Leader

Rheumatoid arthritis and infection: a population approach

The favoured aetiological model for rheumatoid arthritis is an immunological reaction to one or more specific environmental insults, most likely infection with a micro-organism, in a genetically susceptible host. The identification of such an agent has been the target of considerable study, with only limited success. This review examines the available epidemiological evidence for the involvement of both an infectious agent in general and specific micro-organisms in particular.

Does rheumatoid arthritis cluster?

Rheumatoid arthritis in general does not tend to cluster either in time or place, characteristics which when present suggest an infectious cause. The lack of ‘place’ as a risk factor is shown by the disease’s virtual ubiquity geographically. The disease is manifestly rare in some population groups, but compared with other chronic diseases the between-population variation in prevalence is low. Few infectious agents show the same ubiquity, though, as will be discussed below, Epstein-Barr virus is an interesting exception. Lyme disease is an example of a disease which shows profound clustering both in place and time (late summer). The subsequent identification of *Borrelia burgdorferi* as the spirochaete responsible highlighted the advantage of detecting the incriminating agent in a disease which clusters. Similarities in the synovial histology and lymphocyte responses between Lyme disease and rheumatoid arthritis have stimulated those seeking an infective cause for the latter despite it being more endemic, and clinically different.

Rheumatoid arthritis is likely to be a disease with a long latency and any evidence for infection might only be apparent some years before clinical onset and thus difficult to detect in established disease. An appropriate epidemiological tool to investigate exposure before infection is to study birth cohorts—that is, compare the risk of disease in groups with different periods of birth. One explanation for any such variation is that successive birth cohorts might have been exposed to different risks of infection because of the tendency of some infectious diseases to occur in relatively short lived epidemics. There appears to be a birth cohort effect in regard to rheumatoid factor positivity, both in the general population and in patients with rheumatoid arthritis. A recent study on juvenile arthritis suggested a clustering of births around 1963, a year which coincided with an epidemic of a particular strain of influenza. Such data as these, though of some interest, are manifestly subject to many interpretations.

Clustering within families has also been shown for rheumatoid arthritis, an observation consistent with a genetic or an environmental factor, or both. More detailed investigation of such families has failed to provide evidence to support the link with environmental factor. Thus both for affected sibling pairs and spouse couples there was a considerable median delay between the onset of disease in both the affected members, an observation against a common environmental exposure. Investigation of sibling pairs discordant for disease but HLA identical showed no evidence of difference in exposure to a long list of possible infectious agents.

Other circumstantial support for an infective aetiology came from the observation 10 years ago of an increased risk from tonsillectomy and appendectomy for the development of rheumatoid arthritis, with the suggestion that such surgery reduced host defence mechanisms. Despite a further study confirming this association three other studies failed to reproduce this result and there have been criticisms of the methodology of the first study.

Epstein-Barr virus

More convincing evidence of an infectious aetiology requires the study of specific organisms. There have, however, been inadequate population based studies, and investigations have tended to concentrate on prevalent—that is, established—cases in patients attending hospital frequently, tested against other hospital derived comparison groups. The most widely studied agent has been the Epstein-Barr virus following the first report in 1975 of an antibody to
this virus in the sera of patients with rheumatoid arthritis. This was the first of a number of serepidemiological studies comparing antibody prevalence with a number of different Epstein-Barr virus associated antigens in patients with rheumatoid arthritis and controls. These investigations confirmed the increased prevalence of high titres of antibodies against a variety of Epstein-Barr related antigens in patients with rheumatoid arthritis: viral capsid antigen, early antigen, Epstein-Barr nuclear antigen, and human parvovirus hepatitis B virus is virtually unknown in countries with a low prevalence of human parvovirus. One explanation for these observations, in the face of the ubiquity of infection with Epstein-Barr virus, is the effect of age. In countries with a low prevalence of rheumatoid arthritis, infection with Epstein-Barr virus is virtually universal by the age of 3 and the infection is clinically silent; whereas in countries with a high prevalence infection occurs at a later age and is more likely to be clinically apparent with, for example, infectious mononucleosis. The increased prevalence of rheumatoid arthritis nuclear antigen in rheumatoid arthritis is also seen, however, in most populations, including Mexican and American Indians and Afghans. The evidence for Epstein-Barr virus infection as a cause of rheumatoid arthritis is also constrained by the fact that Epstein-Barr virus is arthropathic only very rarely, unlike rubella, hepatitis, and mumps.

Human parvovirus

Another widely studied agent has been human parvovirus, with strong evidence in humans, particularly adult women, of an arthritis following infection with this agent. An editorial in the Lancet in 1985 concluded that human parvovirus probably had little relevance for rheumatoid arthritis despite two reports from the United Kingdom. The first of these showed that 19/153 patients with early synovitis had evidence of human parvovirus infection. The second described joint problems in 17 patients following a human parvovirus outbreak. Neither study had appropriate controls and there were no patients with a persistent arthritis. Interestingly, HLA analysis of the Bath patients showed that the DR4 positive rate was similar to that found in rheumatoid arthritis, suggesting perhaps a similar genetic predisposition to both disorders. In a further serological study comparing rheumatoid arthritis with non-specific inflammatory arthritis and normal controls two patients with rheumatoid arthritis had evidence of recent human parvovirus infection (IgM positive) and there was a higher rate of IgM positivity in the group with rheumatoid arthritis (92%) than in the other two groups (68 and 61% respectively). Human parvovirus like Epstein-Barr virus infection is very common, especially with increasing age, and evidence of infection is a poor predictor of subsequent rheumatoid arthritis. A serologically distinct parvovirus, RA-1, has been isolated from the synovium of patients with rheumatoid arthritis, and further studies showed that isolates from cultured synovial cells from patients with rheumatoid arthritis reacted with antisera to RA-1 in 6/11 patients with rheumatoid arthritis but in 0/6 controls. There are little data, however, on the basic epidemiology of this virus.

