Many genes, many clinical features

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The important part of this meeting will be behind closed doors, with the ARA Committee deciding the diagnostic criteria for Reiter's syndrome (RS). These will vary, depending on whether they are for the diagnosis and management of individual patients, for population surveys, or for genetic analysis. For genetics it is essential to set aside classical definitions of disease—as if the textbooks had not been written—and then to study individual clinical features both in isolation and in various combinations.

In simple form, the Figure illustrates the puzzle we have been discussing and are hoping to understand. Essentially it is an overlapping jumble of clinical features which we have divided arbitrarily and defined as diseases. By drawing lines at different parts of the Figure it is possible to indicate three ways of defining ankylosing spondylitis and also the syndrome familiar to paediatricians—childhood pauciarticular arthritis in the lower limbs associated with acute uveitis and usually leading to spondylitis in adult life.

Alternatively, we can take several features and call it RS. The definition indicated in the Figure is neither watertight nor satisfactory. Yersinia infection may lead to urethritis, salmonella to conjunctivitis, or Crohn's disease to uveitis, and keratoderma may be exactly like pustular psoriasis. Also, as Dr. Czonka illustrated so elegantly, *RS is difficult to define because it is always incomplete. He had to see 410 patients to appreciate the complete picture of the disease. One possible explanation of this pronounced variation is that our responses may be genetically determined. All of us may be programmed to respond individually, with the environmental trigger influencing relatively little the details of the ways in which we each respond: each man has his own disease.

We can also consider individual clinical features as they occur in isolation (not classified as RS). Sacroiliitis, spondylitis, acute anterior uveitis without associated disease, seronegative peripheral arthritis, pustular psoriasis, and chronic circinate balanitis without urethritis or other disease are all individually related to B27. But we shall not solve our problems by studying single genes and individual clinical features. For the composition of such an intricate pattern of disease as this I believe we must contemplate several genes interacting to help, hinder, or mask each other. So, how can clinicians observe the interaction between gene products?

B27 is present in RS in only 65% of patients with peripheral arthritis alone. Add sacroiliitis, uveitis, or balanitis—each individually associated with B27—and in the combination the incidence of B27 is almost 100%, as one might expect. But take ankylosing spondylitis and then add psoriasis, ulcerative colitis, or Crohn's disease—they themselves not associated with B27—and the incidence of B27 drops from 90%–95% to 65%–75%.

* Why the reduction? The answer is crucial. The most likely explanation is that genes for psoriasis or

*See 'Clinical aspects of Reiter's syndrome' at p. 4.
inflammatory bowel disease themselves contribute to the spondylitic process and make the presence of B27 less necessary. What is the evidence that this may be so? Firstly, in people with B27 the incidence of spondylitis is undoubtedly greater in those with ulcerative colitis, Crohn’s disease, or psoriasis than it is without these diseases. In individuals, some patients with several diseases or clinical features do not have B27 (when one might expect it most), again suggesting that the presence of genes for other diseases may make B27 less necessary.

Unfortunately, the mechanisms of polygenic inheritance in human families are usually concealed by their own complexity. In occasional families, however, many members are affected and the genetic factors are so powerful that we can observe the interaction between gene products. Each family is different. Only spondylitis is seen in some, while in other families with strong susceptibility to spondylitis we find psoriasis and chronic inflammatory bowel disease far more often than by chance. We may also see the opposite. The genes for bowel or skin disease may not achieve clinical expression as such but nevertheless predispose to rheumatic disease. An an example, one patient’s father had severe ulcerative colitis. The patient did not inherit colitis. Instead she had classical spondylitis without B27.

To sum up, about half the patients with spondylitis without B27 will have obvious skin or bowel disease during their lifetime—six times as often as with spondylitis in the presence of B27. Of the remainder, I believe that many will have genes for psoriasis, ulcerative colitis, Crohn’s, and possibly other diseases. This attractive hypothesis could be tested by further clinical investigation of such patients, and particularly by more extensive studies of families and of different races. Or perhaps it must await better markers for psoriasis and inflammatory bowel disease. By a like argument, in RS without B27 there might be genes predisposing to psoriasis and in acute uveitis without B27 there might be genes for ulcerative colitis, Crohn’s disease, sarcoidosis, or psoriasis.

