MEDICAL GRAND ROUNDS

SOUTHWESTERN MEDICAL SCHOOL
DALLAS, TEXAS

Rheum.

ANKYLOSING SPONDYLITIS AND REITER'S SYNDROME

WHAT DOES IT MEAN TO BE B27-POSITIVE?
J.C. WOODROW(1)

HUGO E. JASIN, M.D.
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INTRODUCTION

The underlying pathogenic mechanisms involved in the association between the spondyloarthropathies and related disorders, and the HLA-B27 phenotype constitute one of the most tantalizing unanswered questions in medicine today. In this discussion, we will attempt to describe the clinical and pathophysiologic aspects of ankylosing spondilitis and Reiter's syndrome, the two diseases that play a central role within the group of inter-related spondyloarthropathies. As it ofter happens in many advancing areas of biomedical research, much of the newly acquired knowledge in this field is either controversial or presently unconfirmed. However, it is likely that the clues provided by accruing data may lead to valuable insights into the complex interplay between susceptibility genes and environmental factors. Given the status of our present knowledge, this discussion will leave unanswered many of the key questions dealing with the role of genetics and of infectious agents.

TABLE 1

HLA-B27 RELATED DISEASES

ANKYLOSING SPONDYLITIS
REITER'S SYNDROME
REACTIVE ARTHRITIS
PSORIATIC ARTHRITIS
ENTEROPATHIC ARTHROPATHIES
ULCERATIVE COLITIS
CROHN'S DISEASE
WHIPPLE'S DISEASE
JUVENILE CHRONIC ARTHRITIS
ACUTE ANTERIOR UVEITIS
?BEHCET'S SYNDROME

ANKYLOSING SPONDYLITIS

Ankylosing Spondylitis (AS) is a condition characterized by inflammatory involvement of the axial skeleton with a tendency to develop stiffening and fusion of the cartilaginous joints of the spine. Even the historical aspects of this disease are somewhat controversial. Ossification of ligaments and bony fusion of the spine have been described in egyptian skeletons dating back to 2900 BC. However, some experts believe that these lesions represent hypertrophic hyperostosis and not AS (2). In fact, it has been suggested that AS is only of recent appearance. The first well documented description seems to be that of Connor in 1693.

CLINICAL FEATURES (3,4)

Spine. A typical presentation of a patient with AS is that of a male in his late teens or early twenties complaining of low back stiffness and pain. These symptoms are often worse in the morning or after a prolonged resting period and are improved by exercise. The degree of severity of the initial manifestations may range from slight discomfort lasting only a few minutes in the morning to severe lumbar muscle spasm and inability to move the affected area.

TABLE 2

BACK PAIN IN ANKYLOSING SPONDYLITIS

AGE OF ONSET BELOW 40 YEARS
INSIDIOUS ONSET
DURATION GREATER THAN THREE MONTHS
ASSOCIATION WITH MORNING STIFFNESS
IMPROVEMENT WITH EXERCISE

From Calin, A.(4)

The decrease in lumbar spine motion early in the disease may be mainly caused by muscle spasm rather than joint ankylosis. Thus, it is not uncommon to observe dramatic improvement in mobility soon after initiation of treatment with anti-inflammatory agents. As the disease progresses, there is progressive fusion of the vertebrae with loss of lumbar lordosis and accentuation of the thoracic and cervical kyphosis. Involvement of the thoracic spine is associated with loss of normal thoracic expansion which often is reduced to less than 0.5 inch. In

severe cases, the end-stage of the disease is that of: "a cachectic man, imprisoned in a fetal position of flexion, walking with a shuffling gait, his eyes transfixed to the floor"(3). The disease follows a capricious course, some patients may go into complete remission after minimal or moderate involvement of the sacroilliac joints and lumbar spine, only to recurr in some cases many years later. Others experience exacerbations and remissions over a period of years or decades with relentless progression of the disease to complete spinal immobility.

Peripheral joints. A significant proportion of patients with AS may have involvement of peripheral joints at some time during the course of the disease (5-7). The hips and shoulders are most commonly affected, but most other large joints, and occasionally the small joints of hands and feet may also show inflammatory involvement. The incidence of peripheral arthritis in AS has been reported as ranging from 18 to 55% of cases with hip and shoulders excluded, and as high as 64% when hips and shoulders are included (8). Low back pain usually precedes peripheral joint involvement, but as many as 23% may show peripheral arthritis as the initial manifestation of the disease (9). Since the majority of these patients have polyarticular involvement these patients are often misdiagnosed as having seronegative rheumatoid arthritis or juvenile rheumatoid arthritis depending on the age of onset. Although the pattern of joint involvement may be indistinguishable from that of rheumatoid arthritis, the roentgenographic characteristics listed in table 3 may be helpful in establishing the right diagnosis.

TABLE 3

ROENTGENOGRAPHIC DIFFERENCES BETWEEN ANKYLOSING SPONDYLITIS AND RHEUMATOID ARTHRITIS

1) GREATER ASYMMETRY
2) LESS PERIARTICULAR OSTEOPOROSIS
3) SMALLER EROSIVE CHANGES
4) PROPENSITY TO BONY ANKYLOSIS
5) MARGINAL PERIOSTITIS

Eye Involvement. Acute non-granulomatous iritis develops in 25% of patients with AS at some time during the course of the disease (10,11). Over 10% of the patients may have a history of iritis prior to the development of clinical spondylitis. Thus, about half of a group

of patients with isolated acute anterior uveitis may show subclinical evidence of spondylitis (12) while of the remaining, 30% have no detectable spine disease but may be HLA-B27-positive (13).

TABLE 4

UVEITIS AND HLA-B27 PHENOTYPE

ASSOCIATED DISEASE	HLA B27+	HLA B27-
YES	18	3
NO	8	21

From Brewerton et al. (13)

Cardiovascular Disease. Aortic incompetence and conduction defects are well recognized complications of AS. These abnormalities may be of clinical importance in 3.5 to 5% of all patients with the disease (14). The prevalence of aortic or cardiac involvement increases up to 20% in patients with evidence of peripheral joint involvement and disease duration of over 30 years.

TABLE 5

AORTIC INSUFFICIENCY IN ANKYLOSING SPONDYLITIS

PATIENTS	NUMBER	NUMBER WITH AI
ANKYLOSING SPONDYLITIS	519	21
RHEUMATOID ARTHRITIS	508	3

From Graham and Smythe (14)

It is clear, however, that a significant proportion of patients may have subclinical involvement. Data from available autopsy series (15) show that as many as 20% of all patients may have anatomical evidence of aortic valve involvement. In a recent echocardiography study of 36 patients, 11 were found to have evidence of subaortic fibrous ridging or marked leaflet thickening. None of these patients had clinically evident aortic regurgitation (16).

