Introduction

Opening remarks

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About 25 years ago it was common to speak of the so-called 'variants of rheumatoid arthritis'.³³⁴ These included ankylosing spondylitis (AS), Reiter's syndrome, and psoriatic arthritis. Their chronic peripheral polyarthritis had a certain resemblance to rheumatoid arthritis (RA) and this led to the association. They were in fact classified as atypical or special forms of rheumatoid arthritis by the International League as late as 1957. As it became obvious that the rheumatoid factor was a reliable marker of rheumatoid arthritis and that these patients were by and large seronegative, the idea that they were rheumatoid variants lost its attractiveness. In the classification of the ARA in 1963 they were listed as independent polyarthritides. And yet the term 'variants', if not 'rheumatoid variants', tended to hang on, essentially because they did have certain features in common.

As the entities of colitic arthritis and colitic spondylitis³³⁹ began to be delineated and as it became clear that Crohn's disease¹⁴⁵ was associated with joint symptoms, the syndrome of enterocolitic arthritis was added to the group of variants. Recently the list has been enlarged further. Thus when rheumatologists were mainly preoccupied with linking the collagen diseases together it was refreshing to find another group of conditions within their purview that stood distinctly apart from the collagen diseases and yet had impressive clinical associations with each other. What this group had in common, of course, was a tendency to develop sacroiliitis and ankylosing spondylitis, and for this reason Wright and Moll³³³ suggested they should be called 'seronegative spondarthritides.'

Much interesting speculation developed on what might cause the high incidence of sacroiliitis and spondylitis in this group, and the idea that inflammation in either the urethra, prostate, or colon was the precipitating factor suggested itself. Romanus²⁵⁸ in Sweden and others after him found that patients

with ankylosing spondylitis had a chronic prostatovesiculitis. To transmit an infectious or inflammatory agent from the genitourinary tract to the spine and to the eye they invoked Batson's circulation.²¹ Batson's circulation (Figs 1, 2) is a thin-walled venous circulation that drains the pelvic venous plexus and communicates with the spine and even with the structures of the head. Batson originally investigated it as a possible pathway of metastasis to the spine for carcinoma of the prostate. Urologists are still quite familiar with it. In effect, here was a convenient mechanism for transmitting inflammatory agents to the sacroiliac joints and the spine in ankylosing spondylitis, infectious colitis, enterocolitis,¹⁴² and particularly Reiter's syndrome.

Another interesting link in this group of spondarthritides has been that between Reiter's syndrome and psoriatic arthritis. This was first pointed out by Wright and Reed³³⁷ in 1964. They emphasised the

Fig. 1 Batson's circulation (Batson²¹) Extensive venous spread from injected deep dorsal vein of penis into the vertebral system. (By permission of the J. B. Lippincott Company.)

Fig. 2 *Batson's circulation AP caudal view (Batson^{21a})*
(By permission of the Editor, American Journal of Radiology.)

similarity between keratoderma blennorrhagica and pustular psoriasis of the palms and soles and described 11 patients who had classical lesions of psoriasis at the same time as keratoderma blennorrhagica. In addition there was a distinct temporal relationship between the appearance of keratoderma and the appearance of psoriasis. I have personally seen two patients who for a month or so had a urethral discharge, polyarthritis, and keratoderma and then developed the lesions of psoriasis and the picture of classical psoriatic arthropathy.

The second of these patients was treated with 6-mercaptopurine. On this treatment his psoriatic skin lesions cleared and his active arthritis disappeared although his joint deformities remained. During a sustained remission the 6-MP was cut. Three months later he again developed a urethritis, conjunctivitis, and active polyarthritis which converted itself a second time, after a month or so, into psoriatic arthropathy.

For many years there has been an awareness that there are hereditary features to ankylosing spondylitis. The early studies of de Blécourt *et al.*²⁹ published in 1961, found the incidence of this disease to be 22 times greater in relatives of probands than

in controls. Emery and Lawrence⁹⁸ later concluded that ankylosing spondylitis was inherited by a polygenic mechanism. Wright and Moll³³⁵ have reported the aggregation of sacroiliitis and ankylosing spondylitis in relatives of patients with psoriatic arthritis and patients with ulcerative colitis.

A genetic aspect of these variants became apparent to me when I came to work in Dallas from New York. I had been accustomed to seeing a fair number of ankylosing spondylitis patients around the Bellevue Hospital Arthritis Clinic in New York. I found myself missing them in the arthritis clinic in Dallas, which was largely attended by black patients. Yet when I made rounds in the Veterans Hospital in Dallas there they were—and always white. The same seemed to be true for Reiter's syndrome, although we were not so sure about that. John Baum proceeded to investigate this situation in a group of veterans hospitals. It became clear that the incidence of ankylosing spondylitis in whites in these hospitals was between 3 and 10 times greater than in blacks. When he inspected the African literature he found that ankylosing spondylitis was indeed very rare. It is almost non-existent among South African blacks. Indeed, J. C. Woodrow³²⁷ has pointed out the virtual absence of the HLA-B27 marker in African blacks.

So, as of 1973 one could say of the spondarthritides that they tended to develop sacroiliitis and ankylosing spondylitis and that there was evidence, at least in one pair of patients, of a transition from Reiter's syndrome to psoriatic arthropathy. There was also evidence of a racial selectivity and genetic overlap. But perhaps I have belaboured this point. The almost blinding light that the B27 discovery has thrown on this meandering tale goes far to illuminate any mysteries it may have held.

Still, in spite of the B27 discovery, we are not yet home free with these seronegative spondarthritides. It would be easy to take a perhaps simple-minded view of these diseases in relation to ankylosing spondylitis—that is, that they are 'environmental' risk factors for the B27-positive patient (to borrow a term of Russell²⁶³) such as might be absorbed from the colon in bacillary dysentery, or *Yersinia* enterocolitis, or ulcerative or granulomatous colitis; from the urethra in Reiter's syndrome; from the prostate of the patient with ankylosing spondylitis; or from the skin of the patient with pustular psoriasis. Antigens absorbed from these sites would be uniquely capable of stimulating an immune response recognition site controlled by a gene closely linked to the B27 gene to produce sacroiliitis, ankylosing spondylitis, and even iritis.

There would, however, be serious objections to such a proposal. (1) Psoriasis or colitis may follow ankylosing spondylitis by many years rather than precede it. (2) Spinal involvement progresses in the absence of evidence of active psoriasis, colitis, or urethritis. (3) Unaffected relatives of patients with inflammatory bowel disease have been found to develop sacroiliitis and ankylosing spondylitis more often than control populations,¹ suggesting a genetic influence of genes for inflammatory bowel disease.²¹⁹ (4) Patients with psoriatic arthropathy or inflammatory bowel disease develop ankylosing spondy-

litis with a much lower frequency of B27 positivity than seen in the Marie-Strumpell ankylosing spondylitis group, again suggesting the influence of genes associated with psoriasis or inflammatory bowel disease on the ankylosing spondylitis gene in the development of sacroiliitis or ankylosing spondylitis. So there is evidence for a genetic interplay between heredity in the spondarthrides and the heredity of ankylosing spondylitis which we do not as yet understand. These are some of the important questions that this conference will have to touch upon.