"THE LEEDS IDEA": AN HISTORICAL ACCOUNT OF THE SPONDARTHRITIS CONCEPT

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SUMMARY

In the 1960s, Professor Verna Wright became increasingly interested in possible relationships between certain seronegative "variants of rheumatoid arthritis", as they were then generally known.

At the Rheumatism Research Unit, a department within the division of medicine at Leeds University, he gathered around him a succession of research workers, whom he inspired to study aspects of these relationships. The focus was on family studies, as it was thought that genetic factors could be important. The striking association previously noted between sacroiliitis or full-blown ankylosing spondylitis and several of these disorders to be studied - e.g., psoriatic arthritis, ulcerative colitis, and the arthritis associated with Crohn's disease - was to be central for each of these studies.

As a provisional collective name for these possibly related conditions, the term "Spondarthritides" was chosen.

These were the days before HLA B27, and so the research tools were simply clinical, radiological (for sacroiliitis) and serological (for rheumatoid factor). The research programme confirmed not only links between the primary disorders with ankylosing spondylitis, but also links between the disorders themselves.

Over subsequent years, the spondarthritis concept (dubbed by some "The Leeds Idea") has gained further strength from HLA studies internationally. And membership of the group of conditions fulfilling spondarthritis criteria has grown substantially. It is hoped that this now consolidated framework of spondylitis-related entities will pave the way for further research, with exciting prospects of gene-based prevention and/or cure through the increasing sophistication of molecular biology.

Key words: Seronegative spondarthritides, psoriatic arthritis, ankylosing spndylitis

BACKGROUND TO THE SPONDARTHRITIS CONCEPT

An invitation to contribute an article entitled 'The Leeds Idea' provides a welcome opportunity to sketch the background of a line of thinking that originated from the then head of the Rheumatism Research Unit at Leeds, the late Professor Verna Wright (Fig. l), and his research team almost four decades ago. This is thus an historical account rather than a comprehensive review of developments from the earliest thoughts to present-day, post-millennial, evidence.

In the 1960s Verna Wright grew increasingly interested in possible interrelationships between certain seronegative 'variants of rheumatoid arthritis', as they were then termed. The term 'seronegative' referred to seronegativity for rheumatoid factor. Wright's earliest publication alluding to this type of interrelationship was in collaboration with W. B. Reed, and explored the link between Reiter's syndrome and psoriatic arthritis (1).

In Wright's earlier years as a rheumatologist he had expanded on a growing notion that the association between psoriasis and arthritis was one of significance rather than coincidence. For decades before that, the presence of psoriasis and inflammatory arthritis had been ascribed to the chance association of the relatively common skin disorder, psoriasis, with the relatively common arthritis, rheumatoid arthritis. His several publications from the mid-1950s onwards much strengthened the concept that psoriatic arthritis was a distinct entity (for example 2, 3).

These were the days well before HLA typing, and when rheumatological classifications in this field depended largely on clinical, radiological and serological (for rheumatoid factor) observations.

In addition to this strong evidence for the specific

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Figure 1 - Professor Verna Wright (ink drawing by the author).

identity of psoriatic arthritis was the observation that there seemed to be a statistical association with sacroiliitis or even full-blown ankylosing spondylitis (3-7). And before this, in 1960, Acheson published the observation of an association between ulcerative colitis, regional enteritis (Crohn's disease), and ankylosing spondylitis (8). This paper was one of the many of that period that encouraged us to explore spondylitis associations in more detail.

In parallel with these new lines of thinking was the proposal that there may be interrelationships between the various forms of seronegative 'variants of rheumatoid arthritis'. In addition to psoriatic arthritis and ankylosing spondylitis, other seronegative arthritides then attracting attention in this context were Reiter's disease (or syndrome) and the inflammatory arthritides associated with ulcerative colitis and Crohn's disease. And even Whipple's disease and Behçet's syndrome appeared to be in some way relevant.

This was a far cry from the system proposed by the American Rheumatism Association in 1963 (9) in which rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Reiter's disease were classified as separate entities. And it was only then that the arthritides of ulcerative colitis, Crohn's disease, Whipple's disease and Behçet's syndrome appeared for the first time in the classification.

Thus, in those times of some four decades ago, international thoughts on rheumatological classification and nomenclature were somewhat different from those of today.

