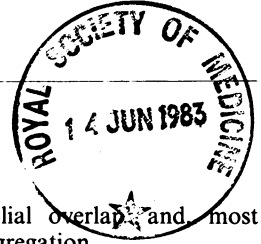# Editorials

Seronegative arthropathies

The idea of 'seronegative arthropathies' represents the most recent milestone in the evolution of rheumatological nomenclature. In its most primitive form, up to the end of the last century, rheumatic ailments were crudely divided into 'rheumatism' and 'the gout'. In due course, finer distinctions emerged, and three main nosological entities held sway for some years. These were rheumatoid arthritis, osteoarthritis, and gout. The concept of rheumatoid arthritis was strengthened by the discovery of rheumatoid factor (Waaler 1940, Rose et al. 1948) – serological testing of large numbers of patients with clinical features of rheumatoid arthritis revealing that about 80% were seropositive for this factor. A subpopulation of those who are seronegative constitute 'the seronegative arthropathies'.

The term 'seronegative arthropathy' in its broadest sense implies a heterogeneous collection of disorders. These include (1) seronegative rheumatoid arthritis which may or may not convert to seropositivity; (2) a group of disorders, quite distinct from rheumatoid arthritis, in which seronegativity remains a permanent feature. The term 'seronegative arthropathy (or arthritis)' often refers more specifically to this second group of disorders, which were termed 'the seronegative spondarthritides' by the Leeds group some years ago (Moll et al. 1974).

The seronegative spondarthritides (alternatively termed spondyloarthropathies or spondylarthropathies, particularly in the USA) were designated with the 'spond' prefix because of the crucial finding that ankylosing spondylitis tends to be associated with each member of this group. The early phase of the spondarthritis concept (Wright & Moll 1976, Moll et al. 1978) listed the following disorders which were considered to fulfil membership criteria: uncomplicated ankylosing spondylitis, Reiter's disease, psoriatic arthritis, enteropathic arthropathies (arthropathy associated with ulcerative colitis, Crohn's disease, or Whipple's disease), Behçet's syndrome, and certain forms of juvenile chronic polyarthritis. In addition to the common denominator of ankylosing spondylitis or sacro-iliitis, these conditions manifested other shared features. These included inflammatory and often asymmetrical peripheral arthritis, evidence of

'clinical overlap', 'familial overlap' and, most importantly, familial aggregation.

The centre of the spondarthritis proposals was therefore based not only on the non-rheumatoid nature of these disorders (previously alluded to by others such as McEwen et al. 1958), but also on the finding that convincing clinical and genetic relationships bind the disorders together.

Clinical overlap has been observed between all major members of the spondarthritis network. Clinical features ('co-diseases') providing a basis for the overlap phenomena include psoriasiform skin and nail changes, ocular, genitourinary and bowel inflammation, erythema nodosum, pyoderma gangrenosum, and thrombophlebitis. Overlap features so strongly in some patients that it is often difficult to make a definitive diagnosis. An example of this is shown by patients with features of both psoriatic arthritis and Reiter's disease (Wright & Reed 1964). Another example is provided by shared features between ankylosing spondylitis and ulcerative colitis and Crohn's disease (Acheson 1960).

Familial overlap represented another phenomenon which helped to consolidate the concept of the spondarthritides. Overlap took many forms, but a particularly consistent observation was the finding of ankylosing spondylitis or sacroiliitis in the close relatives of probands with various co-diseases, including psoriatic arthritis (Moll 1971), Reiter's disease (Lawrence 1974), ulcerative colitis and Crohn's disease (Hammer et al. 1968). The degree of familial overlap varied between reports and between pedigrees, but quite striking examples were beginning to emerge, some showing individual pedigrees containing three, or even more, different seronegative co-diseases.

In addition to familial overlap, evidence for familial clustering of index diseases started to be reported. By and large, these data arose from a series of controlled family studies conducted in Leeds (Baker 1965, 1966, Moll 1971, Moll & Wright 1973, Haslock 1972, 1973, Haslock et al. 1974, Chamberlain 1978). These studies had an advantage from the epidemiological and genetic standpoint in that they all shared similar methodologies and the same geographical catchment area. By means of clinical and radiological testing, these family studies revealed a convincing aggregation of each of the seronegative disorders examined (psoriasis, psoriatic arthritis, Crohn's disease, and Behçet's syndrome). Moreover, by

means of spouse controls it was possible to deduce that some, at least, of the aggregation must be due to genetic as opposed to environmental factors. Together with previous evidence from scattered sources, which had already drawn attention to familial clustering among other seronegative disorders – namely, Reiter's disease (Paronen 1948), Whipple's disease (Puite & Tesluk 1955), ulcerative colitis (Houghton & Naish 1958), and ankylosing spondylitis (Kellgren 1964) – the concept of the spondarthritides grew further. Indeed, it was now becoming clear that genetic factors were paramount in aetiology, as well as providing a means to explain multivarious clinical interrelationships manifested by the group.