Pulmonary Disease. Involvement of the costovertebral joints with eventual fusion results in a decrease of the normal chest expansion. Thus,

changes are usually associated with restricted ventilation and subsequent reduction in lung volume. In general, maximum ventilatory capacity and gas exchange are well preserved. However, hyperventilation and abnormal relation between ventilation and perfusion due to relative overexpansion of the lower and underexpansion of the upper portions of the lung have been reported in a number of patients (17).

Another well recognized pulmonary manifestation in patients with long-standing disease consists of a distinctive bilateral apical fibrocavitary disease that may be misdiagnosed as tuberculosis (18,19). Although most patients are usually asymptomatic, cavitary colonization with aspergillus and other opportunistic agents has been reported in isolated cases.

Neurologic Disease. One of the most common causes of death and disability in patients with AS is the occurrence of spinal fractures following relatively minor trauma. This is due to the fact that the spine becomes a rigid, bony bar lacking normal flexibility. Moreover, osteoporosis commonly develops in the involved vertebrae thus rendering the spine very vulnerable to fracture (20,21).

Cauda equina syndrome has been reported in a small group of patients with advanced AS (22). These patients complain of pain, paresthesia, or weakness localized to the buttocks and upper thighs, and of loss of sphincter control. Myelography reveals the presence of lumbo-sacral arachnoidal diverticulae probably developing as a consequence of chronic arachnoiditis. It is of interest that 40% of patients with AS may have elevated cerebrospinal fluid protein (23).

EPIDEMIOLOGY AND GENETICS

With the discovery of the close association between AS and HLA-B27 in 1973 (24,25) the controversy regarding the true prevalence of AS in populations has not been resolved. Prior to 1973 there was reasonable consensus as to two important points: 1) that the prevalence of AS in the general population ranged between 0.5 and 2.3 per 1000, and 2) that AS was found 20 to 50 times more often in first-degree relatives of AS patients attending hospitals.

Marked geographic and ethnic differences have now become apparent. As shown in Table 6, AS is quite rare in Orientals and African Blacks. In Black Americans the prevalence is somewhat higher (26) probably due to the admixture of caucasian genes in this heterogeneous population. In contrast to the low prevalence of AS in Blacks and Orientals, North American indians of several different tribes have shown a striking high prevalence approaching 10 percent among the Mille-lac band of Chippewas.

TABLE 6

PREVALENCE OF AS AND HLA-B27 BY RACIAL ETHNIC GROUP

	PREVALENCE OF AS (PER 1000)	FREQUENCY OF HLA-B27 %
CAUCASIANS		
USA, ENGLAND	0.9	8
HUNGARY	2.3	13
NORTH AMERICAN INDIANS		
HAIDA	60.0	50
PIMA	60.0	19
BELLA-COOLA	27.0	25
CHIPPEWA	93.0	23
AFRICAN BLACKS	0.4	0
ORIENTALS	0.1	1

From Hochberg, M.C. (56)

It is now clear that there is a close association between the prevalence of AS and the frequency of HLA-B27 in each ethnic group or population. The greater than 90 percent incidence of HLA-B27 in caucasians with AS indicating a relative risk of over 100 suggests that this histocompatibility gene may be a marker for disease severity. HLA-B27-negative patients with AS rarely have uveitis or cardiac involvement (24,27) and many tend to have less severe disease with isolated sacroiliitis as the only manifestation (28). It is also clear, however, that other genetic and environmental factors must play an important role in triggering clinical expression of disease. Of 15 pairs of monozygotic twins where the proband had AS, only 8 (53%) showed concordance for the disease. It may be argued that this is an underestimate since additional unaffected twins may yet develop the disease (30,31).

There is a marked sex effect on the severity of AS. The male:female ratio approaches 4-5:1 in most patients series and population surveys.

The ratio for bilateral sacroiliitis, however has been reported to approach unity in normals age 55 and above (29). Moreover, the incidence of HLA-B27 positivity in asymptomatic sacroiliitis is the same for both sexes.

TABLE 7

ANKYLOSING SPONDYLITIS IN MEN AND WOMEN

	MALES	FEMALES
HLA-B27	90%	90%
DELAY IN DIAGNOSIS	3 YEARS	10 YEARS
PROGRESS	+++	+
SEVERITY	+++	+
SPINAL ANKYLOSIS	++	+
OSTEITIS PUBIS	+	+++

Modified from Calin (4)

Another point that deserves emphasis is the striking increase in the frequency of AS in B27-positive relatives of probands with the disease compared to B27-positive controls (Table 8)

TABLE 8

PREVALENCE IN FIRST-DEGREE RELATIVES OF AS PROBANDS

YEAR	AS IN FIRST DEGREE RELATIVES (%)	AS IN THE POPULATION (%)	REFERENCES
1955	2.5	0.18	32
1961	4.6	0.08	33
1967	3.6	0.18	34

From Van der Linden et al. (35)

A significant problem in the evaluation of the role of HLA-B27 in disease expression has been the difficulty in establishing criteria with adequate sensitivity and specificity to detect early and mild cases of the disease and at the same time exclude conditions resembling AS. Most of the surveys reporting prevalences around 0.1 percent have used the New York criteria which has high specificity but low sensitivity.

TABLE 9

CLINICAL CRITERIA FOR ANKYLOSING SPONDYLITIS (NEW YORK, 1966)

A. DIAGNOSIS

LIMITATION OF MOTION OF THE LUMBAR SPINE IN ALL THREE PLANES-ANTERIOR FLEXION, LATERAL FLEXION, AND EXTENSION.

HISTORY OR THE PRESENCE OF PAIN AT THE DORSOLUMBAR JUNCTION OR IN THE LUMBAR SPINE.

LIMITATION OF CHEST EXPANSION TO 1 IN. (2.5 CM) OR LESS MEASURED AT THE LEVEL OF THE FOURTH INTERCOSTAL SPACE.

B. GRADING

DEFINITE AS

GRADE 3-4 BILATERAL SACROILIITIS WITH AT LEAST ONE CLINICAL CRITERION.

GRADE 3-4 UNILATERAL OR GRADE 2 BILATERAL SACROILIITIS WTH CLINICAL CRITERION 1 (LIMITATION OF BACK MOVEMENT IN ALL THREE PLANES), OR WITH BOTH CLINICAL CRITERIA 2 AND 3 (BACK PAIN AND LIMITATION OF CHEST EXPANSION).

PROBABLE AS

GRADE 3-4 BILATERAL SACROILIITIS WITH NO CLINICAL CRITERIA.

Assuming a prevalence of HLA-B27 of 8% among the caucasion population it may be calculated that about 1-1.5 percent of HLA-B27 positive individuals may be affected with AS.

Recently, two studies of normal HLA-B27 individuals (36,37) revealed a prevalence of definite ankylosing spondylitis of 18 and 13 percent among 78 and 24 persons respectively. In one of the studies (36) the male: female ratio was almost 1(20:17). The large differences in prevalence between these studies and previous population surveys have been ascribed to overreading of roentgenographic sacroiliitis, since the authors observed a remarkably high prevalence of 3 to 6 percent of sacroiliitis in B27-negative normal individuals.