FORMING THE CONCEPT

This early background led Wright to examine the possibility of relationships deriving from psoriatic arthritis and other seronegative arthritides in more detail. This he did by encouraging a succession of research workers within the Rheumatism Research Unit at Leeds (a department within the University's division of medicine), of which he was head.

The remit, as a broad plan to extend over some years, and planned to record the results as research theses and publications, was primarily to examine the relevance of genetic factors through controlled family studies. Accordingly, in the late 1960s there started research projects on what were considered to be key disorders in this group of conditions.

Ian Macrae started with a study of ulcerative colitis families. This was followed by my family study of psoriatic arthritis and by lan Haslock's family study of patients with Crohn's disease. Each study looked especially at the prevalence of sacroiliitis within these families. Later, similar studies were carried out by Anne Chamberlain on Behçet's patients, and by Max Roberts, who did further work in the field of psoriasis.

This interest of the Leeds group continues to this day, for example by the work of Philip Helliwell.

In those early days it was felt that a concept was needed to provide a guiding structure in the forming of hypotheses. After much discussion, we chose 'seronegative spondarthritides' as the term for this group of conditions that appeared to display strong associations, with ankylosing spondylitis/sacroiliitis as a central feature. Hence the 'spond-' prefix. In later years, the prefix in some quarters became 'spondyl-' or 'spondylo-'. However, at Leeds we continued with the original term, feeling this to be less unwieldy than the longer alternatives, with their additional syllables. And the 'spondyl-' or

'spondylo-' prefixes also raised the possibility of confusion with various names given to ankylosing spondylitis in the literature abroad, viz: ankylosing spondyloarthritis, spondylarthritis ankylopoetica, spondylarthritis ankylosante, spondilartrite anchilopoetica, and espondilartritis anquilosante.
Over the years, as the concept gained support through increasing evidence, the term became shortened to 'spondarthritides', certain nosological equivalents from other centres being 'spondyloarthropathies', spondylarthritides', 'spondyloarthritrides', 'enthesopathies', and 'HLA B27 - positive disorders'. We also needed to propose a set of working criteria for membership of the spondarthritis group, although with the realization that these may need to be modified in the future. Thus, we suggested the following:

1. Absence of rheumatoid and antinuclear factors.
2. Absence of rheumatoid nodules.
3. Inflammatory peripheral arthritis (often asymmetrical).
4. Radiological sacroiliitis, with or without ankylosing spondylitis.
5. Evidence of clinical 'overlap' between members of the group. This, we felt, should include two or more of the following:

- psoriasiform skin or nail lesions;
- ocular inflammation, including conjunctivitis or anterior uveitis;
- buccal ulceration, or ulceration of small or large bowel;
- genital ulceration;
- genitourinary infection (particularly urethritis and/or prostatitis);
- erythema nodosum;
- pyoderma gangrenosum;
- thrombophlebitis.

The first list of likely members of the group, and meriting further study, comprised seven conditions:

1. Uncomplicated ankylosing spondylitis.
2. Psoriatic arthritis.
3. Reiter's disease.
4. Ulcerative colitis.
5. Crohn's disease.
6. Whipple's disease.
7. Behçet's syndrome.

Subsequent evidence led us to revise this to an expanded list often conditions:

1. – 6., as above.
7. Juvenile chronic arthritis.
8. Reactive arthritis.
9. Acute anterior uveitis.
10. Behçet's syndrome.

By and large, this modified list has stood the test of time, through studies in UK departments and in centres abroad. However, the place of some conditions in this system remains contentious, or even doubtful - Whipple's disease and Behçet's syndrome, for example.
Also, either within the Leeds group or in other units, certain additional entities have been proposed over the years, either for definite inclusion or as more borderline entities worthy of further study. These include: 'uncomplicated seronegative polyarthritis' (i.e., arthritides without the presence of a 'co-disease' at the time of study), especially where the arthritis is peripheral and asymmetrical; the enthesopathies (local or systemic); the bone changes associated with vinyl chloride disease; and ankylosing hyperostosis (Forestier's disease).
Doubtless other conditions will be added to, or subtracted from, this list in the future, as HLA genetics becomes even more refined, more widely used, and better understood.