The early studies of HLA antigens in sarcoidosis, were disappointing. We therefore asked ourselves why patients with this disease develop widely different clinical features. Collaborating with Drs. D. G. James and E. Neville of the Royal Northern Hospital, we showed that patients with sarcoidosis who have B8 are about 16 times as likely to develop arthritis.42 Also, there is an association with B8 in erythema nodosum alone, in erythema nodosum with arthritis, and in arthritis alone. Seemingly in sarcoidosis there is an inherited susceptibility to erythema nodosum and to arthritis, both having B8 as a genetic marker. We have not yet repeated the investigations using D and Ia typing. Nor do we know whether B8 is associated with erythema nodosum in other clinical situations.

Similarly, others have shown that B8 is associated with Sjögren’s syndrome, although not in the presence of rheumatoid disease. In this instance it has been established that there is an even closer association with Dw3.

Thanks to Peter Stastny we know that people with Dw4 are six times as likely to have seropositive rheumatoid arthritis (RA). And there is a comparable association with DRw4.24 In addition to the HLA association with RA, there is a debated association with fibrosing alveolitis. With Professor M. Turner-Warwick and Dr. A. Milford Ward we have now studied the \( \alpha_1 \)-antitrypsin phenotypes in this situation.24 MS and MZ were not increased in RA without chest disease, but MZ was increased in fibrosing alveolitis without rheumatic disease, and both MZ and MS were increased in fibrosing alveolitis with RA. Thus two distinct genetic systems appear to be involved in this syndrome: the major histocompatibility complex on the sixth chromosome—for RA and possibly for fibrosing alveolitis—and the Pi system, which controls the \( \alpha_1 \)-antitrypsin phenotypes and is on a different chromosome as yet undetermined. Interestingly, and possibly importantly, the Pi system is in genetic linkage with the Gm system and the constant region of the IgG heavy chain.

Acute anterior uveitis is associated clinically with ankylosing spondylitis, RS, reactive arthritis, ulcerative colitis, Crohn’s disease, psoriasis (all usually when accompanied by sacroilitis), and also sarcoidosis (not accompanied by sacroilitis). Thanks to Professor E. S. Perkins and his colleagues at Moorfields Eye Hospital, we were able to show that B27 is present in 42% of patients with acute anterior uveitis without rheumatic or other associated disease. Interestingly, B27 is almost invariably present in acute uveitis with spondylitis or RS but not with sarcoidosis, from which I would conclude that the acute uveitis with sarcoidosis is a different process although it looks the same.

We have recently established an association between the \( \alpha_1 \)-antitrypsin phenotype MZ and acute anterior uveitis.44 This association with MZ applies in the absence of rheumatic disease, and particularly in the absence of both rheumatic disease and B27. In classic ankylosing spondylitis without uveitis MZ is probably not increased, but it is definitely increased in spondylitis with uveitis. Thus
even in the presence of spondylitis, or ‘spondylitis susceptibility genes’, the phenotype MZ can further increase the risk of uveitis more than tenfold. So we now know that MZ predisposes to fibrosing alveolitis in rheumatoid arthritis and to uveitis in spondylitis—an unexpected combination providing two excellent examples of gene interaction. I would hesitate to suggest how these findings might influence the battle between the protagonists of immune response genes or molecular mimicry.

Now a different question: Does heredity influence the distribution of peripheral joints affected? RA, sarcoid arthritis, RS, and the peripheral arthritis associated with ankylosing spondylitis all have characteristic distributions of joints affected. To this extent, Dw4, DRw4, B8, and B27 could be said to influence the distribution of arthritis. What about psoriasis? Could the finger involvement in psoriatic arthritis be genetically determined? For a long time clinicians have known that patients with psoriasis may have relatives with seronegative finger arthritis resembling RA who do not themselves have psoriasis. In our patients who had both B27 and sacroiliitis finger arthritis was present in 10% of those with ankylosing spondylitis, RS, or chronic inflammatory bowel disease and in 65% of those with psoriasis. This finger arthritis was related to psoriasis but was not dependent on B27, sacroiliitis, B13, or Bw17. Next to psoriasis, could there be a gene influencing finger involvement? In which case, how does it relate to RA?

