THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER
AT DALLAS

DEPARTMENT OF INTERNAL MEDICINE

GRAND ROUNDS

DISEASES ASSOCIATED WITH HLA-B27

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Management of Medical Information in the 1980's.

The pages that follow contain a selected review of the literature on the subject of *"Diseases Associated with HLA-B27"*. It was compiled during the month of May 1980. It is believed to contain most of the useful references of the last two years. A few older references have been included to document certain points.

This material was used in the preparation of a lecture to be delivered by the author on June 12, 1980. The lecture will not necessarily follow the same format and will certainly not consist of a reading of the present text.

The lecture will be available on videotape through the offices of the Dallas Area Hospital Television System, for souvenir purposes. It is the author's opinion that, in most cases, viewing such tapes is not an efficient way of obtaining information.

Hopefully, in the future, bibliographic reviews of the type that follows, will be available through on-line electronic systems for instantaneous retrieval, when needed, in the physician's office.

INDEX

1a. General Reviews - HLA System

(1) Albert, E.D. and Gotze, D., The major histocompatibility system in man, in The Major Histocompatibility System in Man and Animals, D. Gotze, editor, Springer-Verlag, New York, 1977, pp. 7-77.

Reviewer's summary:
Good basic discussion of HLA, including HLA and disease associations.

(2) Svejgaard, A., Hauge, M., Jersild, C., Platz, P., Ryder, L.P., Staub Nielsen, L. and Thomsen, M., The HLA system. An introductory survey. Monographs in Human Genetics Volume 7, S. Karger, New York, 1979.

Reviewer's summary:
Extensive review including discussion of HLA and disease associations and an appendix on methodology.

(3) Ryder, L.P., Andersen, E., and Svejgaard, A., HLA and Disease Registry. Third Report. Munksgaard, Copenhagen, 1979.

Reviewer's summary:
The data included are derived from two sources: the largest fraction consists of published results and has been ascertained by screening the literature and/or pre- and reprints sent to the authors. The other fraction is based on unpublished data sent to the authors either before being published or as data not intended for publication. The purpose is to give an accurate picture, as much as possible, and not to credit the investigators making the original observations. Most extensive source of up to date information available.

1b. General Reviews - B27 and spondylitis

(4) Brewerton, D.A. and James, D.C.O., The histocompatibility antigen (HL-A27) and disease, Sem. Arthritis Rheum. 4:191-207, 1975.

Author's summary:
Ankylosing Spondylitis: HL-A27 was present in 72 of 75 patients compared with 3 of 75 controls. HL-A27 was found in 32 of 60 first-degree relatives.
Reiter's disease: HL-A27 was present in 3 of 33 patients with nonspecific urethritis and in 47 of 63 patients with Reiter's disease. Preliminary reports from Finland suggest an association between HL-A27 and Reiter's disease following Shigella dysentery. In Finland, HL-A27 has been reported in 43 of 49 patients with Yersinia arthritis. The same workers in Finland have reported HL-A27 in 14 of 15 patients with arthritis following Salmonella infection.
Ulcerative Colitis and Crohn's Disease: HL-A27 is not increased in ulcerative colitis or Crohn's disease without rheumatic disease and probable not in Enteropathic Peripheral Arthritis. It was

present in 13 of 18 with ulcerative colitis and spondylitis, and in four of five with Crohn's disease and spondylitis.
Psoriasis: In Psoriasis, other workers have reported an increase in HL-A13 and HL-A17(W17), but not of HL-A27. In Psoriatic Arthritis, HL-A27 was present in 26 of 69.
Juvenile Chronic Polyarthritis: In two published series other workers have reported HL-A27 in 11 of 26 and 18 of 46 patients.
Acute Anterior Uveitis: In 100 patients attending Eye Departments with acute anterior Uveitis, HL-A27 was present in 29 of 33 with associated diseases and in 29 of 67 with no associated disease.

(5) Brewerton, D.A., HLA-B27 and the inheritance of susceptibility to rheumatic disease, Arthritis Rheum. 19:656-668, 1976.

Reviewer's summary:
The following topics are discussed. Histocompatibility Antigens, Animal Studies, The Major Histocompatibility Complex, Association with Nonrheumatic Diseases, Possible Associations in Rheumatic Diseases, Ankylosing Spondylitis, Acute Anterior Uveitis, Polyarthritis in Childhood, Ulcerative Colitis and Crohn's Disease, Psoriasis and Arthritis, Reiter's Disease Following Urethritis, Postdysenteric Reiter's Disease, Acute Arthritis Following Specific Infections.

(6) Wright, V., Seronegative polyarthritis. A unified concept, Arthritis Rheum. 21:619-633, 1978.

Author's summary:
A unified concept of seronegative polyarthritis, termed seronegative spondarthritis, has been given. It is suggested that there is a group of diseases comprising ankylosing spondylitis, psoriasis, Reiter's syndrome, ulcerative colitis, Crohn's disease, Whipple's disease, Behcet's syndrome, and possibly Still's disease, that are bound together by a common thread. They are characterized by absence of rheumatoid factor in the blood, absence of subcutaneous nodules clinically, a peripheral polyarthritis, radiologic sacroiliitis, with or without ankylosing spondylitis, clinical interrelationships between features such as psoriasiform skin or nail lesions, ocular or genitourinary inflammation, buccal, genital, or bowel ulceration, erythema nodosum, pyoderma gangrenosum, thrombophlebitis, and familial aggregation. The importance of this concept lies first in diagnosis. Back pain in patients with conditions such as ulcerative colitis should not be ascribed necessarily to a protruded intervertebral disc, nor to nonspecific accompaniment of bowel disease. It is important prognostically, in that the outlook for the arthritis is better than that for rheumatoid arthritis. It is vital from the point of view of treatment since these patients may need to be treated as spondylitics. It also has implications etiologically, since at least one of these diseases is due to infection. This may point the way to a deeper understanding of the cause of these types of arthritis.

(7) Wright, V., A unifying concept for the spondyloarthropathies, Clin. Ortho. 143:8-14, 1979.

Author's summary:
A group of diseases - ankylosing spondylitis, sporiatic arthritis, Reiter's disease, ulcerative colitis, Crohn's disease, juvenile arthritis (Still's disease), Whipple's disease, and Behcet's syndrome, which previously were thought to be variants of rheumatoid arthritis, now appear to be distinct from that disease but linked together in a group termed "seronegative spondyloarthropathies." Detailed studies have been made of the clinical, radiologic, and serologic features of these individual diseases. Extensive family studies have been done epidemiologically and through examining pedigrees. These have demonstrated clinical interrelations and familial aggregation. Ankylosing spondylitis is a feature of all the groups. Studies in which B27 was found more frequently in each of these groups confirm the interrelation and suggest a genetic predisposition with a gene related to B27. There is other evidence for environmental factors such as infection in certain of the diseases. The findings have important implications in the management of the disorders.

(8) Bluestone, R. and Pearson, C.M., Ankylosing spondylitis and Reiter's syndrome: their interrelationship and association with HLA-B27, Adv. Int. Med. 24:1-19, 1979.

Author's summary:
Ankylosing spondylitis and Reiter's syndrome are relatively common rheumatic diseases predominantly affecting men. Although the two diseases are easily distinguishable in their classic form, they possess in common many clinical and pathologic features. Recent observations on the frequent association of a single histocompatibility antigen with both of these diseases call for a reassessment of thir clinical similarities and an exploration of the possibility that they share important pathogenetic mechanisms.

(9) Schumacher, T.M., Genant, H.K., Kellet, M.J., Mall, J.C. and Fye, K.H., HLA-B27 associated arthropathies, Radiology 126:289-297, 1978.

Author's summary:
The association between histo-compatibility antigens and disease is reviewed, in particular that between HLA-B27 and spondylitic disorders, i.e., ankylosing spondylitis, Reiter's arthritis, psoriatic arthritis, and ankylosing hyperostosis. We determined whether the presence of HLA-B27 predicted specific radiographic findings, and, conversely, whether specific radiographic changes predicted antigenic status. The prevalences of the HLA-B27 antigen in our patients were: ankylosing spondylitis, 100%; Reiter's arthritis, 93%; psoriatic arthritis, 55%; and ankylosing hyperostosis, 12%. The only specific radiographic finding associated with B27 positivity was severe spondylitis in psoriasis.

2. *Ankylosing Spondylitis.*

(10) Brewerton, D.A., Hart, F.D., Nicholls, A., Caffrey, M., James, D.C.O., and Sturrock, R.D., Ankylosing spondylitis and HL-A27, Lancet 1:904-907, 1973.

Author's summary:
Using a standard microcytotoxicity technique of tissue typing, the HL-A27 antigen was identified in 72 out of 75 patients with classical ankylosing spondylitis and in 3 out of 75 controls. The same antigen was found in 31 out of 60 first-degree relatives.

(11) Schlosstein, L., Terasaki, P.I., Bluestone, R. and Pearson, C.M., Association of an HL-A antigen, W27, with ankylosing spondylitis, New Engl. J. Med. 288:704-706, 1973.

Author's summary:
The frequencies of 24 HL-A antigens were examined in 40 patients with ankylosing spondylitis, 119 with rheumatoid arthritis, and 66 with gout. No significant deviation from control frequencies of HL-A specificities was noted in patients with gout and rheumatoid arthritis. Specificity W27 was noted in 35 of 40 patients with ankylosing spondylitis, or 88 per cent, as compared to 8 per cent of the 906 normal controls ($p < 0.0001$). There was concomitant reduction in HL-A7 of the second segregant series associated with the increased frequency of occurrence of W27, but this decrease was of borderline significance ($p < 0.05$). This association between W27 and ankylosing spondylitis is so marked that it is possible to assume either very close genetic linkage of a specific immune responsiveness gene to the disease or perhaps a strong immunologic cross-reaction between W27 and the etiologic agent involved.

(12) Blumberg, B. and Ragan, C., The natural history of rheumatoid spondylitis, Medicine 35:1-31, 1956.

Author's summary:
1. The diagnosis of rheumatoid spondylitis or variants of this name was made in 311 patients at this clinic from 1928 to 1954. One hundred and two came in for examination, 40 were contacted by phone or letter and information from the chart was used for the remainder.
2. Seventy-six per cent of the group contacted were in functional Class 1. Only 5 were leading a bed and chair existence. The functional status in the average patient was well maintained during most of his life. Pain was greatest during the early phase of the disease but in most patients decreased in the latter years. X-ray changes and physical deformity appeared to progress relentlessly in most of the patients.
3. Treatment should be directed towards maintaining functional ability. Body restricting procedures should be avoided.
4. In the majority of patients, the acute phase is present during the early years for a period short with respect to the entire life

span of the disease. Sclerosis and ankylosis may take years to proceed to completion.

5. Etiology, pathology and certain clinical features are discussed.

(13) Bluestone, R., Immunogenetics and ankylosing spondylitis, Clin. Rheum. Dis. 3:255-264, 1977.

Author's summary:
The strong association between ankylosing spondylitis and HLA-B27 is established fact. Potential explanations for this association involve two main theories. HLA-B27 may alter tissue susceptibility to specific infectious agents, either directly or by a means of antigenic cross-reactivity. Alternatively, the gene coding for HLA-B27 may be closely linked to a disease susceptibility gene comparable to the immune response genes described in other species. This immune response gene may either govern host reactivity to infectious agents or may govern the propagation of true autoimmune disease following initial alteration of host antigens by exogenous stimuli. There are at present insufficient data to support or refute either of these main hypotheses. Lack of information about putative infectious agents and inadequate methodologies with which to explore cell mediated immunity may limit investigation for the present. However, as adequate tools become available they can be readily applied to well-defined populations of patients with AS and to their tissue-typed first degree realtives.

(14) Forouzesh, S. and Bluestone, R., The clinical spectrum of ankylosing spondylitis, Clin. Ortho. 143:53-58, 1979.

Author's summary:
Ankylosing spondylitis is more common in young men than in young women and is insidious in onset. Typically, patients complain of pain and stiffness around the sacroiliac region. As the disease progresses, pain is often felt in the mid-lumbar, thoracic and cervical regions resulting in a significant reduction in the range of motion of the entire spine. About one fourth of the patients display involvement of proximal synovial joints. Acute anterior uveitis may precede AS or can occur when the disease is otherwise in apparent remission. Each patient with established disease should be carefully evaluated for cardiovascular, pulmonary, and neurologic complications. Early detection of AS is important, since proper management may well prevent the severe fixed deformities of the spine and root joints that is liable to occur in these patients.

(15) Masi, A.T. and Medsger, T.A. Jr., A new look at the epidemiology of ankylosing spondylitis and related syndromes, Clin. Ortho. 143: 15-29, 1979.

Author's summary:
Among the rheumatic diseases, none so clearly illustrates the relations between host and environmental factors as the sero-negative spondyloarthropathy group of disorders. The strongest

association is with the histocompatibility antigen HLA-B27, which accounts for a striking susceptibility to these diseases and is present in over 90% of individuals with idiopathic ankylosing spondylitis. Next in importance appears to be a difference in sex penetrance with males predominating in all categories. The most dramatic sex relationship is with postvenereal Reiter's syndrome which has a male-to-female ratio of nearly 50:1. Another potent host factor is age, with increased predisposition to onset at puberty and young adulthood in HLA-B27-positive patients. Environmental or possible infectious agent influences are most apparent in Reiter's syndrome, where the antecedent circumstances of venereal contact and bacillary dysentery are frequent precipitating events. Secondary forms of peripheral arthritis, radiographic sacroilitis, and ankylosing spondylitis frequently occur in psoriasis and inflammatory bowel disease; in the case of peripheral arthritis, there is no or a significantly reduced association with HLA-B27 compared to AS or RS. Secondary factors seem to be contributing to spondyloarthropathy in these disorders. These interrelations emphasize the powerful effects of host characteristics on the type of rheumatic disease syndrome acquired and provice superb opportunities for more precise understanding of disease pathogenesis and ultimate control through the integration or epidemiologic, clinical, and laboratory research.

(16) Resnick, D., Radiology of seronegative spondyloarthropathies, Clin. Ortho. 143:38-45, 1979.

Author's summary:
Radiographic manifestations of the seronegative spondyloarthropathies superficially resemble the findings of rheumatoid arthritis although they differ in both distribution and pattern of disease. Ankylosing spondylitis has a predilection for the axial skeleton; psoriatic arthritis may involve distal interphalangeal joints; and Reiter's syndrome is most commonly associated with asymmetrical lower extremity alterations. The absence of osteoporosis and the presence of bony proliferation are also noted in these disorders. Sacroillitis and spondylitis, which can be observed in any of these diseases, may have distinctive features. In ankylosing spondylitis, bilateral sacroiliac joint alterations and typical syndesmophytes are common; in Reiter's syndrome and psoriasis, asymmetrical sacroiliac joint changes and bulky spinal outgrowths may be observed. The physician should be aware of typical roentgen findings in each of the spondyloarthropathies.

(17) Spencer, D.G., Park, W.M., Dick. H.M., Papazoglou, S.N. and Buchanan, W.W., Radiological manifestations in 200 patients with ankylosing spondylitis: correlation with clinical features and HLA-B27, J. Rheum. 6:305-315, 1979.