The significant enrichment in B27-positive affected first-degree relatives of AS probands and the low prevalence in the B27-positive population at large suggest several possibilities for the role of this gene in disease expression:

1) HLA-B27 may be polymorphic and only one or few subtypes may be associated with AS.

2) HLA-B27 is not the major gene for AS but is a closely linked locus.

3) HLA-B27 is a major gene for AS but other genetic factors are in operation.

1) HLA-B27 is polymorphic. HLA-B27 polymorphism has been found by the use of monoclonal antibodies (38) and by cytotoxic T-cell lines able to detect minor differences in the gene product (39,40). These studies have separated two major subtypes in caucasians and a third in orientals. Thus far, monoclonal antibodies and cytotoxic cell lines have been unable to discriminate between B27-positive normal caucasians and B27-positive patients with AS. The data available is still too meager to answer this question in Oriental populations. Thus, these studies have disclosed fine differences between HLA-B27 genes. It is possible that more refined studies at the DNA level may reveal other subtypes associated with disease susceptibility.

2) The major gene for AS is closely linked to HLA-B27. The familiar segregation and high prevalence of AS in B27-positive relatives of probands and the low incidence of disease in the B27-positive population suggest the possibility of an AS gene closely linked to the B locus. This hypothesis is considered unlikely in view of the data showing that the association with B27 is world-wide and true for diverse ethnic groups. An extremely marked degree of linkage disquilibrium maintained over a considerable period of time would have to be postulated. Moreover, an additional hypothesis may be

needed of a peculiar genetic mechanism which is suppressing recombination between the B locus and the hypothesized locus for the AS gene.

3) Other genetic factors may be in operation. If B27 heterogeneity turns out not to be relevant to susceptibility to AS, it follows that other genes interacting with B27 may have to be postulated to explain the genetic data. There is no information regarding genes outside the major histocompatibility locus playing a role in AS. With regard to genes within the MHC, it has been reported that in B27 negative AS patients, psoriasis-associated haplotypes involving CW6 may be seen more frequently in these patients.

In summary, the information available does not allow us to choose between the two most plausible hypothesis: the possibility of yet undiscovered HLA-B27 subtypes; or the requirement for additional genes presumably acting in concert with HLA-B27 and with environmental factors.

REITER'S SYNDROME

Many investigators believe that Reiter's syndrome may provide the clues to unravel the pathogenesis of the B27-related spondyloarthropathies because in its epidemic form, it follows a bout of diarrheal disease involving a well defined etiologic agent. Moreover, several different organisms have been implicated as etiologic factors (Table 10), suggesting that there may be one or more characteristics in common to the infectious agents capable of inducing the disease.

TABLE 10

INFECTIOUS AGENTS IN REITER'S SYNDROME

DIARRHEAL DISEASE
SHIGELLA FLEXNERI
SALMONELLAE
YERSINIA ENTEROCOLITICA
CAMPYLOBACTER FETUS
NONSPECIFIC URETHRITIS
CHLAMYDIA
UREAPLASMA UREALYTICUM?

CLINICAL FEATURES

Reiter's syndrome is defined by the classic triad of arthritis, conjunctivitis and urethritis. This set of criteria may be too unsensitive because in a relatively large proportion of cases, transient conjunctivitis may not be detected by the patient or the physician. Thus, the disease may be diagnosed with over 98% specificity (41) in patients with arthritis lasting for at least 1 month following an episode of urethritis, cervicitis or diarrhea.

TABLE 11

CLINICAL FEATURES OF REITER'S SYNDROME

ARTHRITIS
URETHRITIS, CYSTITIS, CERVICITIS
CONJUNCTIVITIS, UVEITIS
BALANITIS
ORAL ULCERATION
KERATODERMIA BLENNORRHAGICA

The prevalence and incidence of the disease is unknown but it has been assumed to be less than 1 per 1000. However, it may be much more frequent among sexually active young males. Reiter's syndrome was the leading cause of hospitalization for arthritis among men aged 15-35 in a U.S. Air Force hospital (42). There is a striking male preponderance of 10 or 20:1 particularly in the postvenereal form of the disease.

TABLE 12

INITIAL CLINICAL FEATURES

FEATURE	FREQUENCY %
POLYARTHRITIS	96
MONOARTHRITIS	4
URETHRITIS	90
EYE DISEASE	63
BACK PAIN	72
HEEL PAIN	56
TENDINITIS	52
ORAL ULCERS	27
BALANITIS	46
KERATODERMIA	22

Modified from Calin (43)

Arthritis. As a rule, the patient presents to the physician with a chief conplaint of arthritis involving more than one joint. The distribution of affected joints may be a valuable element to arrive at the diagnosis. Weight-bearing joints, knees, ankles and feet are involved most frequently. The pattern of involvement differs significantly from that of rheumatoid arthritis in that in Reiter's syndrome it tends to be more asymmetrical. The affected joints appear diffusely inflammed, very painful, and they frequently collect large effusions. "Sausage" fingers or toes with involvement of proximal and distal interphalangeal joints and diffuse dactilitis are common.

Entesopathy (44). Entesopathy or entesitis is a common feature of B27-related arthropathies. These terms are used to mean involvement or inflammation at the sites of tendinous insertions into bone. Both in Reiter's syndrome and AS, the area of insertion may show bony erosions and evidence of reactive new bone formation or "whiskering". In Reiter's syndrome, Achiles tendinitis, heel pain with or without calcaneal spurs, and periostitis of phalanges in association with dactilitis are commonly observed.

Spinal Involvement. Backpain is a frequent symptom in acute Reiter's syndrome. Radiological evidence of sacroiliitis may be present in as many as 10-50 percent of patients with severe or protracted disease. In these patients the pattern of involvement is frequently unilateral. In a smaller group of patients, the disease may involve the lumbar and thoracic spine as in AS. There are some differences, however, in the pattern of roentgenologic appearance that may suggest the association with previous Reiter's syndrome. (Table 13)

TABLE 13

SPINAL INVOLVEMENT IN REITER'S SYNDROME

UNILATERAL SACROILIITIS
ASYMMETRICAL SYNDESMOPHYTES
NON-MARGINAL SYNDESMOPHYTES
BONY BRIDGING

Since both AS and Reiter's syndrome have a high frequency of HLA-B27 positive affected individuals, it is not known if this represents a cause-effect association or just a common genetic background in a highly selected population.

Urogenital Disease. Urethritis preceding or concomitant with the development of arthritis may be a prominent symptom or it may be so subtle that it may not be noticed by the patient. On occasion, only persistent questioning regarding unusual staining of the patient's underwear may be the only evidence. Prostatitis is said to be present in 80 percent of the patients. Acute hemorrhagic cystitis has been reported in some patients.