SUPPORT FOR THE CONCEPT

In the early 1970s, before the HLA B27 era was launched in 1973 in Britain and the USA, these Leeds studies were nearing completion, or had already been completed and published. And by 1976 the concept was further consolidated in 'Seronegative Polyarthritis' (10), published by North-Holland. This was followed by 'Ankylosing Spondylitis' (11), published by Churchill Livingstone.
These publications provided the concept with broad international dissemination, as did the spondarthritis chapters in the 1978 (12) and 1986 (13) editions of'Copeman', the standard British textbook of rheumatology of that period.
These publications, and Leeds articles in peer-reviewed journals, tended to retain the term 'spondarthritis' over the years, while the concept was continually updated in response to new evidence.
According to Wright's original plan, the foundation studies providing support for the concept were either presented as doctoral dissertations or as articles for publication, and covered, in those early years, three conditions by means of family studies. These were, in the order in which they appeared: psoriatic arthritis (7, 14); Crohn's disease (15-17); and ulcerative colitis (18). A short period after, Chamberlain's Leeds study of Behcet's syndrome

was published (19), but this failed to show links with sacroiliitis or spondylitis in probands or their relatives. Thus, this study threw doubt about the inclusion of Behçet's syndrome as one of the spondarthritides, and thus helped to refine further the component disorders of the spondarthritis complex - and provided a good example of the value of negative findings.

Generally, however, the Leeds studies confirmed that sacroiliitis/spondylitis provided a unifying denominator within the concept. This, in pre-HLA B27 days, was thought to be due to genetic factors, as prevalence rates differed significantly between blood relatives and spouse controls.

However, in those early days, before the availability of genetic markers (HLA genotypes), our studies depended purely on phenotypic evidence. In other words, we were limited to clinical, radiological and serological evidence, studied by means of controlled epidemiological studies involving probands, their relatives, and their spouses as controls. Thus, our approach was very much clinically epidemiological, rather than epidemiological based on molecular biology.

This clinical rather than laboratory approach allowed not only the collection of statistical information but, importantly, also a number of interesting observations within individual subjects suggesting associations between putative members of the group. These 'overlap' instances heightened our suspicions that links, from whatever cause - genetic, environmental, or both, permeated the group. Among these many examples were: similarities between certain patterns or psoriatic arthritis and Reiter's disease; shared features between ankylosing spondylitis and the arthritis of ulcerative colitis and of Crohn's disease; and similarities between Reiter's disease and 'reactive arthritis', the latter then being a new concept.

In addition to these 'overlaps' within single individuals, we also noted the interesting occurrences of 'overlap' within some of the pedigrees studied, for example psoriasis in one relative and spondylitis or colitis in another. Moreover, this clustering of spondarthritic features between individuals seemed to occur in each of the earlier family studies. The clustering was at a low level, but was often statistically significant and sufficient to alert us to the existence of a true phenomenon rather than associations based on chance.

Notable among these family observations were the existence of sacroiliitis in first-degree relatives, and also increased occurrences of seronegative arthritis and of spondarthritis co-disease, such as psoriasis or inflammatory bowel disease.

Thus, from an early stage of these controlled studies, and from isolated observations before the studies were started (which had triggered suspicions of association in the first place, and which were the founding thoughts underlying the series of family studies), we felt increasingly confident that we could be looking at an arthritis complex of interwoven familial disorders, quite unlike that associated with rheumatoid arthritis.

Statistical analysis of individual studies and collective appraisal of the separate studies over the years increasingly strengthened support for those earlier observations, and thus lent additional weight to the spondarthritis concept.

THE PRESENT AND FUTURE

Since 1973, HLA studies have gone a long way towards explaining these earlier clinico-radiological observations. And after the initial realization of the significance of HLA B27 in relation to sacroiliitis/spondylitis came valuable evidence of B27 subtypes and other genetic markers and associations within the HLA complex (for example HLA markers for psoriasis).

This is not the place to review this ever-growing source of evidence, but it allows the conclusion that the original warp and weft of the clinical spondarthritis carpet is gradually - over the past three decades - being mirrored by laboratory (HLA) findings.