Author's summary:
The radiological manifestations of 200 patients with ankylosing spondylitis were appraised, and correlated with the patient's

sex, anterior uveitis, and HLA-B27. Radiological findings in female patients were no different from male patients. Only syndesmophyte formation in the spine was found significantly more frequently in patients with uveitis and HLA-B27. Osteoporosis of the spine correlated strongly with a later age of onset, longer duration of the disease, older age at the time of study, Romanus lesions, syndesmophytes, spinal fusion, osteitis pubis, and widespread radiological destructive peripheral joint disease. Syndesmophytes were most frequently present at the dorso-lumbar junction. Spondylodiscitis was present in 8 patients and was most commonly present in the thoracic spine.

(18) Esdaile, J., Hawkins, D. and Rosenthall, L., Radionuclide joint imaging in the seronegative spondyloarthropathies, Clin. Ortho. 143:46-52, 1979.

Author's summary:
Radionuclide joint imaging (RJI) of the peripheral and axial skeleton is a recent advance in the detection of early articular inflammation and has proven useful in establishing the extent and pattern of this involvement. The bone-seeking agents - the radiophosphates - are the radiopharmaceuticals presently favored for RJI in adults. They are more sensitive than the clinical examination in detecting inflammatory joint disease in all peripheral joints with the exception of the shoulders, elbows and knees. Radiophosphate may also be used to evaluate the axial skeleton for inflammatory involvement. The sacroiliac joints may be evaluated by a new technique, quantitative sacrioliac scintigraphy (QSS). Studies to date have demonstrated that QSS is most sensitive in early sacroiliiitis, a time when conventional radiography is normal or shows equivocal abnormalities.

While extremely sensitive as a screening procedure for inflammatory articular disease, RJI is nonspecific diagnostically. Radiophosphate uptake by bone occurs in metabolic bone disease, osteoarthritis, trauma and juxta-articular bony abnormalities such as osteomyelitis and bone infarction. The results obtained by radionuclide joint imaging must be supplemented by the clinical findings and conventional investigations to establish a specific diagnosis.

(19) Ball, J., Articular pathology of ankylosing spondylitis, Clin. Ortho. 143:30-37, 1979.

Author's summary:
The essential articular pathology of AS may be said to reflect the occurence, severity, and overall bias of (a) synovitis which tends to produce articular erosion, and (b) an inflammatory enthesopathy which results in capsular ossification in diarthrodial joints and syndesmophyte formation in cartilaginous joints, both of which are primarily responsible for bony ankylosis. Nonspecific secondary mechanisms contribute to the final picture. These include enchondral ossification, which produces synostosis, osteoporosis and altered

stress distribution which make the axial skeleton susceptible to trivial trauma, the destructive effects of which are sometimes described as spondylodiskitis.

(20) Smythe, H., Therapy of the spondyloarthropathies, Clin. Ortho. 143:84-89, 1979.

Author's summary:
The key to successful therapy for patients with ankylosing spondylitis is a lifelong, carefully devised, and well-instructed exercise program. This program is designed to maintain maximum range of motion within the spine, and the costovertebral and girdle joints, thereby preventing the tendency to flexion contractures and loss of height. The exercise program frequently requires long-term concomitant therapy with nonsteroidal anti-inflammatory drugs, partly to releive the painful perispinal muscle spasm which frequently inhibits the exercise movements. The drugs are not known to alter the natural history of the inflammatory lesion. Local measures directed at ocular, urethral, and mucocutaneous inflammation may be symptomatically beneficial. These simple therapeutic principles ensure a good functional prognosis in the vast majority of patients with spondylitis.

(21) Hochberg, M.C., Borenstein, D.G. and Arnett, F.C., The absence of back pain in classical ankylosing spondylitis, The John Hopkins Medical Journal 143:181-183, 1978.

Author's summary:
Despite the early description of painless spinal ankylosis, the existence of a clinical subset of ankylosing spondylitis with silent axial disease has largely been overlooked. Of 45 patients who met Rome diagnostic criteria for ankylosing spondylitis, five denied ever having back pain either as an initial symptom or during the subsequent course of their illness. All had decreased lumbar spine motion and bilateral radiographic sacroiliitis of at least grade III severity. Chest expansion was decreased in four, and radiographic involvement of the cervical and lumbar spine was observed in three and two patients, respectively. There were no differences observed in sex or race distribution, or frequencies of peripheral arthritis, heel pain, acute uveitis, genito-urinary infection or HLA-B27 positivity when these patients were compared with the remaining patients with back pain. These patients support the existence of a "latent" form of ankylosing spondylitis with silent axial disease.

(22) 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 45: 1014-1027, 1973.

Author's summary;
Clinical and cardiovascular necropsy findings in eight patients with

combined ankylosing spondylitis and aortic regurgitation. All were men (aged 34-55 years), each had peripheral arthritis in addition to spondylitis, all had severe congestive failure, and six had conduction disturbances. In three patients aortic regurgitation was present before distinctive radiologic changes of ankylosing spondylitis were apparent and only two patients had advanced arthritic changes of ankylosing spondylitis. Thus, cardiac dysfunction may be present before signs of spondylitis are apparent, and aortic regurgitation may be severe when signs of spondylitis are minimal. A characteristic cardiovascular morphologic abnormality was present in each patient. The aortic valve cusps and the aorta behind and immediately above the sinuses of Valsalva were thickened, the latter by dense adventitial scar tissue and by intimal fibrous proliferation. In each patient the scar tissue in the root of aorta extended below the base of aortic valve to produce a subaortic fibrous ridge. The subaortic bump involves the base of anterior mitral leaflet and may cause mitral regurgitation. Extension of the fibrous scar into ventricular septum may cause heart block. The distinctive cardiovascular morphologic findings in patients with ankylosing spondylitis clearly separate this condition from syphilis and other entities associated with aortic regurgitation.

(23) Roberts, W.C., Hollingsworth, J.F., Bulkley, B.H., Jaffe, R.B., Epstein, S.E., Stinson, E.B., Combined mitral and aortic regurgitation in ankylosing spondylitis. Angiographic and anatomic features, Am. J. Med. 56:237-243, 1974.

Author's summary:
Clinical and cardiac morphologic features are described in a man with combined aortic and mitral regurgitation associated with ankylosing spondylitis. Although aortic regurgitation is a recognized accompaniment of ankylosing spondylitis, the occurence of henodynamically-significant mitral regurgitation in this arthritic condition has not been documented previously. Histologic study disclosed changes in the anterior m itral leaflet identical to those observed in the wall of the aorta and base of the aortic valve cusps in patients with ankylosing spondylitis. Thus, ankylosing spondylitis may be associated with characteristic lesions in anterior mitral leaflet in addition to those in the ascending aorta and aortic valve. The subaortic bump at the base of the anterior mitral leaflet, the most characteristic cardiovascular lesion of ankylosing spondylitis, may be visualized during life by left ventricular angiography, and its identification allows proper etiologic diagnosis of the valvular regurgitation.

(24) Kinsella, T.D., Johnson, L.G. and Sutherland, R.I., Cardiovascular manifestations of ankylosing spondylitis, Canad. Med. Assoc. J. 111:1309-1311, 1974.

Author's summary:
The incidence of cardiovascular lesions in 97 patients with ankylosing

spondylitis (AS) was found to be 14%; 8 patients had isolated aortic insufficiency (AI), 3 had isolated heart block, 2 had combined AI and heart block, and 1 had mitral insufficiency. In comparison with control groups of 81 patients with rheumatoid arthritis and 99 random hospital patients there was no increased incidence of isolated heart block in patients with AS. Clinical and postmortem findings indicated that the cardiovascular lesions of some patients with AS may antedate articular disease and may regress spontaneously. In addition, the unusual occurrence of AI in two patients with psoriatic spondylitis and in one with AS and regional enteritis is documented.

(25) Stewart, S.R., Robbins, D.L. and Castles, J.J., Acute fulminant aortic and mitral insufficiency in ankylosing spondylitis, New Engl. J. Med. 299:1448-1449, 1978.

Author's summary:
Extraskeletal manifestations of ankylosing spondylitis include aortitis with aortic and rarely mitral valvular insufficiency. Cardiac dysfunction usually develops late and progresses slowly. The acute case of aortitis presented below required emergency bivalvular replacement antedating spondylitis.

(26) Calin, A., Fries, J.F., Stinson, E.B., Payne, R., Normal frequency of HL-A B27 in aortic insufficiency, New Engl. J. Med. 294:397, 1978.

Author's summary:
The relation between uveitis, ankylosing spondylitis, Reiter's syndrome and the histocompatibility antigen HL-A B27 is well documented. Indeed, uveitis may on occasion be considered a "forme fruste" of ankylosing spondylitis since even in the absence of sacroilitis, there is an increased frequency of B27 in this condition.

Aortic insufficiency is a rare but well recognized manifestation of both ankylosing spondylitis and Reiter's syndrome. We have recently seen four cases of "idiopathic" aortic insufficiency, undiagnosed ankylosing spondylitis and B27 positivity. It therefore seemed appropriate to study the histocompatibility status of patients operated on for aortic insufficiency. Patients with a history of congenital valve disease, rheumatic fever or rheumatologic condition were excluded. Fourteen consecutive patients were studied: only one of these new cases was HL-A B27 positive, a frequency comparable to that of the general population.

This subject had neither clinical nor radiologic evidence of ankylosing spondylitis. It thus appears that unlike uveitis, idiopathic aortic insufficiency rarely represents a "forme fruste" of ankylosing spondylitis and that search for B27-positive results and clinical spondylitis in this group will not be particularly fruitful.

(27) Gabay, R., Guignard, D., Chantraine, A., A rare extra-articular manifestation of ankylosing spondylitis: Cauda Equina syndrome, J. Rheumatol. 5:234-235, 1978.

Author's summary:
Cauda Equina syndrome is a very rare and late complication of ankylosing spondylitis (AS) possibly related to an arachnoiditis. This brief report discusses the pathogenesis and the clinical aspects of this complication, illustrated by the observation of a 67 year old white male suffering from AS since 1943.

The 20 reports (Table 1) associating a cauda equina syndrome with AS, including our patient, show a number of common clinical characteristics of this late manifestation of an inactive "burned out" stage of the disease. All patients were males, the neurological syndrome appeared insidiously, and diagnosis was late in the course of the AS. Sphincter disorders were constant and usually the first symptom. As a rule, ankle jerks were absent with sensory impairment. In contrast, motor lesions were less frequent. The results of myelography performed in 17 patients showed that the most frequent findings were diverticula.

3. *Reiter's Disease and Reactive Arthritis.*

(28) Zachariae, H., Hjortshøj, A., Kissmeyer-Nielsen, F., Reiter's disease and HL-A 27, Lancet 2:565-566, 1973.

Author's summary:
The results of this preliminary study showed that in 8 of 9 patients the HL-A 27 antigen was identified. The same antigen was found in only 8.4% of 562 healthy blood-donors. None of our patients had HL-A 13 or 17 antigen.

(29) Woodrow, J.C., HL-A 27 and Reiter's syndrome, Lancet 2:671-672, 1973.

Author's summary:
We have been examining the HL-A phenotypes in Reiter's syndrome, and of 20 cases (19 men and 1 woman) 13 are HL-A 27 positive (65%). A control series shows 12 out of 150 (7.5%) to be HL-A 27 positive, the difference being highly significant. 19 of the patients had urethritis at the onset but 1 patient, a boy of 18, had severe diarrhoea as the apparent initiating event. 1 male patient had evidence that he had developed ankylosing spondylitis eight years at least before his attack of Reiter's syndrome in which, for the first time, acute synovitis occurred in the peripheral joints of the lower limbs following sexual exposure and non-specific urethritis. This underlines the susceptibility that HL-A-27-positive men have to both conditions. The finding also throws new light on the occurrence of spondylitis in association with Reiter's syndrome

and it raises the possibiltiy that in some instances the spondylitis may precede rather than follow Reiter's syndrome. It appears moreover that herein lies the explanation for the finding by Lawrence that 4% of the male relatives of patients with Reiter's syndrome had clinical ankylosing spondylitis compared to 0.5% in the general population.

(30) Kousa, M., Lassus, A., Karvonen, J., Tillikainen, A. and Aho, K., Family study of Reiter's disease and HLA B27 distribution, J. Rheumatol. 4:95-102, 1977.

Author's summary:
Starting from index patients with confirmed Reiter's disease, a clinical and immunogenetic study was performed on 12 families in which there were further cases of arthritis. Altogether 51 family members were investigated and some information was available on 15 additional members. In most families there were two or three affected members in addition to the proband. The manifestations included acute polyarthritis (16 cases), which frequently followed urethritis or occurred as a complication of Yersinia or Shigella infection, and chronic arthritis (9 cases), either ankylosing spondylitis or peripheral arthritis. The latter characteristically had a remitting course, affecting mainly the large joints. Not a single subject had sero-positive rheumatoid arthritis.

The HLA B27 gene was detected in all 12 families, and served as the main indicator of the familial trait for developing arthritis. In individual patients however, the association was not especially close, since there were members with this antigen who did not have arthritis in spite of a seemingly adequate triggering stimulus and others who had arthritis but not the antigen.

(31) Arnett, F.C., McClusky, O.E., Schacter, B.Z. and Lordon, R.E., Incomplete Reiter's syndrome: Discriminating features and HL-A W27 in diagnosis, Ann. Int. Med. 84:8-12, 1976.

Author's summary:
Reiter's syndrome (nonspecific urethritis, conjunctivitis, and arthritis) may present with arthritis alone. There are, however, other discriminating clinical features that contribute to diagnosis. Additionally, the presence of HL-A W27 provides a new diagnostic aid. Thirteen patients were studied and support the validity of the concept of incomplete Reiter's syndrome. Peripheral arthritis was the presenting complaint in all, and none had urethritis or conjunctivitis. The majority were young white men. The arthritis was oligoarticular and asymmetric with lower extremity involvement predominating. Heel pain was a prominent symptom in 10, with periostitis of other sites in 5, and "sausage digits" in 8. Mucocutaneous lesions occurred in 1 and significant weight loss in 6. Only 2 had sacro-illiitis. Chronicity has characterized the course in 12. HL-A W27 was present in 12 of 13. Additional data suggest that Reiter's syndrome may be one of the most common forms of inflammatory arthritis in young men.

(32) Calin, A. and Fries, J.F., An "Experimental" epidemic of Reiter's syndrome revisited. Follow-up evidence on genetic and environmental factors, Ann. Int. Med. 84:564-566, 1976.

Author's summary:
The relation between a specific infective event (shigellosis), a specific disease entity (Reiter's syndrome), and a specific histocompatibilty antigen (HL-A B27) is documented by follow-up study of an epidmeic of post-Shigella Reiter's syndrome. Five of the original 10 patients have been traced, HL-A typed, and clinically assessed 13 years after the initial episode. One of the 5 has minimal disease, remains symptom-free, and is HL-A B27-negative. The remaining 4 have followed a chronic course, have persistent active disease, and are HL-A B27-positive. It is estimated that after this single episode of shigellosis, from one sixth to one third of the persons who were HL-A B27-positive developed Reiter's syndrome. The prognosis for postdysenteric Reiter's syndrome must by guarded, especially in the subject who is B27-positive.