It is of interest that a proportion of patients with post-diarrheal disease have concomitant urethritis suggesting that infectious agents may only trigger the disease, and that the subsequent development of mucosal inflammation has a different pathogenesis. However, Chlamydia trachomatis has been isolated in about half the patients with non-specific urethritis preceding the development of Reiter's Syndrome (45). In parallel with the multi-infectious etiology of the diarrheal form of the disease, it is likely that Chlamydia is one of several agents capable of triggering Reiter's syndrome.

Eye Disease. Conjunctivitis in Reiter's syndrome may be transient and present early in the disease, or it may not be detectable in a signifi-

cant proportion of patients. In patients with recurrent or persistent disease, acute non-granulomatous uveitis can be a serious problem leading to legal blindness in some patients (46).

Mucocutaneous Lesions. Oral ulcers have been reported in up to one third of the patients with Reiter's syndrome. These are characteristically painless superficial erosions involving the palatal mucosa. They may be transient and, as a rule, they are not noticed by the patients.

Similar considerations apply to the distinctive circinate balanitis which is frequently discovered during attending rounds in hospitalized patients.

Keratodermia blennorrhagica occurs most frequently on the soles of the feet, palms and shaft of the penis. The degree of involvment may vary from one or two patches to total body keratodermia which may result in exfoliation or even death (47). Both gross and microscopic appearances of the lesions cannot be distinguished from those of psoriasis.

Cardiovascular Disease. Electrocardiographic abnormalities occur in 5-10 percent of patients. These include P-R interval prolongation, complete hear block, non specific ST segment changes and abnormal Q waves (48). Aortic regurgitation, a late complication of Reiter's syndrome, is clinically and histologically similar to that seen in AS (49).

TABLE 14

CARDIOVASCULAR MANIFESTATIONS IN REITER'S SYNDROME

PROLONGED P-R INTERVAL
COMPLETE HEART BLOCK
NON-SPECIFIC ST SEGMENT CHANGES
ABNORMAL Q WAVES
AORTIC REGURGITATION

COURSE AND PROGNOSIS

Long term follow-up studies (50,51) have shown that contrary to previous belief, the majority of patients with Reiter's syndrome will continue to have active disease for many years after the initial attack.

TABLE 15

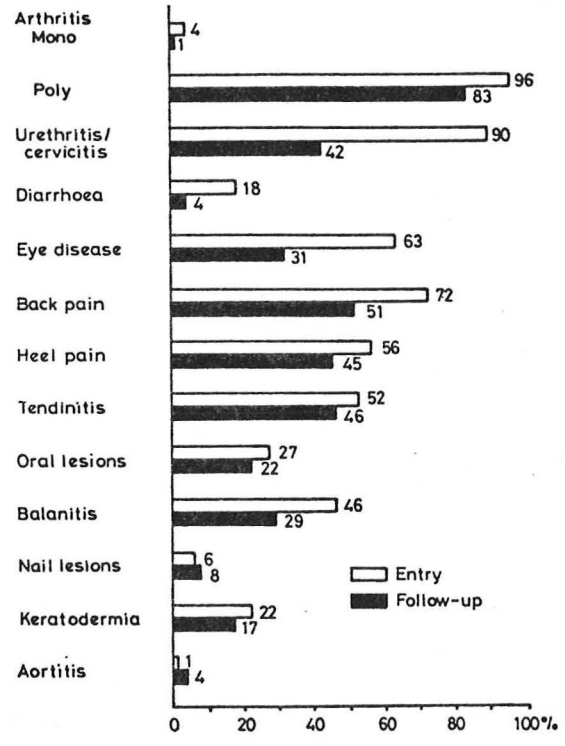
FOLLOW-UP DATA ON 104 CASES WITH REITER'S SYNDROME

	NO	%
NO SYMPTOMS	17	16
ANNOYING SYMPTOMS	23	22
INTERFERENCE WITH JOB	36	35
FORCED TO CHANGE JOBS	16	15
UNEMPLOYABLE	12	12

From Calin et al (50)

In general, the recurrent attacks tend to be milder than the initial bout. However, both articular and extraarticular manifestations persist or recurr over a period of many years (Figure 1).

Figure 1
REITER'S SYNDROME. SIX-YEAR FOLLOW-UP



From Calin et al (50).

In a 20 year follow-up of 100 patients from a total of 344 studied following an epidemic of dysentery (52,53), only 20 percent had become asymptomatic and 42 percent had some degree of permanent disability.

TABLE 16

TWENTY-YEAR FOLLOW-UP STUDY IN EPIDEMIC REITER'S SYNDROME

	FREQUENCY %
ANKYLOSING SPONDYLITIS	32
CHRONIC ARTHRITIS	18
IRITIS	7
PERMANENT DISABILITY	42

From Sairanen et al (53)

Reactive arthritis (54). This term was introduced by Aho et al. in 1973 to describe "an acute non-purulent arthritis which occassionally follows bacterial infections of the intestinal and urinary tract". After excluding entities such as the arthritis of intestinal by-pass surgery and viral arthritis, this disease probably overlaps or is identical with what has been called incomplete Reiter's Syndrome. These patients develop arthritis one to three weeks following an episode of infectious diarrhea or urethritis. Although these patients only infrequently have the complete Reiter's triad, they share the same genetic background in that 60 to 80 percent are HLA-B27 positive (54).

TABLE 17

EXTRAARTICULAR LESIONS IN REACTIVE ARTHRITIS

	POST DIARRHEAL	SEXUALLY ACQUIRED
	%	
DIARRHEA	100	0.2
ORAL ULCERS	2.4	9.8
CIRCINATE BALANITIS	23.7	23.2
KERATODERMIA BLENNORRHAGICA	-	11.6
CONJUNCTIVITIS-IRITIS	88.4	39.1

Modified from Keat (55)

