease, from analogy with spontaneous or induced disease in animals and from experimental observations, old and new, in man.

Nature of the Disease

An investigator introduced for the first time to rheumatoid arthritis and devoid of bias in his approach to the question of ætiology might reasonably look to infection as the most likely factor. He would assemble in support the occasional fever, leucocytosis and lymphadenopathy, the weight loss, the accelerated sedimentation rate and the warm swollen joints of the active case. But he might also observe many of the same phenomena in gout, where there is no question of infection, and he would find in the autoimmune concept a theory of ætiology no less attractive. The antiglobulin which we know as rheumatoid factor may be evidence only of a continuing immune response and its presence is as compatible with an autoimmune process as it is with chronic infection.

Disease in Animals

In animals arthritis occurs in a variety of infective conditions which arise spontaneously as well as in those which are experimentally induced. Perhaps the closest mimic of rheumatoid arthritis in man is the disease induced in pigs by *Erysipelothrix rhusiopathiæ*. Studies of this condition have been reviewed by Gardner (1960). Unlike many other animal diseases in which joints are affected, this produces a persistent chronic arthritis, histologically very similar to rheumatoid arthritis. Perhaps relevant to studies in man is the observation that the causative organisms cannot be isolated during the chronic phase. Chronic arthritis is easier to induce in the pig, possibly because this species readily develops delayed hypersensitivity.

Recent interest in the possible role of mycoplasma in rheumatoid arthritis has focused attention on animal infections with these organisms and it has been pointed out by Sharp & Riggs (1967) that arthritis is a feature in no fewer than 13 of 17 naturally occurring or experimentally induced mycoplasmal diseases. In most of these, the synovial reaction is more characteristic of septic than rheumatoid arthritis but *Mycoplasma hyorhinis* is capable of producing a chronic arthritis in swine. Other features commonly encountered in mycoplasma infections of animals include pleurisy, pericarditis, cellulitis and lesions of the eye. The relationship between this type of organism, L forms of bacteria and listeria is still in some doubt.

Older Observations in Man

These are restricted in value by limitations of technique, often inadequate controls and obsolete classsification of the arthritides. But some of the findings may with profit be re-examined.

The earliest reference is contained in a paper by Max Schueller (1906) which includes the following passage:

'In the year 1892 I discovered a peculiar, very small plump bacillus in the tissues of some joints with villous

excrescences: because of its peculiar shape I gave it the name "dumb-bell bacillus". These organisms produced the same villous process in joints of animals injected with it.'

Of 230 cultures 150 were positive and the organisms were Gram-positive. It is difficult now to identify the nature of the 'chronic villous arthritis' which Schueller distinguished from 'sterile' arthritis deformans.

Rosenow (1914) reported the outcome of culturing lymph nodes draining arthritic joints. Cultures were positive in 35 of 38 cases and the mixed bag of isolates comprised nonhæmolytic streptococci (14), 'anærobic organisms resembling streptococci' (9), *B. welchii* (9), staphylococci (3), *B. mucosus* (1) and gonococcus (1). Rosenow also isolated organisms from some specimens of synovial fluid.

Cadham (1932) also made cultures from lymph nodes and wrote:

'In the cultures from 34 cases thus investigated a peculiar diphtheroid organism was isolated in 27. In 5 cases we found staphylococcus and in one case a Gram-negative bacillus in symbiosis with a staphylococcus . . . Glands removed from 3 patients without arthritis proved negative on culture.'

Cadham's diphtheroids were pleomorphic and in one phase were filterable. Injections of a culture produced arthritis in rabbits. He expressed the view that Schueller's dumb-bells were also diphtheroids. Later Cadham (1942) had isolated diphtheroids from 87 of 131 patients and 2 of 20 controls and was treating rheumatoid arthritis with vaccines prepared from his isolates.

Other investigators during this period reported the isolation of a variety of organisms from blood, synovial fluid and tissue. These included hæmolytic streptococci, *Str. viridans* and indifferent streptococci, staphylococci, more diphtheroids and various pleomorphic forms. Two secured a name in rheumatology, if not in orthodox bacteriological taxonomy, the *Micrococcus deformans* and the *Diplococcus rheumaticus*. From time to time it has been suggested that rheumatoid arthritis is due to a streptococcus capable of dissociating into microbic forms more resistant to immune mechanisms than the original organism.

Recent Work

After remaining dormant for so many years interest in the possible role of infection was reawakened in 1964 by reports from Arai *et al.* (1964) and Bartholomew & Hines (1964) of the isolation of mycoplasma from cases of rheumatoid arthritis. Later a report from Duthie *et al.* (1967) in Edinburgh described the isolation of diphtheroid organisms. In the same year similar isolations were made by Hill *et al.* (1967) at Stoke Mandeville Hospital and preliminary results have been reported in abstract form. The Edinburgh group isolated diphtheroids from 9 of 36 specimens of rheumatoid synovial tissue and from 7 of 48 synovial fluids. Twenty specimens from non-rheumatoid controls yielded no growth. Bacterial cultures were made from cells, from the synovial membranes or fluid, growing in a tissue culture medium. At Stoke Mandeville a different technique of tissue culture was used and diphtheroids were isolated from 18 of 37 specimens of rheumatoid synovial fluid. In contrast to experience in Edinburgh similar isolations were obtained from some (4 of 11) specimens of fluid from osteoarthritis.

In a study reported at the third Pfizer International Symposium in Edinburgh last year and subsequently published, Williams (1968) isolated mycoplasma, serologically related to *Mycoplasma fermentans* from the synovial fluid of 40% of 90 cases of rheumatoid arthritis. At the same meeting Pease (1968) affirmed that diphtheroid bacilli and mycoplasma associated with arthritis both belong to the genus *Listeria*.

If micro-organisms play an ætiological role in rheumatoid arthritis it seems likely that this will prove to be indirect and mediated through a disturbed immune response. Even if further work reveals that mycoplasma or diphtheroids are normal inhabitants of human tissue the possibility will remain that they are capable of initiating a harmful immune response in individuals constitutionally predisposed to rheumatoid arthritis. Indeed the theories of autoimmunity and of infection may not be incompatible.

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