(33) Ford, D.K., The clinical spectrum of Reiter's syndrome and similar postenteric arthropathies, Clin. Ortho. 143:50-65, 1979.

Author's summary:
Certain infections of the genitourinary and gastrointestinal tracts, such as nongonococcal urethritis, dysentery and yersiniosis, precipitate characteristic arthritic syndromes in genetically susceptible individuals. Eye and skin lesions in the form of conjunctivitis, iritis, keratodermia blenorrhagica and erythema nodosum occurring in association with particular distributions of arthritis make recognizable clinical entities. Reiter's syndrome may be diagnosed with certainty from the presence of tender heels, low back pain, a predominance of knee and foot arthritis and pyuria, when the more obvious clinical markers of the syndrome are absent; a flagrant case represents one of the easiest clinical diagnoses in medicine. Diagnosis is important for a good prognosis, optimal treatment and sometimes prophylactic measures. Sacroilitis often progressing to spinal ankylosis is a prominant feature in the B27-positive patient. Erythema nodosum occurs in B27-negative subjects as a response to yersiniosis and ulcerative colitis.

(34) Fox, R., Calin, A., Gerber, R.C. and Gibson, D., The Chronicity of symptoms and disability in Reiter's syndrome, Ann. Int. Med. 91: 190-193, 1979.

Author's summary:
To assess the natural history of Reiter's disease, we evaluated 131 consecutive patients at a university clinic or at a community center. One hundred twenty-two patients (93%) were available for follow-up at a mean of 5.6 years. The results showed that there were no major differences between patients at the two centers; at follow-up, 101 (83%) had some disease activity, 27 (22%) had annoying symptoms, 42

(34%) had sustained disease activity, 19 (16%) had had to change jobs, and 13 (11%) were unemployable; there were no major differences between the 19 (15%) females and 112 (85%) males or between the HLA-B27-positive (83%) and -negative (17%) patients, except for increased prevalence of sacroiliitis and chronic uveitis in HLA-B27-positive patients; and, at entry, only increased heel disease differentiated those destined to have a poor prognosis. Most patients with Reiter's syndrome have persisting symptoms that can lead to chronic disabiltiy.

(35) Aho, K., Ahvonen, P., Lassus, a., Sievers, K., Tilikainen, A., HL-A antigen 27 and reactive arthritis, Lancet 2:157, 1973.

Author's summary:
The antigen HL-A27 was identified in 9 of 11 females and in all of 11 males with yersinia arthritis. The patients were initially selected because of documented and usually severe arthritis. Thus the finding may not apply in cases of mild arthritis or arthralgia. All 6 members of one family contracted yersinia infection. Mother and 3 sons developed arthritis and they all possessed the antigen 27, whereas it was absent in the father and one of the sons, who both had only abdominal disease. Furthermore, the son without arthritic symptoms was a recombinant of maternal HL-A loci, having inherited the antigen 2 which segregated with 27 in other siblings. The antigen 27 is present in 14% of Finns, and it was detected in 2 of 15 patients who contracted the infection within the same period of study but were not classified in the arthritis group.

As in yersinia arthritis, HL-A 27 was detected in all of 5 cases of reactive arthritis following verified gonococcal infection and in 4 of 5 cases of Reiter's syndrome (arthritis following non-gonococcal urethritis and often accompanied by conjunctivitis).

(36) Friis, J. and Svejgaard, A., Salmonella arthritis and HL-A27, Lancet 2:1350, 1974.

Author's summary:
Of 366 patients with bacteriologically verified salmonella infection admitted to the Department of Infectious Diseases, Blegdamshospitalet Copenhagen, during the period January, 1964, to March, 1974, 6 patients had clinical signs of arthritis with joint swelling and tenderness. 3 of these patients had polyarthritis and 3 had monoarthritis.

The frequency of arthritis (1.6%) accords with earlier observations. 5 of the 6 arthritis patients were available for clinical follow-up. All had recovered completely, and there were no clinical signs of sacro-iliitis. This favourable prognosis has been observed by others.

Determination of the antigens of the major histocompatibility system showed that 3 of the 5 patients examined had the antigen HL-A27 (60%). The same antigen was found in 125 of 1541 healthy

Danes (8.1%). This difference is significant (p = 0.005).

(37) Lassus, A., Karvonen, J., Reactive arthritis, Reiter's disease and psoriatic arthritis, Clin. in Rheum. Dis. 3:281-298, 1977.

Author's summary:
The three clinical entities reactive arthritis, Reiter's disease and psoriatic arthritis are all characterized by a seronegative peripheral arthritis and a tendency to develop ankylosing spondylitis and/or sacroiliitis. In addition, patients with any of these diseases frequently have the histocompatibility antigen HLA-B27. In many instances there are difficulties in differentiating between Reiter's disease psoriatic arthritis on the one hand, and between reactive arthritis and Reiter's disease on the other. The three diseases evidently belong to a large complex, which also includes ankylosing spondylitis. The principal genetic marker of this complex is HLA-B27, which, however, has not been shown to be directly involved in the disease process in any of these conditions. This chapter aims to present genetic aspects, aetiological factors and clinical features of reactive arthritis, Reiter's disease and psoriatic arthritis, with special attention to the relationship between the three conditions.

(38) Leirisalo, M., Laitinen, O. and Tiilikainen, HLA phenotypes in patients with rheumatic fever, rheumatic heart disease, and yersinia arthritis, J. Rheumatol. Suppl. 3:78-83, 1977.

Author's summary:
HLA phenotypes were determined in 109 patients with rheumatic fever (RF), 48 patients with Yersinia arthritis (YA), 86 patients with chronic rheumatic heart disease (RHD), and 326 controls. There was an increased frequency of Bw35 in RF as compared to controls (P_c <0.01), while B18 was more common in patients with acute carditis than in those without (P <0.02). HLA frequencies in RHD did not differ significantly from those in controls.

A significant correlation between B27 and YA was observed (P_c <0.001). Carditis or iritis occurred in 10 of 31 B27 positive YA patients but in none of 17 B27 negative patients. Eleven of 31 B27 carriers had signs of urological inflammation vs one of 17 B27 negative patients. In the B27 positive YA group, there were three men with previous ankylosing spondylitis and one with Reiter's syndrome (RS). Also, four patients developed RS during Yersinia infection. This simultaneous occurrence of three B27 positive rheumatic diseases suggests that a patient with one "B27 positive rheumatic disease" is more susceptible to other diseases or symptoms known to be associated with the B27 antigen.

(39) Urman, J.D., Zurier, R.B., Rothfield, N.F., Reiter's syndrome associated with Campylobacter fetus infection, Ann. Int. Med. 86:444-445, 1977.

Author's summary:
Many organisms have been implicated as the cause of Reiter's syndrome. We recently observed a patient with many features of Reiter's syndrome, who was infected with Campylobacter fetus, formerly called Vibrio fetus. The organism was cultured from the blood during two separate flares of disease activity, associated with significant rise in agglutination titer to the organism. We are not aware of other reports associating this organism with Reiter's syndrome.

(40) Berden, J.H., Muytjens, H.L., van de Putte, L.B.A., Reactive arthritis associated with Campylobacter jejuni enteritis, Br. Med. J. 1:380-381, 1979.

Author's summary:
The findings in this case suggest that the oligoarthritis was reactive to the C jejuni enteritis. The arthritis started two weeks after the onset of the enteritis, and the antibody titre against the isolated campylobacter significantly increased. Other known causes for acute arthritis could be excluded. Moreover, reactive arthritis after certain infections occurs especially in HLA-B27-positive patients. This antigen was present in our patient. We do not known of other reports of reactive arthritis associated with C jejuni infections. One report attributes exacerbations of a Reiter syndrome to Campylobacter fetus infections. This species, however, is distinct from C jejuni. C jejuni is now identified more often as a cause of enteritis. Possibly, therefore, reactive arthritis after C jejuni infection is not rare and will be diagnosed more often in the future.

(41) Scott, J.T. and Mair, N.S., Yersinia arthritis, Br. Med. J. 1:1251-1253, 1979.

Author's summary:
Reactive arthritis associated with Yersinia enterocolitica infection is common in parts of Europe, particularly Scandinavia, but has never been documented in the UK. We describe such a case.

(42) Kaslow, R.A., Ryder, R.W. and Calin, A., Search for Reiter's syndrome after an outbreak of Shigella Sonnei dysentery, J. Rheumatol. 6:562-566, 1979.

Author's summary:
Forty-seven % of 4,205 individuals living in a Puerto Rican community developed Shigella sonnei dysentery. Questionnaire and, where relevant, clinical evaluation of 1,970 patients and the remaining 2,235 unaffected residents disclosed no cases of Reiter's syndrome (RS). Among the possible explanations for failure to observe any cases is the important suggestion that S. sonnei is not arthritogenic.

(43) Jones, M.B., Smith, P.W. and Olnhausen, R.W., Reiter's syndrome after salmonella infection: occurrence in HLA-B27 positive brothers, Arthritis Rheum. 22:1141-1142, 1979.

Author's summary:
Reiter's syndrome has occasionally developed after salmonella enteritis. HLA antigens have not been reported for post-salmonella Reiter's syndrome. We report two such cases in adolescent brothers, both of whom had the HLA-B27 antigen.

(44) Weiss, J.J., Thompson, G.R. and Good, A., Reiter's disease after salmonella typhimurium enteritis, J. Rheumatol. 7:211-212, 1980.

Author's summary:
We describe a case of Reiter's disease in an HLA-B27 positive black woman after infection with Salmonella typhimurium. Although reactive arthropathy following Salmonella infections is not unusual, Reiter's disease is rare. This may be the second such case in the English literature, and the first reported in North America.

(45) Stein, H.B., Abdullah, A., Robinson, H.S. and Ford, D.K., Salmonella reactive arthritis in British Columbia, Arthritis Rheum. 22:663, 1979.

Author's summary:
Salmonella reactive arthritis has been reported from Europe but not from North America. Over a period of 1 year, 5 cases of salmonella reactive arthritis were identified in British Columbia. Three patients were adolescents; 4 were males. Stool cultures grew Salmonella typhimurium in 4 cases and Salmonella enteritidis in 1. In 2 cases tested, serum agglutination titers for Salmonella paratyphi B ("O") were mildly elevated to 1 of 80. The arthritis followed the diarrhea by 7 to 10 days and tended to involve the lower limb joints. Two patients had low back involvement with 1 patient developing radiologic sacroiliitis. Joint aspiration in 3 patients showed inflammatory fluid and negative bacterial studies. The patient with sacroiliitis had Reiter's syndrome (conjunctivitis, urethritis, arthritis, and later acute iritis) and is only the second recorded case of this syndrome after Salmonella typhimurium infection. Patients were ill with marked joint inflammation, constitutional symptoms of fever, fatigue, weight loss, malaise, and high sedimentation rates. Patients had anemia, mild leukocytosis, and polyclonal hypergammaglobulinimia. HLA-B27 was present in 4 of 4. Active disease persisted up to 1 year without permanent damage. The sedimentation rate remained elevated for some time after remission. Patients received antibiotics without effect upon joint symptoms. Indomethacin was extremely effective and superior to salicylates and cortiosteroids.

(46) Keat, A.C., Maini, R.N., Pegrum, G.D. and Scott, J.T., The clinical features and HLA associations of reactive arthritis associated with non-gonococcal urethritis, Quart. J. Med. 48:323-342, 1979.

Author's summary:
Fifty-seven patients with arthritis associated with non-gonococcal genital infection have been studied. Synovitis characteristically affected one or a few joints, especially the knee, ankle or metatarsophalangeal joints and was accompanied by tenosynovitis and enthesopathies - each in about one third of the patients. A quarter of the patients had ocular, cutaneous, or mucous membrane lesions (Reiter's syndrome). Although six patients developed a chronic or relapsing course, average duration of the acute episode in the majority was three to five months. Available evidence strongly suggests that infection following sexual intercourse, usually but not always with a new partner, was instrumental in the initiation of the disease. We have suggested the term "sexually acquired reactive arthritis (SARA)" to emphasize the mode of acquisition of the disease, and note that similar syndromes are seen associated with gut infection. We consider that usage of the term Reiter's syndrome is correctly applied to only those cases which exhibited the characteristic triad of urethritis, arthritis and conjunctivitis with or without other cutaneous and mucous membrane lesions. Thirty-six of the 54 patients who were HLA typed (67 per cent) possessed the antigen HLA-B27. Of 30 who presented directly to a rheumatology unit 25 (83 per cent) were HLA-B27 positive. The other 24 patients initially attended a venereology clinic and only 11 (46 per cent) of these bore the antigen. This appears to reflect disease severity, HLA-B27 positive patients having a significantly longer duration of disease symptoms and a higher frequency of extra-articular manifestations, than those lacking this antigen.

(47) Wagner, L.P., Fessel, W.J., HL-A 27 (W27) absent in gonococcal arthritis, Lancet 1:1094-1095, 1975.

Author's summary:
Aho et al suggested that susceptibility to certain forms of infectious arthritis is closely linked with the histocompatibility antigen HL-A 27 (W27), and supported this by finding the antigen in all of 5 patients with gonococcal arthritis as well as in most of their patients with arthritis caused by yersinia. Morris et al, however, failed to demonstrate the antigen in 12 patients with gonococcal arthritis. In view of these conflicting reports, we studied 12 patients (7 women, 5 men; 7 White, 5 Black) with gonococcal arthritis. In 10 patients the diagnosis was bacteriologically proved (positive culture in 9, positive gram stain in one); the other 2 patients had acute arthritis with a typical rash but negative bacteriological findings. HL-A 27 was absent in all 12 patients.

(48) Julkunen, H., Reactive arthritis, Bull. Rheum. Dis. 29:1002-1005, 1978.

Author's summary:
A form of polyarthritis, which has long been observed by many rheumatologists has been found to be associated with certain urogenital, bowel and other infections as a "reactive" form of inflammatory

rheumatic disease. It often follows infection with Salmonella typhimurium, Shigella flexneri, Yersinia enterocolitica and, less clearly, infection with Chlamydia, Streptococcus, Gonococcus and Brucella. Reactive arthritis is often associated with the presence of B27 antigen, which links it with ankylosing spondylitis. This type of polyarthritis has been associated by clinical and follow-up studies with ankylosing spondylitis.

4. Psoriasis

(49) Roux, H., Mercier, P., Serratrice, G., Sany, J., Seignalet, J. and Serre, H., Psoriatic arthritis and HLA antigens, J. Rheumatol. Suppl. 3:64-65, 1977.

Author's summary:
HLA groups including the characteristics of 25 antigens were determined in 108 patients suffering from psoriatic arthritis. These included 18 patients with central forms (pelvospondylitis), and 90 patients with peripheral forms (polyarthritis with or without sacroiliitis). Analysis of the results leads to the following conclustions: central psoriatic arthritis is strongly associated with B27 and BW38, less closely with B13 and sightly with BW17. Peripheral psoriatic arthritis has the same relationship with the HLA system as has psoriasis without arthropathy.