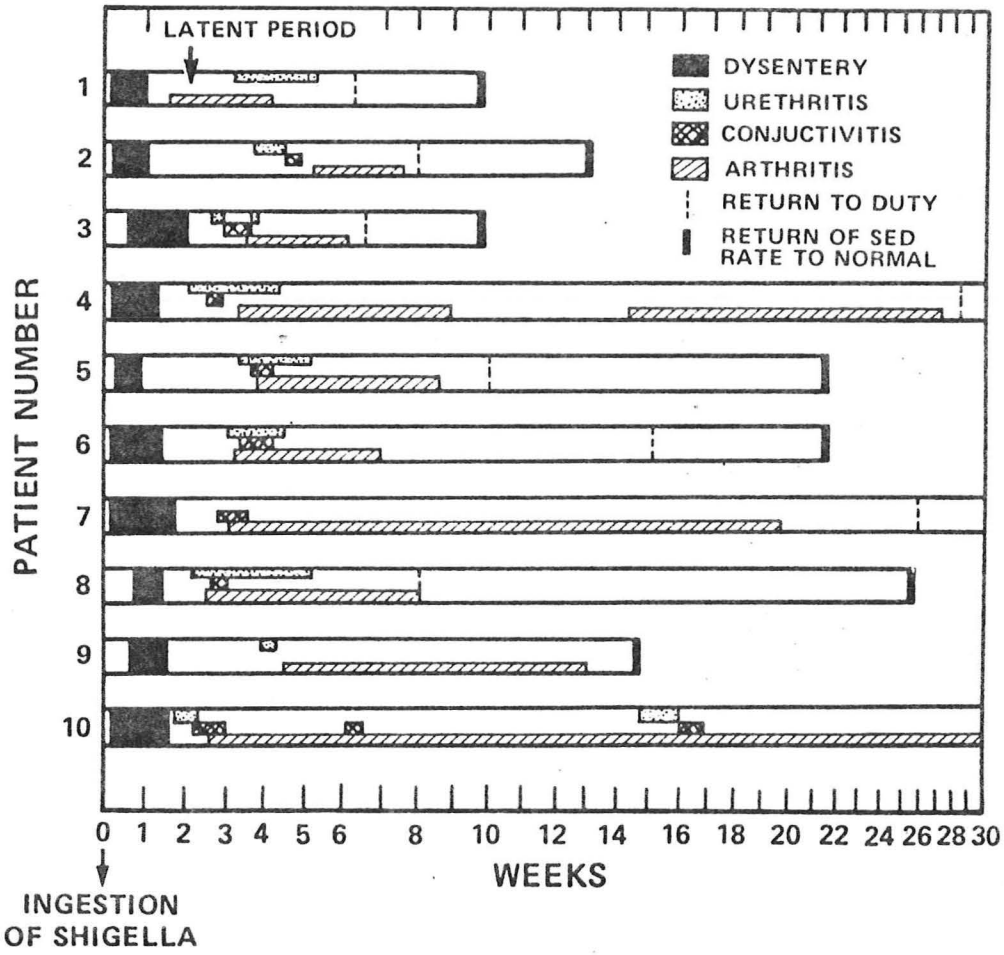
GENETICS

Both Reiter's syndrome and AS share common genetic factors. Several studies indicate that about 80 percent of caucasian patients with Reiter's syndrome are HLA-B27. This association is weaker for black patients where the incidence is only 50-60 percent (56). Familiar aggregation has also been demonstrated for Reiter's syndrome (57,58). In one survey (29,59), family members of probands affected with Reiter's syndrome, higher than control incidence of AS and bilateral sacroiliitis were reported suggesting a common genetic background for both diseases.

The influence of the HLA-B27 phenotype in determining susceptibility to the disease is illustrated in a study dealing with an epidemic of diarrhea in a controlled environment (60). In June of 1962, an American naval vessel, the USS Little Rock, was visiting a port in North Africa known to be endemic for shigellosis. A picnic was prepared in celebration of the ship's anniversary. In spite of elaborate sanitary precautions, two cooks contracted dysentery ashore. These two men took great pain to conceal their condition because they were afraid to miss shore-leave at the conclusion of the picnic. Consequently, their work in the kitchen was interrupted by hurried trips to the toilet. They did not take time for handwashing to make their repeated absences less conspicous. After the ship had sailed, 602 cases of Shigella dysentery out of a crew of 1276 reported to sick bay. From 1 to 5 weeks following the epidemic of diarrhea, ten patients were afflicted with Reiter's syndrome. A follow-up study performed 13 years later (46) provided valuable insight into the natural history and epidemiology of the disease.

Figure 2

CHRONOLOGY OF TEN PATIENTS WITH EPIDEMIC REITER'S SYNDROME



From Noer (60).

Five of the original 10 patients were traced, HL-A typed, and clinically assessed. One of the 5 had minimal disease, remained symptom-free, and was HLA-B27-negative. The remaining 4 have followed a chronic course, had persistent active disease, and were HLA-B27-positive. Two patients had active uveitis, and one of them had been declared legally blind.

TABLE 18

THIRTEEN YEAR FOLLOW-UP OF POSTDYSENTERIC REITER'S SYNDROME

PATIENT	YEAR	ARTHRITIS	URETHRITIS	EYES	SPINE	B27
1	1962	+	+	-	-	
	1975	(+)	(+)	(+)	-	-
4	1962	+++	+	+		
	1975	+++	++	++	++	+
6	1962	+	+	+	-	
	1975	++	++	+++	-	+
7	1962	+++	-	+	-	
	1975	++	++	++++	+	+
10	1962	+++	+	+	-	
	1975	++	++	+	+	+

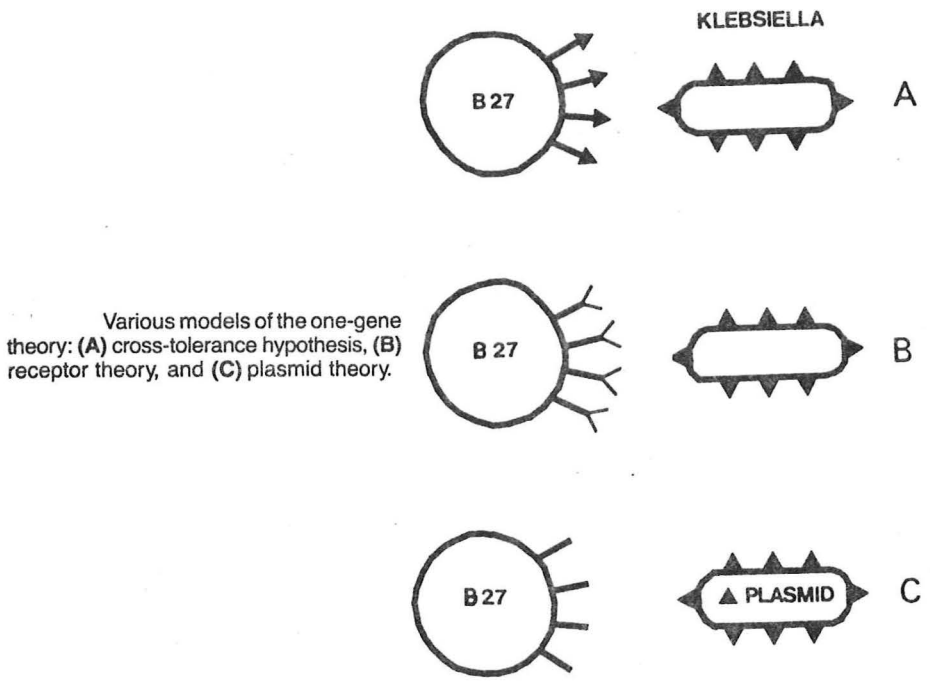
From Calin and Fries (46)

If the assumption is made that 6-8 percent of the 602 crew members affected with dysentery were HLA-B27-positive, then it follows that from one sixth to one third of the persons who were HLA-B27-positive developed Reiter's syndrome. This and the previously mentioned Finnish study (53) suggest that the prognosis for post dysenteric Reiter's syndrome must be guarded, especially in subjects who are B27-positive.