The next phase in the development of the spondarthritis idea stemmed from evidence which was to become pivotal in developing the concept further. This arose from histocompatibility studies which demonstrated a striking relationship between ankylosing spondylitis and the antigen HLA-B27. This evidence, which appeared simultaneously from the UK (Brewerton *et al.* 1973*a*) and the USA (Schlosstein *et al.* 1973), showed that over 95% of patients with ankylosing spondylitis possessed this antigen. Subsequent work by Brewerton's team revealed that the association of HLA-B27 with spondylitis continued in patients in whom spondylitis was associated with various co-diseases, such as Reiter's disease (Brewerton *et al.* 1973*c*), ulcerative colitis (Brewerton *et al.* 1974), and psoriatic arthritis (Brewerton & James 1975).

HLA studies have enabled a broader view of the spondarthritis matrix and, since the original delineation, acute anterior uveitis and reactive arthritis have been added to the group. The evidence for including anterior uveitis has been confirmed by several workers, notably Brewerton *et al.* (1973*b*) and Woodrow *et al* (1975), both of whose studies showed HLA-B27 positivity in over 50% of patients with uveitis. A high frequency of HLA-B27 has also been reported in various 'reactive arthropathies' in addition to sexually-acquired reactive arthritis (Reiter's disease). Much of this evidence comes from Scandinavia and has demonstrated a high frequency of non-infective, non-erosive peripheral arthropathy occurring after certain gastrointestinal infections. Particularly influential in this respect are the organisms of salmonellosis, shigellosis, and *Yersinia enterocolitica* (Aho *et al.* 1974, Friis & Svejgaard 1974, Hakansson *et al.* 1975).

The importance of the phenomenon of reactive arthritis in part relates to the question of environmental factors in the causation of the spondarthritides. Certainly in Reiter's disease and in Whipple's disease there is good evidence for an infective factor in aetiology. Also, it has long been known that psoriasis in children may be provoked by infection, particularly streptococci. Another environmental 'trigger' in psoriasis may be trauma, and it has been suggested that a deep-seated Koebner phenomenon may affect the joints of psoriatic subjects. The inciting agent(s) in ulcerative colitis and Crohn's disease have not been isolated, but it is possible that absorption of food products, microorganisms or their toxins through damaged portions of intestinal mucosa might initiate disease through providing provocative antigens. In the context of bowel microorganisms, recent work by Ebringer *et al.* (1978) has implicated *Klebsiella pneumoniae* in the aetiology of active spondylitis. Although this has not been confirmed in a more recent study (Warren & Brewerton 1979), the 'Klebsiella story' continues, and the final outcome will be awaited with interest.

It is difficult to summarize the present position regarding the aetiology of the spondarthritides, but it is likely that a variety of genetic mechanisms are involved (based on polygenic rather than Mendelian inheritance), and that there is complex interplay between these and a host of environmental factors of the type already described. Moreover, recent studies have pointed to immunological defects within the spondarthritis network, particularly in ankylosing spondylitis (Good *et al.* 1977, Corrigall *et al.* 1978, Wee & Daymond 1978), and it is likely that once initiated by an appropriate blend of genetic and environmental factors, the various diseases are perpetuated by immunological processes.

It is important to stress that the concept involving these seronegative arthropathies is more than of pure academic interest. There are sound practical implications underlying the spondarthritides, and some of these may be expressed as follows:

(1) Considering that these disorders are not 'variants of rheumatoid arthritis', as was once believed, a more optimistic prognosis can be given to the patient because many locomotor manifestations within this group tend to be milder, less extensive, and less prolonged than in the rheumatoid condition.

(2) The high prevalence of sacroiliitis and even of fully established spondylitis in these patients will heighten diagnostic suspicion in seronegative patients (and their relatives) presenting with back pain. In this way, back discomfort will be less readily dismissed as lumbago due to disc disease.

(3) The familial overlap and aggregation characterizing the spondarthritides emphasize the importance of taking an adequate family history from probands. This will almost certainly lead to the uncovering of lanthanic disorders, whether of

rheumatic or non-rheumatic origin.

(4) The use of histocompatibility studies and additional genetic and environmental information for the identification of subpopulations at special risk is an important developing area in modern medicine. It may be possible in the future to extend the principle of active immunization which has been an important means of preventing infectious diseases. Subpopulations of certain rheumatic subjects and spondarthritic disorders at special risk can now be identified, and the possibility of devising immunological and non-immunological methods to remove such risks is now within reach.