(50) de Ceulaer, K., van der Linden, J.M.J.P. and Cats, A., "Sausage-like" toes (Dactylitis) and HLA B27, J. Rheumatol. Suppl. 3:66-68, 1977.

Author's summary:
When "sausage-like" swelling of the toes occurs in the absence of clinical Reiter's disease or psoriasis, definite classification is hardly possible. Nine patients with isolated "sausage toes" (dactylitis) and minor involvement of other joints are described. The relationship between this syndrome and HLA B27 permits better classification and more rational treatment.

(51) Moll, J.M.H., The clinical spectrum of psoriatic arthritis, Clin. Ortho. 143:66-75, 1979.

Author's summary:
Epidemiologic, clinical, radiologic and serologic evidence suggests that psoriatic arthritis is a specific entity and not the coincidental occurrence of 2 common diseases, psoriasis and rheumatoid arthritis. Psoriatic arthritis may be defined as psoriasis associated with inflammatory arthritis (peripheral arthritis or spondylitis or both) and usually a negative serologic test for rheumatoid factor. Clinical characteristics of the disease include: almost equal distribution between males and females; peripheral arthritis involving only a few small joints and asymmetrical fashion; involvement of distal interphalangeal joints; sausage digits; arthritis mutilans; ankylosing

spondylitis; goutlike onset; and higher frequency of nail involvement than occurs in uncomplicated sporiasis. The rash may present with arthritis, or, equally may precede or succeed joint involvement. With regard to pain and disability, the prognosis in psoriatic arthritis is better than in rheumatoid arthritis.

(52) Kammer, G.M., Soter, N.A., Gibson, D.J. and Schur, P.H., Psoriatic arthritis: a clinical, immunologic and HLA study of 100 patients, Seminars in Arthritis Rheum. 9:75-97, 1979.

Author's summary:
Patients with psoriatic arthritis have a distribution of synovitis that permits subclassification into three groups: an asymmetric, oligoarticular arthritis (Group I); a symmetric arthritis (Group II), and a spondyloarthritis with or without peripheral arthritis (Group III). Features that distinguish psoriatic arthritis from similar disorders include the paucity of rheumatoid factors; radiographic demonstration of predominantly IP joint involvement of the hands and feet; the presence of onychodystrophy; a clustering of psoriasis and psoriatic arthritis in the first-degree family members, and the significant association of HLA-B27.

Individuals with an asymmetric, oligoarticular arthritis (Group I) experience intermittent exacerbation of synovitis usually responsive to medical therapy; however, about three-fourths of patients sustain a mild or moderately progressive disease course. In contrast, persons with a symmetric arthritis (Group II) experience a slowly destructive arthritis in about one-half of cases. Spondyloarthritis (Group III) may or may not be associated with a peripheral arthritis, and has a course similar to that of other spondyloarthritides. DIP joint involvement occurred frequently in Group I, less frequently in Group II, and rarely in Group III. Arthritis mutilans occurs uncommonly, can evolve rapidly over months or more slowly over years to produce a destructive arthritis, and evolves with equal frequency from each group.

Many patients have hyperuricemia and/or hypercomplementemia. Genetic studies show a significantly decreased prevalence of B7 in all three groups. HLA B27 was significantly increased in Groups II and III. There was a striking increased frequency of antigen pairs A2 and B27 in all three groups.

Patients with psoriatic arthritis, treated early in the disease with aspirin and hydroxychloroquine, often experinece a beneficial response without exacerbation of psoriasis. Patients with destructive disease often responded to the administration of gold salts. Nonsteroidal antiinflammatory agents were useful in suppressing disease activity but did not induce remission. Phenylbutazone and indomethacin suppressed symptoms of spondyloarthritis.

5. *Inflammatory Bowel Disease, Whipple's Disease, and Intestinal Bypass Syndrome*

(53) Morris, R.I., Metzger, A.L., Bluestone, R. and Terasaki, P.I., HL-A-W27 - A useful discriminator in the arthropathies of inflammatory bowel disease, New Engl. J. Med. 290:1117-1119, 1974.

Reviewer's summary:
Six out of eight patients with inflammatory bowel disease and spondylitis were W27 positive (75%). None of 15 patients without arthritis or 8 patients with peripheral arthritis only were W27 positive. The author's concluded that the findings indicated that W27 is a useful clinical and pathogenetic discriminator between the arthropathies of inflammatory bowel disease and identified a set group of patients markedly at risk for the development of spondylitis and perhaps iritis, but not peripheral arthritis.

(54) van den Berg-Loonen, P.M., Dekker-Saeys, A.J., Meuwissen, S.G.M., Nijenhuis, L.E., Histocompatibility antigens and other markers in ankylosing spondylitis and inflammatory bowel disease, J. Rheumatol. Suppl. 3:57-58, 1977.

Author's summary:
An increased frequency of HLA B27 was confirmed in a series of 118 patients with ankylosing spondylitis. This was significantly higher in patients who acquired the disease at an early age. Other deviating antigen frequencies were found to be due to linkage disequilibrium. An increased frequency of antigen BW16 was noted in B27 negative patients. In ulcerative colitis, a significantly raised incidence of A11 was found, as well as an increased frequency of B18 in Crohn's disease. The only deviating frequency from controls for blood and serum groups was in blood group Kell, which was increased in Crohn's disease.

(55) Nicholls, A., Histocompatibility antigens and the arthritis of chronic inflammatory bowel disease, Clin. Rheum. Dis. 3:265-280, 1977.

Author's summary:
No definite association has been shown between Crohn's disease or ulcerative colitis and the distribution of HLA antigens. No association either occurs with the enteropathic arthritis complicating these diseases. HLA-B27 has been found in a high proportion of patients with spondylitis complicating inflammatory bowel disease, although not as high as in 'idiopathic' ankylosing spondylitis. It seems, however, that the possession of B27 in a patient with inflammatory bowel disease confers a greater risk of the development of ankylosing spondylitis than in subjects without bowel disease.

(56) Huaux, J.-P., Fiasse, R., De Bruyere, M. and de Deuxchaisnes, N., HLA B27 in regional enteritis with and without ankylosing spondylitis or sacroiliitis, J. Rheumatol. Suppl. 3:60-63, 1977.

Author's summary:
The incidence of B27 in patients with ankylosing spondylitis associated with regional enteritis was significantly lower than in ankylosing spondylitis without inflammatory bowel disease. It was significantly higher, however, than in a control group of blood donors.

The incidence of B27 was found to be nil in patients with regional enteritis without ankylosing spondylitis, as well as in patients with regional enteritis and asymptomatic radiographic sacroiliitis. Conversely, all patients with regional enteritis, positive for B27, developed ankylosing spondylitis.

(57) Meuwissen, S.G.M., Dekker-Saeys, B.J., Agenant, D. and Tytgat, G.N.J., Ankylosing spondylitis and inflammatory bowel disease. I. Prevalence of inflammatory bowel disease in patients suffering from ankylosing spondylitis, Ann. Rheum. Dis. 37:30-32, 1978.

Author's summary:
To establish the prevalence of inflammatory bowel disease in ankylosing spondylitis (AS), 79 AS patients underwent detailed medical screening, including sigmoidoscopic and roentgenological examination. 48 had gastrointestinal sysptome and the others did not. In 3 patients a diagnosis of Crohn's disease was made which was previously established. In all other patients inflammatory bowel disease could be excluded. The prevalence of inflammatory bowel disease in this series of patients with AS therefore was 3.8%.

(58) Dekker-Saeys, B.J., Meuwissen, S.G.M., Van Den Berg-Loonen, E.M., De Haas, W.H.D., Agenant, D. and Tytgat, G.M.J., Ankylosing spondylitis and inflammatory bowel disease. II. presvalence of peripheral arthritis, sacroiliitis, and ankylosing spondylitis in patients suffering from inflammatory bowel disease, Ann. Rheum. Dis. 37:33-35, 1978.

Author's summary:
To establish the prevalence of peripheral arthritis, radiographic sacroiliitis, and ankylosing spondylitis in patients with inflammatory bowel disease, 58 consecutive patients suffering from ulcerative colitis (UC) and 51 with Crohn's disease (CD) underwent a detailed rheumatological examination. In addition, all patients were screened for the presence of the antigen HLA B27. Peripheral arthritis was found in 14 (8 UC, 6 CD) patients (12.8%); radiographic sacroiliitis was diagnosed in 11 (5 UC, 6 CD)(10.1%), of whom 10 were asymptomatic; and ankylosing spondylitis was diagnosed in 2 UC and 2 CD patients (3.7%); 18.9% of the UC and 3.9% of the CD patients

were HLA B27 positive. One of the 11 patients with radiographic sacroiliitis and 2 of the 4 with ankylosing spondylitis had the HLA B27 antigen.

Peripheral arthritis, radiographic sacroiliitis, and ankylosing spondylitis are apparently frequent manifestations in patients suffering from inflammatory bowel disease. Asymptomatic radiographic sacroiliitis in these patients appears to differ from idiopathic ankylosing spondylitis, both clinically and genetically. Evaluation of subjective rheumatological complaints, necessary for a confident diagnosis of ankylosing spondylitis, according to the New York criteria is difficult during a flare-up of the inflammatory bowel process, as was shown in 4 CD cases with marked limitation of lumbovertebral function and chest expansion, but no radiological abnormalities of the SI joints.

(59) Dekker-Saeys, B.J., Meuwissen, S.G.M., Van Den Berg-Loonen, E.M., De Haas, W.H.D., Meijers, K.A.F. and Tytgat, G.N.J., Ankylosing spondylitis and inflammatory bowel disease. III. Clinical characteristics and results of histocompatibility typing (HLA B27) in 50 patients with ankylosing spondylitis and inflammatory bowel disease, Ann. Rheum. Dis. 37:36-41, 1978.

Author's summary:
A study was made, in co-operation with several gastroenterology and rheumatology centres, of the clinical and genetic characteristics (HLA B27) of 50 patients suffering from both inflammatory bowel disease (38 Crohn's disease (CD), 12 ulcerated colitis (UC) and ankylosing spondylitis (AS), the latter diagnosis being established according to the New York criteria. 20 CD (52.6%) and 8 UC (66.7%) patients were HLA B27 positive. The presence of HLA B27 was studied in relation to clinical parameters, such as first occurrence of symptoms of AS or inflammatory bowel disease (IBD), a history of peripheral arthritis, iridocyclitis, and a positive history of AS or IBD.

Our patients were found to have heterogeneous clinical features: on one side of the spectrum a group of cases was distinguished with the typical characteristics of idiopathic AS, often being HLA B27 positive. On the other side a smaller group of HLA B27 negative patients was observed, with severe intestinal inflammatory pathology, lacking most of the typical clinical features of idiopathic AS ('secondary' form of AS). Finally, between there two extremes a group of patients was found with less pronounced clinical or genetic characteristics. These different clinical and histocompatibility patterns suggest a mixed aetiopathogenesis of AS in IBD patients. Such a 'syndrome' of AS might harbour both idiopathic AS and forms of AS 'secondary' to the intertinal inflammatory pathology.

(60) Canoso, J.J., Saini, M. and Hermos, J.A., Whipple's disease and ankylosing spondylitis simultaneous occurrence in HLA-B27 positive male, J. Rheumatol. 5:79-84, 1978.

Author's summary:
A 57 year old male had recurrent arthritis and uveitis for 34 years, spinal symptoms for 10 years, and malabsorption for four months leading to the diagnosis of ankylosing spondylitis and Whipple's disease. HLA-B27 was positive. Out of the four cases of Whipple's and ankylosing spondylitis in the literature, only one had been tested for HLA-B27 and was found to be negative.

(61) Rose, E., Espinoza, L.R. and Osterland, C.K., Intestinal bypass arthritis: association with circulating immune complexes and HLA B27, J. Rheumatol. 4:129-134, 1977.

Author's summary:
Two patients are described in whom arthritis following intestinal bypass surgery for obesity was associated with the presence of circulating immune complexes (CIC) and HLA B27. The arthritis was characteristically intermittent and controlled by low dose prednisone, indomethacin, and tetracycline therapy. The findings suggest that immune complexes play a role in the pathogenesis of arhtritis associated with this condition, and that perhaps the association with HLA B27 may predispose to the development of this complication.

(62) Reynolds, T.B., Medical complications of intestinal bypass surgery, Adv. Intern. Med. 23:47-59, 1978.

Reviewer's summary:
The following medical complications of intestinal bypass surgery are reviewed: electrolyte depletion, oxaluria with renal stone formation, polyarthritis, liver disease, also listed are hair loss, colonic pseudo-obstruction, pneumatosis intestinalis, tuberculosis, acute pancreatitis, "bypass enteritis" and gastrointestinal hemorrhage from an unknown site.

(63) Zapanta, M., Aldo-Benson, M., Biegel, A. and Madura, J., Arthritis associated with jejunoileal bypass. Clinical and immunologic evaluation, Arthritis Rheum. 22:711-717, 1979.

Author's summary:
Arthritis is a common complication of small bowel bypass, occurring in 5-20% of the postsurgical patients. Thirteen patients with arthritis related to jejunoileal bypass were studied. These patients had a symmetrical polyarthritis, and 8 also had extraarticular connective tissue disease manifestations. Immunologic evaluations were done on these patients and on a control group of 12 age- and sex-matched postintestinal bypass patients without arthritis. The incidence of positive ANA, rheumatoid factors, immune complexes, and antibodies to intestinal flora was the same in both groups. Patients

in both groups showed similar changes in numbers of circulating T and B lymphocytes. More patients in the group with arthritis than in the control group had elevated IgA levels (38% versus 8%), but the difference was not significant ($P > 0.05$). This study demonstrates that immunologic abnormalities occur after jejeunoileal bypass irrespective of the onset of arthritis or related symptoms. No specific immunologic abnormalities could be associated with the arthritis occurring after small bowel bypass.

(64) Ginsberg, J., Quismorio F.P. Jr., DeWind, L.T., Mongan, E.S., Musculoskeletal symptoms after jejunoileal shunt surgery for intractable obesity. Clinical and immunologic studies, Amer. J. Med. 67:443-448, 1979.

Author's summary:
We studied a group of 27 patients, who underwent jejunoileal bypass surgery for the treatment of morbid obesity, because of the occurrence of musculoskeletal symptoms. These patients were divided into three clinical groups: Group 1 consisted of 13 patients in whom arthritis, arthralgias and morning stiffness and/or myalgia developed following intestinal surgery. Group II consisted of seven patients who had similar musculoskeletal complaints but whose symptoms could not be definitely related to surgery because they antedated the surgery or because of the presence of other known causes of arthritis. Group III consisted of seven control patients who were free of musculoskeletal symptoms prior to or after surgery.

Mixed cryoglobulins consisting of immunoglobulin G, immunoglobulin M and the C1q component of complement (C1q) were commonly found in patients in groups I and II but not in group III. Antibodies to Escherichia coli and rheumatoid factor were found to be selectively concentrated in the cryoproteins indicating that these antibodies participated in the formation of these immune complexes. Circulating immune complexes were detected by a platelet aggregation test in 30 per cent of the patients in group I, 40 per cent of those in group II and none of those in group III. HL-A typing showed no significant correlation with any particular tissue type in the patients.