PATHOGENESIS

We have previously discussed several alternative hypothesis that may explain the close association of HLA-B27 phenotype with the seronegative spondyloarthropathies. The data at hand appear to favor the possibility that the HLA-B27 gene product itself may be directly involved as a pathogenic factor. In this section, we will attempt to discuss some of the theories that may explain the relationship between the genetic factors and the infectious events that frequently precede the onset of these diseases. A word of warning is necessary at this point. Much of the information on which these theories are based has not been easy to reproduce outside the original laboratories. However, we consider that the main hypothesis are still viable since the investigators that were unable to reproduce the results have not postulated alternative theories amenable to empirical acertainment. The three main surviving hypothesis are depicted in figure 3 (61). We will discuss briefly the cross-tolerance (cross-reactive or molecular mimicry) hypothesis and the plasmid theory which is an extension of the receptor theory postulated previously by the same group of Australian investigators.

Figure 3
PATHOGENESIS OF B27-RELATED SPONDYLOARTHROPATHIES



Various models of the one-gene theory: **(A)** cross-tolerance hypothesis, **(B)** receptor theory, and **(C)** plasmid theory.

From Ebringer et al. (61).

The cross-tolerance hypothesis. This theory was first proposed by Ebringer in the contest of AS (62). The following assumptions are made:

1) The HLA-B27 gene product is directly involved in the pathogenesis of the disease.
2) There are bacterial antigens that are structuraly similar to the HLA-B27 gene product.
3) The susceptible hosts are capable of mounting immune responses to these bacterial antigens that cross-react with the membrane-bound autoantigens.
4) Inflammation in the spondyloarthropathies is therefore the direct result of an autoimmune response.

What are the "facts" behind this construct?

1) Rabbit heteroantisera and monoclonal anti-HLA-B27 antibodies cross-react with strains of Shigella, Klebsiella, and Yersinia (63,64).
2) Conversely, Klebsiella antisera react more strongly with lymphocytes from spondylitic or health B27-positive individuals than it does with B27-negative cells (63).
3) Klebsiella species can be recovered from feces in a greater proportion of patients with active ankylosing spondylitis (65) and/or active uveitis (66).
4) Higher titers of anti-Klebsiella IgA antibodies are present in patients with active disease (67).

Support for the role of intestinal infection in B27-related diseases was recently reported by an independent group. Ileocolonoscopy and biopsy were performed in 12 patients with AS or reactive arthritis and 5 B27-negative patients with juvenile rheumatoid arthritis. All 12 B27-positive patients showed microscopic evidence of bowel inflammation and in 7 of 12, naked-eye inspection revealed evidence of ileal inflammation (68). These investigators went on to treat 15 patients with B27-related disease with sufasalazine. After a period of 12 months of treatment, 11 patients had undergone long-lasting remissions and in the remaining 4, significant improvement of the clinical and biological variables was observed (69).

TABLE 19

CLINICAL FINDINGS AND RESULTS OF GASTROINTESTINAL INVESTIGATIONS

Sex, age	Axial involvement	Gastrointestinal manifestations (and outcome of routine GI investigations)	Ileocoloscopy	
			Macro	Micro
B27-positive PAS				
M, 14	+	+ (+)	+	+
F, 16	−	+ (−)	−	+
M, 12	+	− (−)	−	+
M, 16	−	− (−)	+	+
F, 24	−	− (−)	−	+
F, 18	−	− (−)	−	+
M, 34	−	− (−)	+	+
M, 18	−	− (ND)	+	+
M, 50	+	+ (ND)	+	+
M, 25	−	− (−)	+	+
M, 24	−	+ (−)	−	+
F, 58	−	− (ND)	+	+
B27-negative JCA or RA				
M, 28	−	− (−)	−	−
F, 38	−	+ (−)	−	−
M, 26	−	− (ND)	−	−
F, 44	−	− (ND)	−	−
M, 42	−	− (−)	−	−
B27 -positive poly-RA				
M, 51	−	− (ND)	−	−
B27-positive AS				
M, 42	+	− (−)	−	−

PAS = pauciarticular asymmetrical synovitis; Poly = polyarticular; RA = rheumatoid arthritis; JCA = juvenile chronic arthritis; AS = ankylosing spondylitis.

From Mielants and Veys (68)

The plasmid theory. A group of investigators headed by A.F. Geczy have published a series of papers dealing with the relationship between gram-negative enteric bacteria, particularly Klebsiella, and B27-positive lymphocytes obtained from patients with AS.

The initial report presented evidence showing that rabbit antisera against certain strains of Klebsiella were cytotoxic for 85 percent of B27-positive but not B27-negative lymphocytes from AS patients. Moreover, the same antisera kill B27-positive lymphocytes from normal donors but only after they have been "modified" by incubation in medium from cultures of the same bacteria (70,71). The antigen has been detected in a small number of Klebsiella strains, and in Salmonella, Shigella, Escherichia Coli, Staphylococcus, Streptococcus and Clostridia (72,73). These workers report that bacteria isolated from stool cultures of patients with AS appear to carry the antigen whereas only one B27-negative control out of 35 tested was positive (73). Even more startling was the finding that lymphocytes from AS patients, immortalized by Epstein-Barr virus infection, express the factor after many generations in the absence of bacteria (74) and can be shown to release the modifying factor as the original Klebsiella strain (75). These results suggest phenomena with implications unprecedented in cell biology. They suggest that a plasmid present in prokaryotic cells can transfer genetic information to mammalian cells. It should be emphasized that several independent groups have not been able to reproduce many of the observations described above even when the original antisera and cells provided by Geczy were used (76).

Finally, a recent letter to the Lancet from a well respected group of investigators appears to lend some credence to the findings reported by Geczy et al. (71). Blood specimens were collected from 26 Dutch AS patients and 19 health controls and shipped under code to Sidney.

TABLE 20

RESULTS ON 28 HLA-B27-POSITIVE CELLS TESTED BLIND IN AUSTRALIA

AS	NUMBER	GECZY FACTOR		
		PRESENT	EQUIVOCAL	ABSENT
YES	16	9	3	4
NO	12	1	0	11

From Van Rood et al. (77).

The results show that Geczy could reproduce his findings in a blind test. The Klebsiella antisera allowed for a correct identification of B27-positive patients and controls in 23 out of 28 instances.

At the onset of this presentation we predicted that we would raise more questions than provide answers. However, as it frequently happens in most scientific endevours, it is likely that this controversial state of affairs may presage the emergence of an important breakthrough on the complex interplay between disease-associated genes and environmental factors. I do hope that in a forthcoming grand-rounds I may be able to provide the answers.

REFERENCES

1. Woodrow, J.C. Genetic Analysis of ankylosing spondylitis. In "The Spondyloarthropathies", M. Ziff and S.B. Cohen, eds. Advances in Inflammation Research 9:75, 1985.