Further developments within the spondarthritis concept are not easy to predict, but it is likely that new members will be added to the group. In this respect, a newly-reported condition 'pustulotic arthro-osteitis' is of interest. This disorder, recently reported by Japanese workers (Sonozaki *et al.* 1981), shows some features conforming to the spondarthritis idea, but the 53 patients described were all HLA-B27 negative. Another disorder of possible spondarthritic relevance is the intestinal bypass arthritis-dermatitis syndrome (Stein *et al.* 1981) in which an association with ankylosing spondylitis and HLA-B27 has been reported (Rose *et al.* 1977). In many respects this syndrome represents an 'experimental model', iatrogenically-produced, of the clinical complex seen in the enteropathic arthropathies of ulcerative colitis and Crohn's disease.

The question regarding the nosological significance of seronegative polyarthritis without obvious clinical features of rheumatoid arthritis or of the spondarthritides remains unresolved. However, it is likely that at least a proportion of the patients could be included in the spond-arthritis complex. The fact that many are HLA-B27 positive, have an asymmetrical lower limb arthropathy (i.e. non-rheumatoid pattern), show male preponderance and an earlier age of onset (Cleland *et al.* 1975), supports the assumption that these patients are not only 'non-rheumatoid' but also show some features of the spondarthritides.

Since the days when ankylosing spondylitis was thought to be a 'variant of rheumatoid arthritis' (mirrored in its designation by some authorities as 'rheumatoid spondylitis'), as opposed to the nidus of a nexus of genetically-related sero-negative arthropathies (Moll 1980), progress in this field has indeed been far reaching. Further research seems likely to bear additional fruit in the near future, with advances in the understanding of aetiology being more likely to come from family studies and immunogenetics than from pursuing isolated immunological defects.

However, concerning the latter, if methodologies can be standardized and if lesions of metabolic relevance can be separated from pathogenetic epiphenomena, significant advances in our approach to therapy might emerge.

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Arthroscopy of the knee:
some problems[1]

Ten years ago, diagnostic arthroscopy of the knee was seldom performed outside a few specialist centres in Japan and North America and was widely considered to be an interesting but tedious technique of doubtful value. Arthroscopic surgery, although already achieved by Watanabe in Japan and O'Connor in California (O'Connor 1982), was virtually unheard of and no results had been published.

The change in the last decade has been remarkable. Arthroscopy is now the most commonly performed orthopaedic operation in some areas, and arthroscopic surgery is practised widely in many centres around the world. The general acceptance of arthroscopy has been accompanied by a change of attitude among orthopaedic surgeons, and by the recognition of a

[1] Arising from meeting of Section of Orthopaedics, 3 February 1981

number of problems. Complications are encountered with all new techniques, and arthroscopy is no exception. Accounts of surgical disasters, including the loss of limbs following arthroscopic meniscectomy, are now appearing and it is perhaps appropriate to review the problems that exist at present.

The difficulties fall into three categories: academic, technical and educational. Of these, the academic are perhaps the most immediate but probably the least permanent. The unblinking gaze of the arthroscope has been accompanied by the recognition of disorders not previously described, such as the synovial shelf or 'plica' syndrome, and by new concepts such as the selective treatment of meniscal lesions. Whereas complete meniscectomy was the common treatment for meniscal lesions until a few years ago, surgeons are now content to excise the minimum of tissue and leave behind as much of the meniscus as possible, provided that it is intact and stable. Furthermore, so many operations can now be done arthroscopically that in centres where arthroscopic surgery is practised, the indications for arthrotomy are largely confined to total joint replacement, ligament reconstruction and meniscal reattachment – a change in practice little short of revolutionary.

Any development that overturns established techniques to such an extent must be open to close scrutiny, and its justification must depend on meticulous assessment of patients and the publication of results in a proper scientific manner. Such work cannot be prepared overnight and no results of arthroscopic surgery appeared in the English literature until 1978 (Dandy 1978). The bibliography of arthroscopic surgery is now formidable, but a cloud of uncertainty will hang over arthroscopic surgery until the results are properly documented and published so that the indications for operation can be clearly established. When this has been done, at least some of the diagnoses and arthroscopic operations at present performed with such enthusiasm are likely to be found wanting and become obsolete.

A second academic criticism of arthroscopy, which proved unfounded, was the idea that it would lead to a less thorough clinical assessment of patients, and even to atrophy of clinical skills through disuse. In fact, experience of arthroscopy has tended to throw greater emphasis on the importance of a proper clinical examination, because arthroscopic findings in the absence of a clinical history are of no help to the surgeon in deciding whether an arthroscopic abnormality is the cause of symptoms, or simply an incidental finding. Most arthroscopists have also found that the 'feedback' of arthroscopy has improved their clinical acumen by making possible a closer