(65) Williams, H.J., Samuelson, C.O. Jr., Zone, J.J., Nodular nonsuppurative panniculitis associated with jejunoileal bypass surgery, Arch. Dermatol. 115:1091-1093, 1979.

Author's summary:
A 32-year-old woman underwent jejunoileal bypass surgery for morbid obesity. Her postoperative course was marked with many complications of this type of surgery. In addition, tender, erythematous nodules developed on her legs and abdomen that were grossly and microscopically consistent with nodular nonsuppurative panniculitis. She did not have any condition or disease previously reported to be associated with nodular nonsuppurative inflammation. The nodular panniculitis in this patient appears to be a new complication of small-bowel bypass surgery.

(66) Clegg, D.O., Samuelson, C.O. Jr., Williams, H.J. and Ward, J.R., Articular complications of jejunoileal bypass surgery, J. Rheumatol. 7:65-70, 1980.

Author's summary:
Articular complications are now frequently recognized with jejunoileal bypass surgery for morbid obesity. We have evaluated 6 referred patients with these problems and 50 consecutive patients who had this procedure. The arthritis is variable but usually affects multiple joints. Four patients were seen during acute attacks of arthritis and all had cryoprecipitable material in their sera and plasma. Three of these 4 patients had evidence of Group D streptococcal antigen present while their joint disease was active, suggesting a possible role for bacterial antigens in the pathogenesis of the arthritis of jejunoileal bypass.

(67) Utsinger, P.D., Bypass disease: A bacterial antigen-antibody systemic immune complex disease, Arthritis Rheum. 23:000, 1980 (abstract).

Author's summary:
We have established a national registry of complications following intestinal bypass surgery, and have now prospectively studied 85 patients with rheumatic complaints. Seventy patients had a characteristic arthritis which was remittent and intermittent, involving primary knees, ankles, PIP, MCP, and wrists, and which was non-deforming. Four patients developed a chronic non-relapsing symmetrical polyarthritis, associated in two with juxta-articular erosions, and rheumatoid factor, and responding to gold therapy. Four patients had axial skeletal disease with sacroiliitis, decreased lumbar spine motion, and the presence of HLA-B27. Four patients had an intermittent moncarthritis of the knee. Three patients had priximal muscle pain without arthritis or weakness, mildly increased ESR and normal muscle enzymes. Synovial fluid analysis in 65 patients showed from 500 to 39,000 WBC with 10 to 98% pmn. Sixty-nine patients had cutaneous involvement including papulovesicles, vesiculopustules, E nodosum and angioedema. Seventeen patients had Raynaud's phenomemon, 16 paresthesias, 11 fever, 7 pleural effusions, 3 renal insufficiency without oxalosis, 2 pulmonary infiltrates, and 1 pericarditis.

Cryoproteins were found in the serums of 78 patients and consisted of IgG, IgG_3, C1q, C_3 and C_4. Immune complexes were found by the Raji cell technique in 79 patients and by C1q precipitation in 62. Bacterial antigen was found in the cryoproteins of 11 patients by gas chromatography, immunofluorescence, counter immunoelectrophoresis, and complex dissociation by competitive binding with purified bacterial antigen.

Deposits of bacterial antigen, IgG_1, IgG_3, and C_3 were found in the dermal-epidermal junction, the renal glomerulus, and the pulmonary alveolar walls in 7 patients. Acid - micro - elution studies of tissue documented the presence of anti-bacterial antibody in

these depostis.

In consideration of the extensive organ damage which may follow intestinal bypass surgery, it seems prudent that a moratorium be placed on these procedures until risks and benefits can be more clearly defined. We think an appropriate name for these complications is 'bypass disease.'

6. *Juvenile Arthritis*

(68) Rachelefsky, G.S., Terasaki, P.I., Katz, R. and Stiehm, E.R., Increased prevalence of W27 in juvenile rheumatoid arthritis, New Engl. J. Med. 290:892-893, 1974.

Author's summary:
Of the 26 patients with juvenile rheumatoid arthritis in whom typing was ascertained, 42 per cent were found to have the W27 antigen in contrast to 6 per cent in the controls. The difference was highly significant ($p < 0.0001$ by chi-square analysis). HL-A1 was decreased, although correction of the p value by multiplication by the number of comparisons reduces the p value to nonsignificant levels.

(69) Edmonds, J., Morris, R.I., Metzger, A.L., Bluestone, R., Terasaki, P.I., Ansell, B. and Bywaters, E.G.L., Follow-up study of juvenile chronic polyarthritis with particular reference to histocompatibility antigen W.27, Ann. Rheum. Dis. 33:289-292, 1974.

Author's summary:
As the long-term follow-up of children with chronic polyarthritis has suggested that this is not a homogeneous group, tissue typing was performed on 46 patients whose duration of disease was sufficiently long for the pattern to have become established. Six of the seven patients whose illness had begun as juvenile chronic polyarthritis and who had progressed to ankylosing spondylitis had W.27, as did eight patients with sacroiliiitis of ankylosing type. Acute iritis had occurred only in those with sacroiliiitis; fourteen of the fifteen with sacroiliiitis were male. Four of twenty patients with juvenile chronic polyarthritis without sacroiliiitis also had W.27. By contrast, none of the eleven patients who were seropositive and had a pattern of illness resembling adult rheumatoid arthritis were of this tissue type.

(70) Nissila, M., Elomaa, L., Tiilikainen, A., HL-A antigens in juvenile rheumatoid arthritis, New Engl. J. Med. 293:430, 1975.

Author's summary:
Our results on HL-A typing of 47 patients with juvenile rheumatoid arthritis treated at the Rheumatism Foundation Hospital, Heinola, did not show an increased frequency of HL-A27. Neither could we demonstrate an excess of W10.

The association between HL-A27 and juvenile rheumatoid arthritis must then be a delicate one, and may be demonstrable only in selected series of patients. Perhaps the course of the disease will eventually be different in patients with and without HL-A27.

Further studies of possible associations between HL-A genes and juvenile rheumatoid arthritis seem to be indicated.

(71) Gibson, D.J., Carpenter, C.B., Stillman, J.S. and Schur, P.H., Re-examination of histocompatibility antigens found in patients with juvenile rheumatoid arthritis, New Engl. J. Med. 293:636-638, 1975.

Author's summary:
One hundred and twenty-three patients with juvenile rheumatoid arthritis and a similar number of controls were tissue typed for 30 HL-A antigens to determine if there were any associations between particular HL-A antigens and the disease. None were found. However, HL-A7 was found more frequently in patients with juvenile rheumatoid arthritis demonstrating tenosynovitis than in the population with juvenile rheumatoid arthritis as a whole. These observations fail to support the contention of others that HL-A-W27 is found more frequently than expected in such patients.

(72) Ansell, B.M., Chronic arthritis in childhood, Ann. Rheum. Dis. 37: 107-120, 1978.

Reviewer's summary:
This is the text of the Heberden Oration for 1977. It is an excellent discussion of the clinical aspects of arthritis in childhood. It includes a description and a 15 year follow-up of a large number of cases. On the basis of long-term follow-up the patients are sub-grouped into juvenile ankylosing spondylitis, 90% of which were found to be HLA-B27 positive. Sero-positive juvenile rheumatoid arthritis. Sero-negative chronic arthritis, which in turn is defined at onset as systemic monarticular oligoarthritis for two or three joints and as polyarticular. Also discussed are the development of psoriatic arthritis and amyloidosis.

(73) Schaller, J.G., The seronegative spondyloarthropathies of childhood, Clin. Ortho. 143:76-83, 1979.

Author's summary:
Most chronic arthritis in childhood is seronegative. Within "JRA" several distinct subgroups exist: one of these (pauciarticular disease type II) affects predominantly boys more than 8 years of age. It is clearly associated with sacroiliitis, HLA-B27, family history of spondyloarthropathy, and subsequent ankylosing spondylitis in an as yet undefined percentage of patients. This type of disease is probably classified appropriately with the spondyloarthropathies, although patients often may fulfill diagnostic criteria for "JRA" in the first years of their disease, and accounts for about 15% of "JRA".

The other JRA subgroups do not appear to have features of seronegative spondyloarthropathy. Reiter's syndrome and psoriatic arthritis exist in children, but appear to be rare. The arthritis of inflammatory bowel disease in childhood resembles that in adulthood. The recognition of spondyloarthropathy in children, particularly the sizable group of patients with "JRA" pauciarticular disease type II, is of practical importance to permit proper therapy, follow-up, and prevention of deformity.

7. *Seronegative Rheumatoid Arthritis*

(74) Pasternack, A. and Tiilikainen, A., HLA-B27 in rheumatoid arthritis and amyloidosis, Tissue Antigens 9:80-89, 1977.

Author's summary:
To study the role of genetically determined immune responsiveness in the pathogenesis of systemic amyloidosis complicating rheumatoid arthritis the HLA antigens were identified in 26 patients with rheumatoid arthritis complicated by secondary amyloidosis, in 44 patients with rheumatoid arthritis, and in 11 patients with secondary amyloidosis of non-rheumatoid origin. Subjects with ankylosing spondylitis, sacroiliitis without peripheral polyarthritis, Reiter's disease, reactive arthritis, erosive osteoarthritis, psoriatic arthropathy, systemic lupus erythematosus or arthritis associated with a gastrointestinal involvement were excluded from the study. Patients with amyloidosis secondary to rheumatoid arthritis had a high frequency of the HLA specificity B27 and of the haplotype likely to bear A2,B27. The association with B27 was closest in the group of male patients with amyloidosis whose rheumatoid arthritis had begun at an early age and who lacked demonstrable rheumatoid factor in serum. These patients may represent a genetically determined subentity of rheumatoid arthritis.

(75) Esdaile, J.M., Dwosh, I.L, Urowitz, M.B. and Falk, J., HLA B27 in rheumatoid factor-negative polyarthritis, Ann. Inter. Med. 86:699-702, 1977.

Author's summary:
Eighty-three consecutive patients with rheumatoid factor-negative polyarthritis seen during a 1-year period were evaluated clinically, radiologically, and with the B27 test. Patients with definite spondylitis, juvenile chronic polyarthritis, a collagen disease, a known metabolic arthropathy, or primary generalized osteoarthritis were excluded. The patients could be classified into two groups independent of any knowledge of B27 testing. Twenty-five had a spondylitic "varient" syndrome. These could be diagnosed on clinical grounds, and included a male preponderance and a high frequency of B27 positivity. Fifty-eight patients, who could generally be classified by American Rheumatism Association criteria as having definite or classical rheumatoid arthritis, included a female preponderance

and a normal prevalence of B27. Thus the B27 test was not more helpful than clinical diagnosis in the classic spondylitic variant syndromes, nor did it separate out a population of patients from among the seronegative rheumatoid arthritis group.

(76) Sebes, J.I., Nasrallah, N.S., Rabinowitz, J.G. and Masi, A.T., The relationship between HLA-B27 positive peripheral arthritis and Sacroiliitis, Radiology 126:299-302, 1978.

Author's summary:
HLA typing for B27 antigen is a helpful diagnostic aid in the classification of peripheral arthritis patients (especially young patients) who are rheumatoid factor negative. We studied 109 patients with seronegative peripheral arthritis belonging to various clinical categories; 23% proved to be B27 positive in comparison to 7% of normal controls. In spite of a paucity of spinal manifestations there was a high prevalence of sacroiliitis (83%) in the B27 positive peripheral arthritis patients as opposed to only 21% in those without B27 antigen. HLA-B27 typing and radiographs of the sacroiliiac joints are important differential tests.

8. Uveitis

(77) Brewerton, D.A., Nicholls, A., Caffrey, M., Walters, D., James, D.C.O., Acute anterior uveitis and HL-A 27, Lancet 1:994-996, 1973.

Author's summary:
The histocompatibility antigen HL-A27 (W 27) was identified in 26 out of 50 patients with acute anterior uveitis, compared with 2 out of 50 controls. 21 patients had significant, associated diseases, and 18 of these had HL-A27. HL-A27 was present in 8 of the 29 patients with no associated diseases.

(78) Mapstone, R., Woodrow, J.C., Acute anterior uveitis and HL-A 27, Lancet 1:681-682, 1974.

Author's summary:
Of 59 petients with anterior uveitis, 32 (54%) had the HL-A 27 antigen, of whom 15 had associated systemic disease, including 10 with ankylosing spondylitis (2 with psoriasis), 1 with sacro-iliitis, and 2 with Reiter's syndrome (1 with psoriasis). In this group there were 12 males and 3 females. 41 patients had no systemic disease and, of these, 17 had HL-A 27 (41.5%, compared with the control figure of 7.7%). 8 of these 17 patients were males, the ages ranging from 15 to 58 years, the mean being 35 years. 9 were females with an age range of 22 to 70 years. Whilst, therefore, approximately 30% of patients attending with anterior uveitis are HL-A 27 positive and show no systemic manifestations, our results so far show an equal sex incidence and no particular group of females under the age of 35 years.

(79) Ehlers, N., Kissmeyer-Nielsen, F., Kjerbye, K.E., Lamm, L.U., HL-A27 in acute and chronic uveitis, Lancet 1:99, 1974.

Author's summary:
We have studied 30 Caucasian patients with uveitis, admitted to the opthalmological department during the years 1969-73. The control series consists of 562 similarly typed blood-donors, and no matching with the patient group was attempted. The most important finding is a highly significant increased occurrence of HL-A27 from 8% in the controls to 71% in 17 patients with recurrent acute anterior uveitis ($p < 10^{-7}$, Fisher test). Among these patients 6 were reported to have arthritis, of whom 5 possessed HL-A27. In 13 patients with chronic uveitis the frequency of HL-A27 was not increased, and the only significant deviation in HL-A antigens was lack of HL-A1 ($p < 0.005$). This may, however, be considered a chance effect.

(80) James, D.G., Acute anterior uveitis, Clin. Rheum. Dis. 3:299-313, 1977.

Author's summary:
Until recently it was not suspected that heredity influenced susceptibility to acute anterior uveitis, although uveitis was known to be associated with several diseases in which family studies had demonstrated genetic factors, including ankylosing spondylitis, chronic inflammatory bowel disease, Reiter's disease, chronic juvenile polyarthritis, and sarcoidosis. Knowledge of the inheritance of ankylosing spondylitis led to the discovery of the relationship between ankylosing spondylitis and HLA-B27, and this in turn led to evidence that the same antigen was present in almost half the patients attending ophthalmic clinics with acute anterior uveitis and no rheumatic disease.

9. *Other Conditions: Frozen Shoulder, Asbestosis*

(81) Bulgen, D.Y., Hazleman, B.L., Voak, D., HLA-B27 and frozen shoulder, Lancet 1:1042-1044, 1976.

Author's summary:
Histocompatibility antigens were determined in 38 patients with frozen shoulder and 216 normal blood-donors. HLA-B27 was significantly more common in patients with frozen shoulder (42%) than in the controls (10%). The distribution of the other 19 histocompatibility antigens was similar in the patient and control groups. This result may be associated with the suggested immunological pathogenesis of the condition.

(82) Merchant, J.A., Klouda, P.T., Soutar, C.A., Parkes, W.R., Lawler, S.D., Turner-Warwick, M., The HL-A system in asbestos workers, Br. Med. J. 1:189-191, 1975.