2. Bywaters, E.G.L. Historical perspectives in the etiology of ankylosing spondylitis. Brit. J. Rheumatol. 22(suppl)4, 1983.

3. Bluestone, R. Ankylosing Spondylitis. In "Arthritis and Allied Conditions" D.J. McCarty, ed. 10th edition p.819, 1985.

4. Calin, A. Ankylosing Spondylitis. Clinics in Rheumatic Diseases 11,41, 1985.

5. Cruickshank, B. Pathology of ankylosing spondylitis. Clin. Orthop. 74,43, 1971.

6. Resnick, D. Patterns of peripheral joint disease in ankylosing spondylitis. Radiology 110, 523, 1974.

7. Ginsburg, W.W. and Cohen M.D. Mayo Clin Proc. 58, 593, 1983.

8. Engleman, E.G. and Engleman, E.P. Ankylosing spondylitis: recent advances in diagnosis and treatment. Med. Clin. North Am. 61,347, 1977.

9. Polley, H.F., and Slocumb, C.H. Rheumatoid spondylitis: a study of 1035 cases. Ann. Int. Med. 26,240, 1947.

10. Blumberg, B., and Ragan, C. The natural history of rheumatoid spondylitis. Medicine 35, 1, 1956.

11. Hart, F.D. The stiff acking back. The differential diagnosis of ankylosing spondylitis. Lancet. I, 740, 1968.

12. Russell, A.S., Lentle, B.C., Percy, J.S., et al. Scintigraphy of sacroiliac joints in acute anterior uveitis. A study of thirty patients. Ann. Int. Med. 85,606, 1976.

13. Brewerton, D.A., Caffrey, M., Nicholls, A., et al. Acute anterior uveitis and HL-A27. Lancet, II, 994, 1973.

14. Graham, D.C. and Smythe, H.A. The carditis and aortitis of ankylosing spondylitis. Bull Rheum. Dis. 9, 171, 1958.

15. Bulkley, B.H., and Roberts, W.C. Ankylosing spondylitis and aortic regurgitation. Description of the characteristic cardiovascular lesion from study of eight necropsy patients. Circulation 18, 1014, 1973.

16. LaBresh, K.A., Lally, E.V., Sharma, S.C., et al. Two dimensional echocardiographic detection of preclinical aortic root abnormalities in rheumatoid variant diseases. Am. J. Med. 78, 908, 1985.

17. Renzetti, A.D., Nicholas, W., Dutton, R.E., et al. Some effects of ankylosing spondylitis on pulmonary gas exchange. New Engl. J. Med. 262, 215, 1960.

18. Hamilton, K.A. Pulmonary disease manifestations of ankylosing spondylitis. Ann. Int. Med. 31,216, 1949.

19. Applerouth, D., and Gottlieb, N.L. Pulmonary manifestations of ankylosing spondylitis. J. Rheumatol. 2,446, 1975.

20. Murray, G.C., and Persellin, R.H. Cervical fracture complicating ankylosing spondylitis. A report of eight cases and review of the literature. Am. J. Med. 70, 1033, 1981.

21. Hunter, T., and Dubo, H.I.C. Spinal fractures complicating ankylosing spondylitis. Arthritis Rheum. 26, 751, 1983.

22. Russell, M.L., Gordon, D.A., Ogryzlo, M.A., et al. The cauda equina syndrome of ankylosing spondylitis. Ann. Int. Med. 78,551, 1973.

23. Boland, E.W., Headley, N.E., and Hench, D.S. The cerebrospinal fluid in rheumatoid spondylitis. Ann. Rheum. Dis. 7, 195, 1948.

24. Brewerton, D.A., Caffrey, M., Hart, F.D. et al. Ankylosing spondylitis and HL-A27. Lancet I, 904, 1973.

25. Schlosstein, L., Terasaki, P.I., Bluestone, R., et al. High association of an HL-A antigen, W27, with ankylosing spondylitis. N. Engl. J. Med. 288,704, 1973.

26. Baum, J., and Ziff, M. The rarity of ankylosing spondylitis in the Black race. Arthritis Rheum. 14, 12, 1971.

27. Khan, M.A., Kushner, I., and Braun, W.F. Genetic heterogeneity in primary ankylosing spondylitis. J. Rheumatol. 7, 383, 1980.

28. Mohler, E., and Olhagen, B. Studies on the major histocompatibility system in patients with ankylosing spondylitis. Tissue Antigens 6, 237, 1975.

29. Lawrence, J.S. Rheumatism in Populations. London. Heinemann Medical Books 282, 1977.

30. Eastmond, C.J., and Woodrow, J.C. Discordance for ankylosing spondylitis in monozygotic twins. Ann. Rheum. Dis. 36, 360, 1977.

31. Hochberg, M.C., Bias, W.B., and Arnett, F.C. Family studies in HLA-B27 associated arthritis. Medicine 57, 463, 1978.

32. Stecher R.M., and Hersch, A.H. Familiar occurence of ankylosing spondylitis. Br. J. Physiol. Med. 18, 176, 1955.

33. DeBlécourt, J.J., Polman, A., and DeBlécourt, T. Hereditary factors in rheumatoid arthritis and ankylosing spondylitis. Ann. Rheum. Dis. 20, 215, 1961

34. Emery, A.E.H., and Lawrence, J.S. Genetics of ankylosing spondylitis. J. Med. Genet. 4, 239, 1967.

35. Van der Linden, S.M., Valkenburg, H.A., and Cats A. Risk of development of ankylosing spondylitis in HLA-B27-positive individuals. Consensus, conflicts and questions. In "The Spondyloarthropathies" Ziff M., and S.B. Cohen, eds. Advances in Inflammation Research 9, 83, 1985.

36. Calin, A., and Fries, J.F. The striking prevalence of ankylosing spondylitis in health W27 positive males and females. A controlled study. New Engl. J. Med. 293, 835, 1975.

37. Cohen, L.M., Mittal, K.K., Schmid, F.R., et al. Increased risk for spondylitis stigmata in apparently healthy HLA W27 men. Ann. Int. Med. 84, 1, 1976.

38. Grumet, F.C., Fendly, B.M., and Engleman, E.G. Monoclonal anti-HLA-B27 antibody (B27M1): production and lack of detectable typing differences between patients with ankylosing spondylitis, Reiter's syndrome and normal controls. Lancet II, 174, 1981.

39. Breuning, M.H., Spits, H., deVries, J.E. et al. A cloned cytotoxic T lymphocyte (CTL) line recognizing a subtype of HLA-B27. Human Immunol. 9, 231, 1984.

40. Miyachi Y., Wee, S.L., Chen L.K., et al. A cytolytic T lymphocyte clone differentially recognizing HLA-B27 subtypes. Human Immunol. 10, 237, 1984.