Rheumatic diseases are clinically most active at different ages. Consequently we must ask why it is that diseases associated with B27, such as spondylitis, uveitis, and RS, are particularly troublesome between the ages of 15 and 45. One obvious possible explanation is that this coincides with the age of greatest sexual activity. There is another explanation, however. In almost half our patients with B27 and acute uveitis the onset of disease was between the ages of 20 and 30, whereas in patients without B27 it was later. Danish figures show that in psoriasis with w17 or 13 the peak age of onset is between 10 and 20. In both diseases, as in myasthenia gravis, probably ankylosing spondylitis, and possibly RS, the onset is earlier when associated with HLA antigens.

In hospital clinics obvious classic ankylosing spondylitis is undoubtedly more common in men. But in the general population minor degrees of sacroiliitis and spondylitis, if looked for hard enough, are found almost equally in men and women. In other words, sex does not influence the incidence of disease so much as its expression and its severity.

There is, in fact, a whole spectrum of sex ratios from RS at 20:1, through spondylitis and uveitis, round to RA, and on to erythema nodosum, rubella arthritis, and SLE, which occur eight times as often in women. There are classical explanations for some of these sex ratios. In women the hormone balance is said to predispose to SLE. And in men the complicated genitourinary tract and the drainage of Batson’s veins lead to RS or ankylosing spondylitis. Both explanations may be true, but do they really satisfy?

What about an alternative—such as the H-Y antigen? In 1955 it was reported that in some strains of mice male skin grafts were rejected by females. This rejection related to sex was later demonstrated in other strains and other species. It was attributed to the histocompatibility antigen H-Y. Arguments continue about whether there is one antigen or a group of antigens, perhaps coded for by as many as four genetic loci, and whether its genes are on Y or X, on both, or on neither.

The effect of H-Y can be altered by major histocompatibility antigens. Ohno has suggested that the major antigens may act as carriers of H-Y, seemingly an ideal situation for modifying each other’s influence. In man H-Y is probably coded for by genes on the short arm of the Y chromosome.

There are three good reasons for being interested in H-Y. (1) It may be the mediator in embryo that determines the development of our gonads as male or female. (2) H-Y has been suggested as one explanation of the better survival of male to female kidney transplants. (3) H-Y, or something associated with it (and here I am going out on a limb of my own making), could explain why most rheumatic diseases occur predominantly in one or other sex. It might modify our susceptibility to many different diseases. As yet there is not a scrap of evidence that this is true, but if it were H-Y would be the most influential histocompatibility antigen of them all.

Thus one can imagine a man with spondylitis and uveitis being under the genetic influence of HLA, Pi, and H-Y on three different chromosomes. I believe that we are not witnessing a solo by one gene but a symphony of clinical features produced by an orchestra of genes and chromosomes—hence the title of my talk.

Conclusion
It is clear from the excellent deliberations of the past two days that our basic concepts of the rheumatic diseases are currently changing with breathtaking speed. With so many fresh ideas in the wind it is not an easy time for definitions. Also I am one of several at this meeting who are not sure whether the
term Reiter's disease any longer serves a useful purpose. Because the term has been used for so many years perhaps it should be retained for that variable and unpredictable group of clinical features that clearly follow soon after episodes of non-specific urethritis or dysentery—acknowledging that this definition is arbitrary, far from satisfactory, and subject to alteration at short notice. To change the meaning of the term to include patients whose clinical features bear no relation to urethritis or dysentery might turn confusion into chaos. At present, remembering the words of Samuel Butler, I would prefer not to construct a wall of words around any group of criteria.