Author's summary:
In a study of the HL-A system in 56 selected asbestos workers referred to the Pneumoconiosis Medical Panel with definite or suspected asbestosis, the W 27 antigen was found more often than among a control population. Six of the 10 asbestos workers with the W 27 antigen had definite radiographic evidence of asbestosis compared to 13 out of 46 without the W 27 antigen. These observations, if confirmed, suggest that the W 27 antigen may provide a useful marker of an enhanced susceptibility to the tissue-damaging effects of asbestos dust.

(83) Evans, C.C., Lewinsohn, H.C., Evans, J.M., Frequency of HLA antigens in asbestos workers with and without pulmonary fibrosis, Br. Med. J. 1:603-605, 1977.

Author's summary:
HLA antigens were determined in 37 patietns with asbestosis and 37 matched controls with equivalent asbestos exposure but no pulmonary fibrosis. All had worked in the same textile factory. No significant differences in the prevalence of antigens were found between the two groups or between either group and controls who had not been exposed to asbestos. When the data were combined with findings from other pilot studies the previously suggested association between asbestosis and HLA-B27 was not confirmed. Subjects who were positive for HLA-B12 tended to have advanced radiographic fibrosis. Asbestos workers without pulmonary fibrosis had an unexpectedly high frequency of HLA-BW5, which might indicate that this antigen protects against the development of pulmonary fibrosis.

10. Diseases of the Spine Not Associated with B27

(84) Shapiro, R.F., Utsinger, P.D., Wiesner, K.B., Resnick, D., Bryan, B.L. and Castles, J.J., The association of HL-A B27 with Forestier's disease (vertebral ankylosing hyperostosis), J. Rheumatol. 3:4-8, 1976.

Author's summary:
Despite the lack of apophyseal or sacroiliac joint involvement, Forestier's disease (vertebral ankylosing hyperostosis) shares with the inflammatory forms of spondylitis, the roentgenographic appearance of spinal new bone formation. Because of this apparent similarity, the prevalence of the HL-A B27 antigen was determined in 47 white patients with Forestier's disease. Sixteen of the patients (34 per cent) possessed the B27 antigen ($P < 0.001$). The mere presence of B27 therefore, does not confirm the diagnosis of inflammatory spondylitis in all patients with roentgenographic evidence of osseous bridging. Applying available epidemiologic information, these data further suggest that patients with the B27 antigen may be at substantial risk of developing Forestier's disease. As Forestier's disease and virtually all of the other B27 associated arthropathies manifest abundant new bone, an association may exist between this

antigen and genes controlling new bone formation.

(85) Brigode, M. and Francois, R.J., Histocompatibility antigens in vertebral ankylosing hyperostosis, J. Rheumatol. 4:429-434, 1977.

Author's summary:
All known A, B, and C HLA antigens were determined in 50 white patients with vertebral ankylosing hyperostosis. A statistically significant decrease was found for the A9 and A11 specificities. Only three (6%) of the patients possessed the B27 antigen, a frequency which is not different from that of a control population. B27 therefore does not seem to be linked to abundant new bone formation.

(86) Modena, V., Migone, N., Daneo, V., Carbonara, A.O., de Vittorio, S. and Viara, M., Spondylodiscitis and ankylosing spondylitis: HLA typing and nosological implications, Ann. Rheum. Dis. 37:510-512, 1978.

Author's summary:
Nine cases from among 64 patients with ankylosing spondylitis (AS) are described. In addition to bilateral sacroiliitis these cases had a peculiar type of spondylodiscitis characterized by quite diffuse and marked sclerosis of multiple vertebral bodies, with only minimal erosions of the adjacent vertebral plates while classical syndesmophytosis was absent. The antigen HLA-B27 was found only in 1 of these 9 cases. This type of spondylodiscitis could discriminate among all the patients with AS a subgroup with a peculiar clinical pattern and a probably distinctive pathological mechanism.

(87) De Bosset, P., Gordon, D.A., Smythe, H.A., Urowitz, M.B., Koehler, B.E. and Singal, D.P., Comparison of osteitis condensans ilii and ankylosing spondylitis in female patients: clinical, radiological and HLA typing characteristics, J. Chron. Dis., 31:171-181, 1978.

Author's summary:
A study comparing 12 patients with ankylosing spondylitis (AS) to 25 with osteitis condensans ilii (OCI), referred to a rheumatic disease center, was carried out to determine whether OCI represents a varient of AS in women. In the group with OCI, chronic lumbodorsal pain was present in 9, 36% a 'fibrositis' syndrome in 6, 24%, and 16, 64% had recurrent episodes of polyarthralgia. A definite arthritis with effusion developed in 10 patients, 40%. No patient with OCI had iritis or colitis, whereas 4 patients with AS had iritis and four had colitis. Radiographs of the spine showed no evidence of spondylitis in the OCI group. Of the 25 patients with OCI, only 2.8% were HLA B27 positive compared with 11 of 12 patients with AS, 92%. These results suggest that OCI is not a variant of AS in women.

11. *HLA-B27 and Other Histocompatibility Antigens*

a. B27 Serology

(88) Thorsby, E., Kissmeyer-Nielsen, F. and Svejgaard, A., New alleles of the HL-A system: serological and genetic studies, In Histocompatibility Testing 1970, P.I. Terasaki, ed., Munksgaard, Copenhagen, 1970 pp 137-151.

Reviewer's summary:
This paper describes seven new HLA-A and B antigens, including ILN, KH, and Li of the LA series, and FJH,LND,AA, and SL of the Four series. The antigen detected with serum FJH later became known as W27.

(89) Schwartz, B.D., Luehrman, L.K. and Rodey, G.E., Public antigenic determinant on a family of HLA-B molecules. Basis for cross-reactivity and a possible link with disease predisposition, J. Clin. Invest. 64: 938-947, 1979.

Author's summary:
Serologic cross-reactivity among allelic gene products commonly occurs in the HLA complex, but the molecular basis of these serologic phenomena is incompletely characterized. Because of strong cross-reactivity among antigens comprising the B7 cross-reactive group (i.e. HLA-B7,Bw22,B27,B40, and Bw42) and because of the association of several antigens of this group with spondyloarthropathies, we initiated a study of the chemical basis of cross-reactivity among this group of antigens. Using classic serologic procedures, I-Protein A binding assay, and chemical immunoprecipitation techniques, we have defined a new antigenic determinant, tentatively designated "X", which is present on certain HLA-B molecules. By a series of sequential immunoprecipitation experiments, X was shown to be a "public" antigenic determinant distinct from the "private" determinants B7,Bw22,B27, and B40, but present on the same 44,000-dalton glycoprotein molecules. The implications of this finding regarding disease predisposition and HLA typing as a diagnostic aid are discussed.

b. Other B Locus Antigens

(90) van den Berg-Loonen, E.M., Dekker-Saeys, B.J., Meuwissen, S.G.M., Nijenhuis, L.E. and Engelfriet, C.P., Histocompatibility antigens and other genetic markers in ankylosing spondylitis and inflammatory bowel diseases, J. Immunogenetics 4:167-175, 1977.

Author's summary:
Of 118 Dutch patients suffering from ankylosing spondylitis (AS) 81.4% were found to be positive for the HLA antigen B27. The B27 frequency proved to be significantly higher in patients in whom the disease had an eraly onset.

In addition to B27, another HLA antigen may be associated with AS; the antigen Bw16 was found to be significantly increased in B27 negative patients.

HLA phenotype frequencies were also determined in 109 patients with idiopathic inflammatory bowel disease (IBD). In fifty-eight ulcerative colitis (UC) patients a raised incidence of A11 was noticed. In fifty-one patients with Crohn's disease (CD) the antigen B18 showed an increased frequency. Both deviations were statistically significant. In thirty-nine patients suffering from both AS and IBD 50% proved to be B27 positive, which is significantly different from the B27 frequency in patients with AS alone. In the B27 negative patients with AS and IBD an increased frequency of Bw16 was also shown.

(91) Arnett, F.C. Jr., Hochberg, M.C. and Bias, W.B., Cross-reactive HLA antigens in B27-negative Reiter's syndrome and sacroiliitis, The John Hopkins Med. J. 141:193-197, 1977.

Author's summary:
Proposed mechanisms to explain the association of HLA-B27 with Reiter's syndrome (RS) and ankylsoing spondylitis (AS) include abnormal immune response genes linked to HLA or a direct role for HLA antigens in disease pathogenesis. Our studies provide indirect evidence to support the latter hypothesis. Seventy-nine patients (44 with RS, 27 with AS and 8 with idiopathic sacroiliitis {SI}) were evaluated clinically and by HLA phenotyping. Of the 10 patients with RS who were B27-negative, 7 (70%) had another B locus antigen that was immunologically cross-reactive with B27 (B7-group antigen). These included B7 in two, BW22 in four, and BW42 in one. Four of eight patients with sacroiliitis alone had B27, but the remaining four all had B7. Two B27-negative AS patients had no B7-group antigens. Thus, 69% of B27-negative patients had cross-reactive HLA antigens.

(92) Khan, M.A., Kushner, I., Braun, W.E., B27-negative HLA-BW16 in ankylosing spondylitis, Lancet 1:1370-1371, 1978.

Author's summary:
We have studied 10 B27-negative unrelated White patients with primary A.S., 1 of them a female. Patients and controls were typed for twenty-eight HLA antigens of A and B loci. 4 patients (40%) had Bw16 compared with 3.1% of 444 B27-negative normal White controls (χ^2 with Yates' correction=25.87; P {corrected for number of antigens} <0.014), confirming the findings of van den Berg-Loonen et al. 2 of 4 B27-negative patients with psoriatic spondylitis also possessed Bw16.

c. *Other HLA Loci*

(93) Duquesnoy, R.J., Kozin, F. and Rodey, G.E., High prevalence of HLA-B27, Cw1 and Cw2 in patients with seronegative spondyloarthritis, Tissue Antigens 12:58-62, 1978.

Author's summary:
These studies demonstrated that not only B27 but also Cw1 and Cw2 occur with increased frequency in patients with seronegative polyarthritis.

The frequency of Cw1/2 in 43 B27-negative patients was significantly higher than that in normal B27-negative Caucasoid blood donors (35% vs. 13%) and was even higher in patients with sacroiliiitis and spondylitis than in patients without sacroiliac joint involvement (80% vs. 21%). Although a relatively small number of patients with ankylosing spondylitis was tested, we observed that all five (of 29) patients who were negative for B27 were positive for Cw1/2. Three B27-negative patients with Reiter's syndrome were also negative for Cw1/2 and none exhibited sacroiliac joint disease. Thus, the presence of Cw1 or Cw2 in B27-negative patients with seronegative polyarthritis may be associated with increased incidence of sacroiliiitis and spondylitis.

(94) Arnason, A., Thorsteinsson, J., Sigurbergsson, K., Ankylosing spondylitis HLA-B27 and Bf, Lancet 1:339-340, 1978.

Author's summary:
We have typed 19 Icelandic patients with ankylosing spondylitis (AS), all of whom had B27, and 46 individuals with B27 but without symptoms, and sufficient relatives to define the haplotypes. All A.S. patients were Bf^S while 23 of the controls had Bf^F and 23 had Bf^S. We consider this clear evidence that the predisposing determinant is either a "special B27", or at neither the HLA-B nor the Bf locus but on the Bf side of the HLA-B locus.

(95) Wells, L.J., Edwards, J.H., Webley, M., James, D.C.O., Brewerton, D.A., Mackintosh, P., Meakin, M., Ankylosing spondylitis, HLA, and Bf, Lancet 1:104-105, 1979.

Author's summary:
While we see no reason to doubt the relative protection some B27-Bf(F) haplotypes can provide in Iceland, compared with some B27-Bf(S) haplotypes, there is limited evidence of any such difference in Italy or England, and therefore limited evidence incriminating loci other than HLA-B27. The probability of the finding of Arnason et al. arising by chance would seem low, but it is not amenable to any simple computation.

(96) Braun, W.E., Dejelo, C.L., Clough, J.D., Beck, K.A., Schacter, B.Z., Khan, M.A., No association of known DR antigens with ankylosing spondylitis, New Engl. J. Med. 298:744-745, 1978.

Reviewer's summary:
Twenty-two patients with classic ankylosing spondylitis were studied using the 180 DR antiserums of the Oxford Workshop, which define 7 DR antigens. Of the 22 patients with ankylosing spondylitis 16 were white (13 positive and 2 negative for B27) and 6 were American Blacks

(1 positive and 5 negative for B27). DR7 was not found in any of the 22 patients, the frequency of the other DR antigens was not different from controls.

d. Different Ethnic Groups

(97) Gofton, J.P., Chalmers, A., Price, G.E. and Reeve, C.E., HL-A 27 and ankylosing spondylitis in B.C. Indians, J. Rheumatol. 2:314-318, 1975.

Author's summary:
HL-A antigens were determined in Haida and Bella Coola native Indians, two communities known to have a high prevalence of ankylosing spondylitis. Tests were conducted on those with x-ray evidence of sacro-iliitis and on a sample of the community at large. Sacro-iliitis was found to prevail in approximately 10 per cent of adult Haida males and in over two per cent of Bella Coola adult males. Of 20 Haidas with sacro-iliitis, 17 were HL-A 27 positive. Fifty per cent of the Haida community at large were HL-A 27 positive. Three Bella Coolas known to have sacro-iliitis were all HL-A 27 positive, while 25 per cent of the community sampled at large were HL-A positive. About one in five adult Haida males who were HL-A 27 positive showed evidence of sacro-iliitis, a proportion close to that ascertained in Caucasian communities. It would appear, therefore, that the risk of disease in HL-A 27 positive Bella Coola males is considerably lower.

(98) Sonozaki, H., Seki, H., Chang, S., Okuyama, M., and Juji, T., Human lymphocyte antigens, HL-A27, in Japanese patients with ankylosing spondylitis, Tissue Antigens 5:131-136, 1975.

Author's summary:
A high association of HL-A27 specificity with ankylosing spondylitis was found in Japanese patients in spite of a very low frequency of this specficity in a normal Japanese population. These findings coincide well with those in Caucasian patients, and indicate the strong relationship between the susceptibility to ankylosing spondylitis and HL-A27 specificity beyond racial differences.

No particular HL-A patterns were noted in patients with the ossification of the posterior longitudinal ligament of the cervical vertebrae. This observation provides an evidence that this disease is etiologically different from ankylosing spondylitis.

(99) Searles, R.P., Voyles, W.F., Billowitz, E., Troup, G.M. and Messner, R.P. Prevalence of HLA-B27 and sacroiliitis in a prospective study of Zuni Indians, Tissue Antigens 14:174-176, 1979.

Author's summary:
Previous investigations of the association of B27 and back disease in non-Indian populations have been retrospective for X-ray evidence of sacro-iliitis or chronic back pain. Our data represent a prospective study of

HLA-B27 related back disease in the Zuni. The results show that four out of seven (53%) B27 positive males have either X-ray evidence of sacroiliiitis or positive physical findings on back examination.