41. Willkens, R.F., Arnett, F.C., Bitter, T., et al. Reiter's syndrome: Evaluation of preliminary criteria for definite disease. Arthritis Rheum. 24, 844, 1981.

42. Arnett, F.C., McCluskey, O.E., Schacter, B.Z., et al. Incomplete Reiter's syndrome: discriminating features and HL-A W27 in diagnosis. Ann. Int. Med. 84, 8, 1976.

43. Calin, A. Reiter's syndrome in "Spondylarthropathies" A. Calin, ed. p.119, 1984.

44. Ball, J. Entesopathy of rheumatoid and ankylosing spondylitis. Ann Rheum. Dis. 30,213, 1971.

45. Markin, D.H., Pollock, S., Kon, C.C., et al. Chlamydia trachomatis infections in men with Reiter's syndrome. Ann. Int. Med. 100, 207, 1984.

46. Calin, A., and Fries, J.F. An "experimental" epidemic of Reiter's syndrome revisited. Ann. Int. Med. 84, 564, 1976.

47. Carr, J.L., and Friedman M. Keratodermia blennorrhagicum, report of a case with autopsy. Ann. J. Path. 20, 709, 1944.

48. Csonka, G.W., and Oates, J.K. Pericarditis and electrocardiographic changes in Reiter's syndrome. Br. Med. J. 1, 866, 1957.

49. Bulkley, B.H. and Roberts, W.C. Ankylosing spondylitis and aortic regurgitation. Description of the characteristic cardiovascular lesion from study of eight necropsy patients. Circulation 18, 1014, 1973.

50. Calin, A., Fox, R., Gerber, R.C., et al. Prognosis and natural history of Reiter's syndrome. Ann. Rheum. Dis 38 (supp) 29, 1979.

51. Csonka, G.W. Recurrent attacks in Reiter's disease. Arthritis Rheum. 3, 164, 1960.

52. Paronen, I. Reiter's disease: a study of 344 cases observed in Finland. Acta Med. Scand. 131, (supp) 1, 1948.

53. Sairanen, E., Paronen, I., and Mahonen, H. Reiter's syndrome: a follow-up study. Acta Med. Scand. 185, 57, 1969.

54. Aho, K., Ahvonen, P., Lassus, A., et al. HL-A antigen 27 and reactive arthritis. Lancet II, 157, 1973.

55. Keat, A. Reiter's syndrome and reactive arthritis in perspective. New Engl. J. Med. 309, 1606, 1983.

56. Hochberg, M.C. Epidemiology in "Spondylarthropathies" A. Calin, ed. p.34, 1984.

57. Kousa, M., Lassus, A., Karnoven, J. et al. Family study of Reiter's disease and HLA-B27 distribution. J. Rheumatol. 4, 95, 1977.

58. Yunus, M., Calabro, J.J., Miller, K.A., et al. Family studies with HLA typing in Reiter's syndrome. Am. J. Med. 70, 1210, 1981.

59. Lawrence, J.S. Family study of Reiter's disease. Br. J. Vener. Dis. 50, 140, 1974.

60. Noer, H.R. An "experimental" epidemic of Reiter's syndrome. J.A.M.A. 197, 117, 1966.

61. Ebringer, A. Ankylosing spondylitis, immune response genes and molecular mimicry. Lancet I, 1186, 1979.

62. Ebringer, A., Baines, M., Childerstone, M., et al. Etiopathogenesis of ankylosing spondylitis and the cross tolerance hypothesis. In "The spondyloarthropathies" M. Ziff and S. Cohen, eds. Advances in Inflammation Research 9, 101, 1985.

63. Welsh, J., Avakian, H. Cowling, P., et al. Ankylosing spondylitis, HLA-B27 and Klebsiella. Crossreactivity studies with rabbit antisera. Br. J. Exp. Path. 61, 85, 1980.

64. Van Bohemen, C.G., Grumet, F.C., and Zanen, H.C. Identification of HLA-B27 M1 and M2 cross-reactive antigens in Klebsiella, Shigella and Yersinia. Immunology 52, 607, 1984.

65. Ebringer, R.W., Cawdell, D.R., Cowling, P. et al. Sequential studies in ankylosing spondylitis: Association of Klebsiella pneumonia with active disease. Ann. Rheum. Dis. 37, 146, 1978.

66. Ebringer, R., Cawdell, D.R., and Ebringer, A. Association of Klebsiella pneumonia with acute anterior uveitis in ankylosing spondylitis. Br. Med. J. 1, 383, 1979.

67. Trull, A., Ebringer, R., Panayi, G.S., et al. IgA antibodies to Klebsiella pneumonia in ankylosing spondylitis. Scand. J. Rheumatol. 12, 249, 1983.

68. Mielants, H., and Veys, E.M. Inflammation of the ileum in patients with B27-positive reactive arthritis. Lancet I, 288, 1984.

69. Mielants, H., and Veys, E.M. HLA-B27 related arthritis and bowel inflammation. Part 1. Sulfasalazine (Salazopyrin) in HLA-B27 related reactive arthritis. J. Rheumatol. 12, 1287, 1985.

70. Druery, C., Bashir, H., Geczy, A.F., et al. Search for Klebsiella cell wall components cross-reactive with lymphocytes of B27+ AS+ individuals. Hum. Immunol. I, 151, 1980.

71. Geczy, A.F., Alexander, K., Bashir, H.V., et al. A factor(s) in Klebsiella culture filtrates specifically modifies an HLA-B27 associated cell-surface component. Nature, 283, 782, 1980.

72. Prendergast, J.K., Sullivan, J.S., Geczy, A.F., et al. Possible role of enteric organisms in the pathogenesis of ankylosing spondylitis and other seronegative arthropathies. Infect. Immunol. 41, 935, 1983.

73. Prendergast, J.K., McGuigan, L.E., Geczy, A.F., et al. Persistence of HLA-B27 cross-reactive bacteria in bowel flora of patients with ankylosing spondylitis. Infect. Immunol. 46, 686, 1984.

74. Alexander, K., Edwards, C., Misko, I.S., et al. The distribution of a specific HLA-B27-associated cell surface component on the tissues of patients with ankylosing spondylitis. Clin. Exp. Immunol. 45, 158, 1981.

75. Orban, P., Sullivan, J.S., Geczy, A.F., et al. A factor shed by lymphoblastoid cell lines of HLA-B27-positive patients with ankylosing spondylitis specifically modifies the cells of HLA-B27-positive individuals. Clin. Exp. Immunol. 53, 10, 1983.

76. Kinsella, T.D. Review of research on the role of Klebsiella antigens in the spondyloarthropathies. In "The Spondyloarthropathies". M. Ziff and S.B. Cohen, eds. Advances in Inflammation Research 9, 139, 1985.

77. Van Rood, J.J., Van Leeuwen A., Ivanyi, P., et al. Blind confirmation of Geczy factor in ankylosing spondylitis. Lancet II, 943, 1985.