Other micro-organisms

Retroviruses have also been investigated particularly owing to the similarity between rheumatoid arthritis and the arthritis produced by lentivirus in animals—for example, caprine arthritis encephalitis in goats. In humans, however, attempts to show evidence of retrovirus infection in rheumatoid arthritis have been unsuccessful. There are also very good mycoplasma induced animal models of rheumatoid arthritis, and in such instances chronicity and severity, as in humans, are related to genetic factors. Clinical and epidemiological studies in humans have, however, failed to support a mycoplasma source for rheumatoid arthritis, though a recent report showed the isolation of mycoplasma antigens from the synovial fluid of six patients with rheumatoid arthritis. Probably, the response to mycobacterial antigen is enhanced in HLA-DR4 positive individuals. There have been studies of numerous other micro-organisms, not only viruses and bacteria but also protozoa, which have shed little further light on the main question.

Conclusions

There are therefore difficulties in investigating an infective cause for this disease. Clinically and epidemiologically rheumatoid arthritis does not behave like an infectious disease. Further, the persistence of the abnormal immune response...
which histopathologically is similar to that induced by a chronic infection, may not require the persistence of microbial antigen. The conventional application of Koch's postulates to a putative aetiological agent in rheumatoid arthritis is thus likely to be too restrictive in disclosing possible agents.\(^{41}\) Host factors are probably more important in determining disease susceptibility, which epidemiologically makes identification of any environmental agent difficult, especially in a disease with a subclinical phase of unknown duration.\(^{42}\) Immunopathologically it still remains likely that infection initiates the abnormal immune response in rheumatoid arthritis. Cross sectional studies of established disease seem destined, however, to be of little help in identifying the responsible agents. Future work should concentrate on studying early clinical or preferably subclinical disease in genotypically defined subgroups.

**References**

Notes and news

International Society for Rheumatic Therapy

The International Society for Rheumatic Therapy (ISRT) invites doctors and allied health professionals who treat patients with arthritis to apply for membership. The aim of the society is to achieve better patient care through the exchange and dissemination of knowledge between these groups. A congress of the ISRT will be held in London from 26 to 30 June 1990, and details of the meeting and application forms for ISRT membership can be obtained from the ISRT Secretariat, Pinewood Studios, Iver Health, Bucks SL0 ODH, UK or the ISRT Secretariat, 488 Madison Avenue (21st floor), New York, NY 10022, USA.

Rheumatology 1990

A rheumatology symposium entitled 'Rheumatology 1990' to celebrate 25 years of rheumatology at the Centre for Rheumatic Diseases, Glasgow, will be held at the Royal College of Physicians and Surgeons in Glasgow, Scotland on 22 and 23 March 1990. For further details please contact Dr Hilary Capell, Centre for Rheumatic Diseases, Royal Infirmary, Glasgow G4 OSF, Scotland.

VIth Eular symposium

The VIth Eular symposium will be held from 16 to 19 May 1990 in Athens, Greece at the Hotel Athenaeum Inter-Continental. Further information from EULAR 90, Symposium Secretariat, 10 Loukianou str, GR-106 75 Athens, Greece. Tel 01 72 18 276 or 72 28 784. Fax (01) 72 18 276.

Call for papers

East-Coast conference on biomechanics, 26-28 August 1990*. Please send one page abstract by 1 February 1990 to Professor H S Ranu, Department of Biomechanics, Suncom, New York Institute of Technology, Old Westbury, New York 11568, USA. Tel: 516 626 6926. Fax: 516 626 1306.

*Please note the new dates.

British Cervical Spine Society

The annual meeting of the above society will be held at the Watershed Conference Centre, Bristol, on 10/11 November 1989. Further information from Mr M J Torrens, FRCS, Department of Neurosurgery, Frenchay Hospital, Bristol, BS16 1LE. Tel: 0272 701212 (ext 2373).

Humanistic medicine

A course entitled 'Teaching humanistic medicine: an exploration of goals, techniques and experiences' will be held on 4-5 November 1989 at New York University Medical Center, New York City. CME: 15 category A credit hours. Fee: $250.

This two day programme will review the state of the art of teaching humanistic medicine. Leading faculty and representative students will share methods, experiences and ideas about the critical issues. Contrasting goals and techniques will be explored and examined in large and small groups by video and live interactional methods, workshops, and theatre. Details from NYU Medical Center, Post-Graduate Medical School, 550 First Avenue, New York, NY 10016, USA. Tel. (212) 340 5295.