(100) Calin, A., Bennett, P.H., Jupiter, B.J. and Terasaki, P.I., HLA B27 and sacroiliiitis in Pima Indians - association in males only, J. Rheumatol. Suppl. 3:44-48, 1977.

Author's summary:
Since HLA B27 and ankylosing spondylitis are more common in American Indians than other Americans, the association between radiological sacroiliiitis (SI) and HLA B27 was examined among the Pima Indians. SI (grade II to IV) was found in 20 per cent of randomly selected Pima adults. B27 was present in 50 per cent of males, but in only nine per cent of females with SI, vs. a population frequency of 18 per cent. Among first degree relatives of probands with SI, radiologic changes were found no more frequently than in a randomly selected age matched control series. Uveitis occurred in 18 per cent of the B27 positive subjects, but in only five per cent of the B27 negative subjects ($p < 0.05$). B27 was associated with SI and uveitis in Pima males, but no association was demonstrated between B27 and SI in Pima females.

(101) Khan, M.A., Braun, W.E., Kushner, I., Grecek, D.E., Muir, W.G. and Steinberg, A.G., HLA B27 in ankylosing spondylitis: differences in frequency and relative risk in American Blacks and Caucasians, J. Rheumatol. 3:39-43, 1977.

Author's summary:
Twenty-eight HLA alleles of the A and B loci were determined in 23 American Blacks and 50 Caucasians with primary ankylosing spondylitis (AS). The prevalence of HLA B27 was significantly increased in American Black patients (48 per cent) vs. Black controls (two per cent), but was much less than the 94 per cent found in Caucasian patients (controls eight per cent). The lower prevalence of B27 in American Black patients vs. Caucasian patients was significant ($p < 0.001$), and indicated that susceptibility to AS is not as closely associated with B27 in Blacks as in Caucasians. No other HLA antigen was significantly associated with AS in either racial group. Among B27 positive individuals, the relative risk of developing AS was significantly lower in American Blacks than in Caucasians. These data indicate that for diagnostic purposes, the absence of B27 is less important in ruling out AS in Blacks than in Caucasians.

(102) Khan, M.A., Kushner, I. and Braun, W.E., A subgroup of ankylosing spondylitis associated with HLA-B7 in American Blacks, Arthritis Rhuam. 21:528-530, 1978.

Author's summary:
In a study of 34 American black patients with primary ankylosing spondylitis, 18 were found to be HLA-B27-negative. Of these, 10 possessed

HLA-B7 (55.6%) compared to 23.7% of 59 B27-negative black controls ($P < 0.025$, relative risk = 4). On comparing these 10 B7-positive patients (group I) with 16 B27-positive black patients (group II), a difference in mean age at onset of disease was found: 33.6 years in group I and 22.2 years in group II ($P < 0.005$). In addition, a family history of ankylosing spondylitis was absent in group I patients but present in 6 patients in group II ($P = 0.034$). These findings indicate an association between HLA-B7 and ankylosing spondylitis in American blacks and suggest that these patients who lack B27 but possess B7 represent a subgroup of patients with this disease.

(103) Brautbar, C., Porat, S., Nelken, D., Gabriel, K.R. and Cohen, T., HLA B27 and ankylosing spondylitis in the Israeli population, J. Rheumatol. Suppl. 3:24-32, 1977.

Author's summary:
The distribution of 24 HLA antigens of the A and B loci was investigated in 38 Israeli ankylosing spondylitis (AS) patients of various ethnic origins. This was compared with the distribution in rheumatoid arthritis (RA) and osteoarthritis (OA), as well as in 456 controls representing the Jewish population and 260 controls representing the Arab population. Included in the study were Ashkenazi Jews and non-Ashkenazi Jews, as well as Moslem and Christian Arabs.

The frequency of HLA B27 among AS patients (79 per cent) was significantly greater ($P < 10^{-10}$) than among the controls (three per cent). Ashkenazi Jews showed a higher relative risk than non-Ashkenazi Jews and Arabs. Six of the AS patients were offspring of consanguineous marriages, but this was not higher than expected and therefore no indication for rare recessive genes contributing to the disease could be demonstrated. This study confirms the association between AS and B27, and extends our knowledge to the heterogeneous population of Israel not previously investigated. A significant but weak association of B27 with RA was noted. No correlation of other HLA antigens with RA or OA was observed.

(104) Davatchi, F., Nikbin, B and Ala, F., Histocompatibility antigens (HLA) and rheumatic diseases in Iran, J. Rheumatol. Suppl. 3:36-38, 1977.

Author's summary:
One hundred and sixty-six patients with different forms of rheumatic diseases were tissue typed for 26 antigens of the A and B locus of the HLA system, using a modified KN cytotoxicity test. Among 25 patients with confirmed ankylosing spondylitis, 23 had HLA B27 (92 per cent), compared to 2.5 per cent in the normal controls. This confirms the strong association of HLA B27 with ankylosing spondylitis Eight patients had doubtful AS, five of whom were positive for B27. In 21 patients with mechanical disorders of the spine no B27 was found. Thirty-six patients with osteoarthrosis of the knee joints did not show any significant relationship with any HLA antigens. Twenty-one patients with systemic lupus erythematosus showed an increase of HLA B13 and B17.

(105) Malaviya, A.N., Mehra, N.K., Adhar, G., Jindal, K., Bhargawa, S., Batta, R.K., Vaidya, M.C. and Sankaran, B., HLA B27 in patients with seronegative spondarthritides, J. Rheumatol. 6:413-416, 1979.

Author's summary:
We investigated the pattern of genetic susceptibility to rheumatic diseases in Indians by means of HLA analysis. HLA B27 was present in more than 90% of cases included under the broad category or seronegative spondarthritides. In this respect our data resembled results reported for Caucasian populations. In our population, however, the phenotype frequency of HLA B27 was low as reported from Japan.

12. Genetics

(106) de Blecourt, J.J., Polman, A. and de Blecourt-Meindersma, T., Hereditary factors in rheumatoid arthritis and ankylosing spondylitis, Ann. Rheum. Dis. 20:215-223, 1961.

Author's summary:
7,405 relatives (down to and including third-degree kin) of 300 probands (100 with rheumatoid arthritis, 100 with ankylosing spondylitis, and 100 normal controls) were examined for rheumatoid arthritis or ankylosing spondylitis.

The frequency of rheumatoid arthritis among relatives of the rheumatoid arthritis group was 2.8times as high as that in the control group; the frequency of ankylosing spondylitis among relatives of the spondylitis group was 22.6 times as high as that in the control group. Ankylosing spondylitis was as frequent in the rheumatoid arthritis group as in the control group. The same holds true for rheumatoid arthritis relative to ankylosing spondylitis. Both rheumatoid arthritis and ankylosing spondylitis, therefore, probably involve a non-sex-linked dominant heredity mechanism with differences in penetrance between males and females.

One-third of all Dutch families are thus believed to be affected by rheumatoid arthritis.

(107) Bennett, P.H., Burch, T.A., New York symposium on population studies in the rheumatic diseases: new diagnostic criteria, Bull. Rheum. Dis. 17:453-458, 1967.

Author's summary:
ANKYLOSING SPONDYLITIS
The subcommittee felt that the minimal requirements of a population study are:
1. An A.P. radiograph of the pelvis (see x-ray section for limitations).
2. Clinical examination
RADIOLOGIC CRITERIA OF SACRO-ILIITIS
X-ray grading:
Grade 0 - normal

Grade 1 - suspicious
2 - abnormal with erosions or sclerosis
3 - unequivocal abnormal, moderate, or advanced sacro-iliitis showing one or more of: erosions, sclerosis, widening, narrowing, partial ankylosis
4 - total ankylosis

CLINICAL CRITERIA

1. Major limitation of the lumbar spine in three planes, anterior flexion, lateral flexion and extension.
2. A history of, or presence of pain at the dorsolumbar junction or in the lumbar spine.
3. Limited chest expansion of one inch or less (measured at the 4th inter-costal space).

DEFINITION FOR PREVALENCE STUDIES

Definite AS:
* Grade 3 or 4 bilateral sacro-iliitis and one clinical criterion.
* Grade 2 bilateral or grade 3 or 4 unilateral sacro-iliitis plus either clinical criterion #1 or both #2 and #3.

Probable AS:
* Grade 3 or 4 bilateral sacro-iliitis without a clinical criterion.

(108) Emery, A.E.H. and Lawrence, J.S., Genetics of ankylosing spondylitis, J. Med. Genet. 4:239-244, 1967.

Author's summary:
Previous studies, based on the familial incidence of overt clinical disease, have suggested that ankylosing spondylitis is due to an autosomal dominant gene. This hypothesis seems rather unsatisfactory because penetrance would have to be very low to account for the fact that only about 4% of first-degree relatives are affected with the clinical form.

In the present investigation the familial incidence of radiographic evidence of bilateral sacro-iliitis, with or without other manifestations of ankylosing spondylitis, has been studied in 188 first-degree relatives of 76 patients with spondylitis. Of first-degree relatives, 16% were found to be affected compared with 3.7% of controls. Evidence is presented wiich suggests that it is multigenic in causation. The heritability of the liability to the disease based on the incidence of clinical disease in relatives and controls was estimated to be 70.0± 9.3% and when based on the incidence of sacro-iliitis, with or without other manifestations of ankylosing spondylitis, to be 72.5± 10.2%.

(109) van der Linden, J.M.J.P., Keuning, J.J., Wuisman, J.H.C., Cats, A., van Rood, J.J., HL-A 27 and ankylosing spondylitis, Lancet 1:520, 1975.

Author's summary:
We have had the opportunity of studying a family in which ankylosing spondylitis was found in 5 sons and their father.

The father and the 5 sons had clear symptoms and signs of spondylitis. HL-A 27 was present in all members with A.S. except the father. The son without HL-A 27 and the mother with HL-A 27 did not show clinical or radiological evidence of A.S. There was no history of A.S. in the antecedents of either the father or the mother.

In this pedigree we see that A.S. developed in male children who inherited HL-A 27 from their mother, independent of the HL-A haplotype they inherited from their father who also had A.S. but was HL-A 27 negative.

Possibly, in the absence of HL-A 27, A.S. may occur if an as yet unidentified recessive gene is present in a homozygous form. In the present family there is a 1 in 16 chance that the father is homozygous for each pair of genes, because his parents were first cousins. The observation that neither his parents nor any of his brothers and sisters have A.S. also argues against the existence of a single gene which can express the disease.

(110) Christiansen, F.T., Owen, E.T., Dawkins, R.L. and Hanraham, P., Symptoms and signs among relatives of patients with HLA B27 ankylosing spondylitis: Correlation between back pain, spinal movement, sacroiliitis, and HLA antigens, J. Rheumatol. suppl. 3: 11-17, 1977.

Author's summary:
In order to determine the prevalence of ankylosing spondylitis and the prevalence and pattern of back pain amonst the relatives of patients with ankylosing spondylitis, 63 first degree relatives of 14 propositi were assessed by means of questionnaire, physical examination, and radiology. There were no significant differences in the responses of the B27 positive and negative relatives in relation to prevalence, severity and character of back pain. Ankylosing spondylitis was found in 6.5 per cent of B27 positive relatives and 3.1 per cent of B27 negative relatives; sacroiliitis being present in 12.9 per cent of B27 positive relatives and 6.3 per cent of B27 negative relatives. A family studied is presented as a possible crossover between HLA B locus and disease "predisposition" genes. It is suggested patterns of back pain may not be as discriminating as has been thought.

(111) Daneo, V., Migone, N., Modena, V., Bianchi, S.D., Alfieri, G., Diotallevi, P., Carbonara, A.O. and Piazza, A., Family studies and HLA typing in ankylosing spondylitis and sacroiliitis, J. Rheumatol. Suppl. 3:5-10, 1977.

Author's summary:
The families of 21 ankylosing spondylitis (AS) and 16 sacroiliitis (SI) patients were investigated and typed for HLA markers. The association of HLA B27 with AS was confirmed, but no strong evidence for the same or other HLA markers being associated with SI was found. Inheritance patterns in families were analyzed according to the multifactorial and monofactorial models. It is proposed that a major gene associated or interacting with the B27 product controls the susceptibility to AS, and that this gene behaves as a dominant with incomplete penetrance. The problem as to whether linkage disequilibrium maintained by selective pressure, or functional epistasis between the "disease gene" and the B27 antigen may be the acting mechanism of ssociation, remains to be elucidated.

(112) Hochberg, M.C., Bias, W.B. and Arnett, F.C., Family studies in HLA-B27 associated arthritis, Medicine 57:463-475, 1978.

Author's summary:
1. We studied 110 patients with an HLA-B27 associated arthropathy, 36 with ankylosing spondylitis (AS), 10 with idiopathic sacroiliitis (SI), 53 with Reiter's syndrome (RS), and 11 with seronegative, childhood-onset arthritis (JCP) to determine the frequency of related axial or peripheral arthritis in relatives of patients with these disorders, examine the intra-familial relationships between disease and HLA-B27 or other HLA antigens, and determine whether the pattern of arthritis present in the proband "breeds true" in affected family members.

2. Minimally, 16 percent of the probands had first- or second-degree relatives with a related inflammatory axial or peripheral arthritis. This included six (17%) with AS, three (30%) with SI, six (11%) with RS and three (27%) with JCP.

3. All of the 21 affected first- and second-degree relatives of the 13 B27-positive probands had HLA-B27, while there were 19 B27-positive and 20 B27-negative relatives without disease. In addition, there were 2 B27-negative probands with affected first-degree relatives; both affected relatives shared a haplotype with the proband. None of their family members had B27.

4. The presence of either an axial or peripheral pattern of articular involvement in the affected relatives showed a high degree of concordance with the pattern of arthritis in the corresponding proband.

5. Although HLA-B27 is strongly associated with this group of rheumatic disorders, the finding of normal B27-positive relatives, especially discordant monozygotic twins, as well as affected B27-negative individuals in families of B27-negative probands, suggests the presence of other genetic and/or environmental factors operative in disease pathogenesis and/or expression.

(113) Marcusson, J., Moller, E, Rosenthal, L., Lindwall, N. and Thyresson, N., Psoriasis and arthritic lesions in relation to the inheritance of HLA genotypes: a family study, Acta Dermatovener 58:511-520, 1978.

Author's summary:
This family consists of forth-eight subjects, all of whom have been examined with regard to the presence of psoriasis and nearly all for the presence of arthritic lesions (sacroiliiitis and peripheral arthritis). All the members have been tissue typed not only for HLA-A,B and C locus products but also for D locus products. This has enabled us to study the entire HLA chromosomal region. In the family concerned we have found that those subjects haploidentical with the proband have to a very large degree, either one or all clinical manifestations, which demonstrates a close genetic relationship between joint (especially sacro-iliiitis) and cutaneous manifestations. These finding prompt us to repeat our previously made proposal about different phenotypic expressions of the same genotype. In this family study the disease-associated haplotypes did not contain the genes for B13, 17 or 37 antigens which are known to occur frequently in psoriatic patients. However, not all psoriasis patients have these antigens. Despite that, we believe that the gene(s) which increase the likelihood of developing psoriasis are identical in all patients and therefore family studies where the porband does not carry the particular psoriasis associated B-alleles are equally illuminating as to the inheritance pattern of disease.