This raises the hope that gene-based therapies might arise from this molecular research, but none is yet in sight from the point of view of the clinical practitioner. However, recent advances in cancer molecular research, not least the recent licensing of a vaccine to prevent cervical cancer, are encouraging. These could pave the way to prevent or treat diseases, including rheumatic disorders such as the spondarthritides, caused by more complex factors, such as those involving genetic factors, rather than 'simpler' disorders based on a viral cause.

Why has progress remained relatively slow since the superimposition of HLA research and, on a broader scale, the impressive advances of mapping details of the human genome?

I would suggest this is due to a set of interacting complexities. First, there is the nature of the genetic inheritance mechanism. This, throughout the spon-

darthritis group, appears to be polygenic, i.e. the operation of several genes of small effect, rather than Mendelian-single-gene disorders of large effect.

However, even this is not clear-cut. For example, for many years there was confusion in the case of the genetics of psoriasis. This disorder seemed to show Mendelian patterns in some families and polygenic patterns in others.

Another complexity is due to the likelihood of the relevance of environmental factors, whether these be microbial, chemical, physical, psychological, or combinations of these.

Identification of these environmental factors will not be enough without an understanding of the way they might interact with genetic factors at molecular level.

And added to the 'simple' premise that genetic-plus-environmental factors trigger disease, are factors due to the research process itself. For example, conformity between selection criteria, adequate controls, agreement between laboratory techniques, and last but not least, methods of statistical evaluation. Unless international gold standards are agreed across this range of research aspects, progress can be expected to be hampered. However, it is encouraging that since the early days of 'molecular epidemiology' many advances have been made in this direction.

A further problem in the spondarthritis field is the fact that many of the conditions required for study, whether they be diseases, disorders or syndromes, are relatively uncommon, or even rare. And thus the case material for the spondarthritis researcher is more limited than in the field of research into more common rheumatic disorders such as osteoarthritis, rheumatoid arthritis, and soft-tissue conditions. This limitation in some instances may require the pooling of index cases from different geographical areas in order to generate sufficient numbers to achieve statistical significance. But clearly this has its disadvantages, compared with studies carried out under one roof, with the consistency of approach that this implies.

However, this 'quick-quick-slow' historical pattern of the spondarthritis research story should not detract from the encouraging progress evident in recent years. And it is to be hoped that this will lead to more effective therapy, or even cure, of the many disorders belonging to the spondarthritis tapestry; now clearly seen to be even more complex than it appeared in the days when the idea was first conceived (Fig. 2).

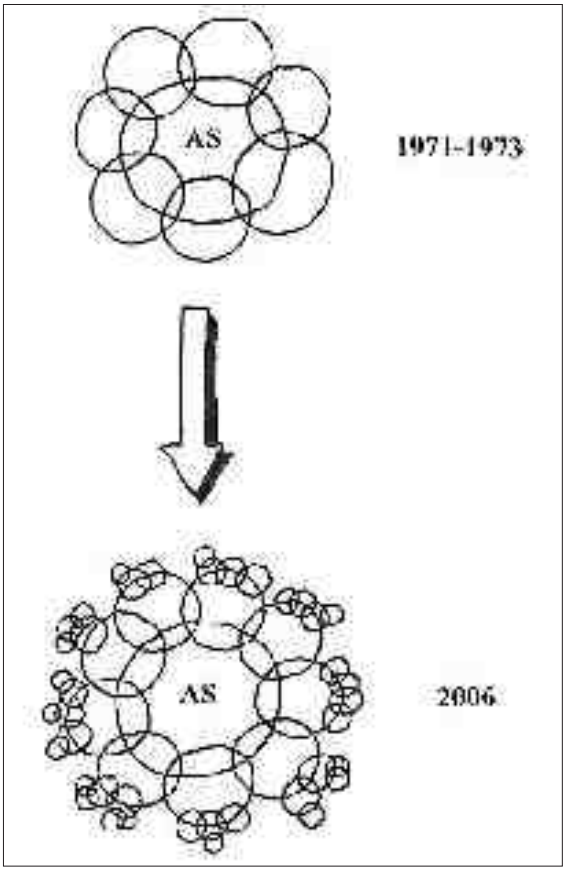

Figure 2 - Increasing complexity of the spondarthritis network over three decades, including the central place of ankylosing spondylitis (AS) - schematic.

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