(114) Khan, M.A., Kushner, I., Braun, W.E., Zachary, A.A. and Steinberg, A.G., HLA-B27 homozygosity in ankylosing spondylitis: relationship to risk and severity, Tissue Antigens 11434-438, 1978.

Author's summary:
The close association of ankylosing spondylitis (AS) with the histo-compatibility antigen HLA-B27 is well established (Brewerton et al. 1973, Schlosstein et al. 1973). To determine whether B27 homozygosity has any effect on susceptibility to AS, we compared the observed and expected frequencies of apparent B27 homozygosity (i.e., where B27 is the only antigen detectable at the B locus) in B27-positive AS patients. This approach had been suggested by Cohen et al. (1976). In addition, we investigated the possible relationship of B27 homozygosity to disease severity by comparing disease manifestation in heterozygous and apparently homozygous patients.

13. *Clinical Use of Testing for HLA-B27*

(115) Nagi, S.Z., Riley, J.e. and Newby, L.G., A social epidemiology of back pain in a general population, J. Chron. Dis. 26:769-779, 1973.

Author's summary:
This paper presented data on the prevalence of persistent back pain and associated disabilities in a general population, the distribution of these symptoms according to selected socio-demographic and psychological

characteristics, and the patterns of utilization of health services by persons who did and did not report suffering from back problems. Data represent self-reports of a probability sample of the general population in the SMSA of Columbus, Ohio, between the ages of 18 and 64. About 18 per cent of the total sample reported persistent back pain. All of the sociodemographic and psychological factors showed significant differential distributions except race and occupation. Explanations were offered within the framework of emotional or physical stress that may precipitate or aggravate conditions conducive to back pain, and differential exposure risks of accidents and injury. Persons with back complaints reported greater utilization of health services even when comparisons were limited to those with functional limitations. More of the people with persistent back pain who report limitations in functioning have used health care services compared with others in the sample who also reported functional limitations, presumable resulting from health conditions other than back pain.

(116) Golding, D.N., Jenkins, W.J., Histocompatibility testing in doubtful cases of ankylosing spondylitis, Lancet 2:522-523, 1974.

Author's summary:
HL-A typing fo patients seems to be helpful in establishing a definite diagnosis in the early stages of sacro-iliitis and it will be interesting to follow this group of patients over the next few years to see if definite radiological changes develop.

(117) Calin, A. and Fries, J.F., Striking prevalence of ankylosing spondylitis in "healthy" W27 positive males and females. A controlled study, New Engl. J. Med. 293:835-839, 1975.

Author's summary:
Ankylosing spondylitis is diagnosed once or twice in each 1000 males and one tenth as frequently in females, but the true prevalence is unknown. Identification of genetic marker, HL-A W27, for susceptible persons has provided a tool facilitating epidemiologic studies and allowing identification of "control" populations without the marker.

Evaluation by postal questionnaires, and pelvic radiography of 78 HL-A W27-positive blood donors selected from a group of apparently healthy subjects revealed 14 who satisfied the criteria for definite ankylosing spondylitis. The prevalence was similar in both sexes. One hundred and twenty-six W27-negative controls matched for race, sex, and age failed to yield a single case.

For a person of either sex with HL-A W27, there appears to be about a 20 per cent chance that ankylosing spondylitis will develop, suggesting a prevalence of 10 to 15 per thousand. Hitherto accepted figures may underestimate the frequency by a factor of 10 to 20.

(118) Grahame, R., Kennedy, L. and Wood, P.H.N., HL-A 27 and the diagnosis of back problems, Rheumatol. Rehabil. 14:168-172, 1975.

Author's summary:
Too much of the information required for rigorous assessment of the diagnostic value of a positive HL-A 27 test is not available. Certainly there would seem to be no case for population screening, not least because effective prophylaxis is not possible. At present sacroiliac radiographs have greater value in the clinical situation, and it seems unlikely that the contribution they make to diagnosis will be challenged. The absence of the HL-A 27 antigen may have some value as an exclusion test, but careful prospective studies are required, as well as a more detailed cost-benefit appraisal of this test.

(119) Cohen, L.M., Mittal, K.K., Schmid, F.R., Rogers, L.F. and Cohen, K.L., Increased risk for spondylitis stigmata in apparently healthy HL-AW27 men, Ann. Int. Med. 84:1-7, 1976.

Author's summary:
Evidence for ankylosing spondylitis was sought by clinical, radiologic, and ophthalmologic examination in HL-AW27-positive men, aged 18 or older, selected from a tissue-donor population. Back pain of 3 months duration or longer ($P < 0.05$), back stiffness, restricted lumbar flexion and chest expansion, sacroiliac erosions ($P < 0.05$) and sclerosis, and ophthalmologic sequels of anterior uveitis were found more often in the 24 men of the W27 group than in a control group of 31 men lacking this antigen. Based upon accepted criteria, 3 W27 persons had definite spondylitis and an additional 3 W27 persons and one control subject had findings strongly suggestive of spondylitis ($P < 0.05$). This striking frequency, if extrapolated to the general population, would place approximately 1 of 4 W27-positive men at risk for this disease.

(120) Arnett, F.C. Jr., The implications of HL-A W27, Ann. Int. Med. 84: 94-95, 1976.

Author's summary:
Of equal importance is the clinical applicability of W27 in the diagnosis of rheumatic disorders. As the test becomes more widely available, it may prove as useful a laboratory aid as rheumatoid factor, serum uric acid, and antinuclear antibodies. Certain clinical situations where W27 may be a diagnostic aid are already apparent. These include (1) the patient (especially the young man) with back pain suggestive of spondylitis in whom radiographs do not yet show characteristic changes; (2) the patient with incompletely expressed Reiter's syndrome; (3) as a diagnostic discriminator between Reiter's syndrome and the peripheral arthritis of psoriasis and inflammatory bowel disease (when spondylitis is absent); (4) the patient in whom Reiter's syndrome versus gonococcal arhtritis is suspected (although careful bacteriologic studies are still indicated); (5) the patient with chronic juvenile arthritis in whom the disease category is important for prognostic and therapeutic reasons; and (6) the patient with psoriasis, inflammatory bowel disease, or acute anterior uveitis who may be at risk for future spondylitis.

(121) Goldin, R.H., Bluestone, R., Tissue typing in the rheumatic diseases, Clin. Rheum. Dis. 2:231-252, 1976.

Author's summary:
Any student of medical sciences soon learns that an appropriate diagnosis is based upon deductions gleaned from a series of clues provided by a patient's hsitory, examination, and certain laboratory data. The presence of the HL-A27 antigen, or its absence, provides such a clue for the rheumatic diseases. It should be emphasizsed that the presence of HL-A27 is not diagnostic of any disease or group of diseases. Conversely, its absence does not rule out a given entity. Under appropriate circumstances, however, tissue typing provides support for or against the presence of a seronegative spondyloarthropathy. Such information may by of great assistance in managing persons with persistent back pain, with unusual arthritic manifestations, or a suspected arthritis of infectious aetiology unresponsive to antibiotics. Particular importance may be found in applying this knowledge to family studies. In such patients and in others with rheumatic problems of unusual character, lymphocyte typing for the 27 antigen must be performed.

(122) Curtis, D.L., Epstein, W.V., Implications of W27 screening, New Engl. J. Med. 294:226, 1976.

Author's summary:
Since 18 per cent of the United States population are often bothered with back pain we must visualize an immense cost associated with screening for a condition that even in its more overt form commonly has benign natural history. Since there is no available therapeutic modality that is known to affect pathogenesis or change the natural history of the disease, the psychologic, economic and social costs of extending this very important preliminary observation must be carefully considered.

(123) Calin, A., Fries, J.F., Schurman, D. and Payne, R., The close correlation between symptoms and disease expression in HLA B27 positive individuals, J. Rheumatol. 4:277-281, 1977.

Author's summary:
Following demonstration that 20% of presumed "healthy" HLA B27 positive individuals develop symptomatic ankylosing spondylitis, a controlled follow-up assessment of the remaining "asymptomatic" 80% was performed. The clinical and radiological study revealed that there is a close correlation between symptoms and radiologic change in HLA B27 positive subjects; those individuals remaining symptom free have normal pelvic radiographs. Ankylosing spondylitis or "asymptomatic sacroiliitis" does not exist in a subclinical manner throughout the entire group of B27 positive subjects. Evaluation of the pelvic radiographs of both symptomatic and asymptomatic HLA B27 positive subjects an symptomatic HLA B27

negative controls demonstrated that osteitis pubis and fluffy periostitis are equally distributed among the three gourps, only the frequency of sacroiliiitis being statistically greater in the B27 positive symptomatic subjects.

(124) Calin, A., Porta, J., Fries, J.F., Schurman, D.J., Clinical history as a screening test for ankylosing spondylitis, JAMA 237:2613-2614, 1977.

Author's summary:
A controlled study of 138 subjects demonstrated that the clinical history may be sensitive (95%) and specific (85%) in the differential diagnosis of ankylosing spondylitis when reliance on five specific historic features is made.

Back pain that is insidious in onset, in a patient younger than 40 years, persisting for at least three months, associated with morning stiffness and improving with exercise is characteristic of inflammatory spinal disease.

(125) Alcalay, M., Amor, B., Haider, F., Alcalay, D., Orfila, J., Tanzer, J. and Bontoux, D., Ankylosing spondylitis and chlamydial infection in apparently healthy HLA B27 blood donors, J. Rheumatol. 6:439-446, 1979.

Author's summary:
We studied 2 groups of 40 apparently healthy blood donors respectively HLA B27 positive and negative; 25 were men and 15 women, all free of a clinical history of ankylosing spondylitis (AS) or Reiter's syndrome. Among the B27 positive subjects, 24 (15 men and 9 women) had radiographic signs of minimal (5 cases) or suspicious (6 cases) sacroiliiitis; of these 11 donors 3 men satisfied the New York criteria for definite AS. Among the B27 negative subjects 12 (6 men and 6 women) had a history of back pain, but none met the diagnostic criteria of AS.

These results suggest an actual frequency of AS in France 10 times higher than the frequency of diagnosed cases, but a lower prevalence of AS in France than in the Western Hemisphere. No latent cases of Reiter's syndrome were diagnosed possibly because of the rarity of the syndrome in the Poitiers area. Lymphocyte transformation tests (LTT) in the presence of ornithoa-psittacoa antigen, and tests for anti-chlamydial antibodies did not yield significantly more positive results in B27 positive subjects. There was, however, a significant correlation between positive LTT and the possession of birds. This study also demonstrates that chlamydial infection in our B27 positive subjects was not sufficient to induce Reiter's syndrome.

(126) Christiansen, F.T., Hawkins, B.R., Dawkins, R.L., Owen, E.T. and Potter, R.M., The prevalence of ankylosing spondylitis among B27 positive normal individuals - a reassessment, J. Rheumatol. 6:713-718, 1979.

Author's summary:
Previous workers reported symptomatic, but undiagnosed, ankylosing

spondylitis (AS) in some 20% of blood donors with HLA B27. As part of and outgoing population study, we compared 139 B27 positive individuals with 128 controls and found no differences in spinal mobility or back pain. There were no differences when all available radiographs were compared. No case of AS was identified. It is concluded that AS occurs in far less than 20% of B27 positive individuals and that the prevalence of AS is of the order predicted by conventional epidemiological surveys. Although HLA typing can be helpful in excluding AS suspected on clinical grounds, it cannot be used to confirm the diagnosis.

(127) Russell, A.S., The prevalence of ankylosing spondylitis, J. Rheumatol. 6:603-605, 1979.

Author's summary:
If the apparent differences in the prevalence of AS are real, reflecting environmental and genetic differences, we need to confirm this. On the other hand, if the differences reflect the subjective nature of the radiological assessment and the inadequacy and variability of the clinical criteria, this could readily be established by appropriate exchanges of radiographs or observers.

It is nice to have a clear ending: all authors accept that HLA typing is not of value as a screening test for AS and most agree that it is not of any positive diagnostic help in the individual patient.

(128) Khan, M.A., Clinical application of the HLA-B27 test in rheumatic diseases, Arch. Intern. Med. 140:177-180, 1980.

Author's summary:
Testing for the histocompatibility antigen HLA-B27 has been suggested as a valuable diagnostic aid in patients with ankylosing spondylitis and associated spondyloarthropathies, and B27 typing is becoming more readily availabe commercially at a number of clinical pathology laboratories. A current evaluation of B27 typing as a diagnostic test is presented, together with some guidlines for the clinical application of this test in the diagnosis of certain rheumatic diseases.

(129) Calin, A., HLA-B27: to type or not to type?, Ann. Intern. Med. 92:208-211, 1980.

Author's summary:
The association between the histocompatibility antigen HLA-B27 and the seronegative sponlylarthritides such as ankylosing spondylitis and Reiter's syndrome is dramatic. A question that arises in practice is, when should a clinician request HLA-B27 typing in the assessment of a patientwith a rheumatologic complaint? Generally, diagnosis of these spondylarthropathies depends on history, clinical and radiologic examination, and, occasionally, confirmatory laboratory tests. This paper reviews the criteria for the diagnosis of the sponlylarthritides, discusses the sensitivity and specificity of HLA-B27 typing in these conditions, analyzes the relation between HLA-B27 status and prognosis

and defines the role of genetic counseling. It is concluded that knowledge of the patient's HLA-B27 status provides only minimal help to the physician. Indiscriminate typing is to be deprecated.

14. Pathogenesis

(130) Ebringer, R.W., Cawdell, D.R., Cowling, P., and Ebringer, A., Sequential studies in ankylosing spondylitis, Ann. Rheum. Dis. 37:146-151, 1978.

Author's summary:
A study of 163 patients with ankylosing spondylitis seen on 433 occasions showed that active inflammatory disease was strongly associated with the presence of Klebsiella pneumoniae in the faeces ($P < 0.001$). Sequential studies showed that in patients with inactive disease the presence of a positive culture for Klebsiella was associated with the subsequent development of active inflammatory disease ($P < 0.001$). These findings support the hypothesis that Kl. pneumoniae may be an initiating agent in ankylosing spondylitis.

(131) Ebringer, R., Cawdell, D., Klebsiella pneumoniae and acute anterior uveitis in ankylosing spondylitis, Br. Med. J. v:383, 1979.

Author's summary:
Positive cultures for Klebsiella pneumoniae were found in 13 of 17 episodes (76%) of acute anterior uveitis. Klebsiella Enterobacter species were identified in 229 out 763 occasions (30%), at which acute anterior uveitis was not found. The incidence in hospital controls, outpatients with rueumatoid arthritis, and female physiotherapy students was 33%, 20%, and 10% respectively. Many of the patients with AAU had positive cultures for Klebsiella for some months before the development of AAU as well as at the time of assessment.

(132) Seager, K., Bashir, H.V., Geczy, A.F., Edmonds, J., and de Vere-Tyndall, A., Evidence for a specific B27-associated cell surface marker on lymphocytes of patients with ankylosing spondylitis, Nature 277:68 70, 1979.

Reviewer's summary:
B27 positive individuals affected with ankylosing spondylitis were found to have a significantly lower *in vitro* responsiveness to Klebsiella as compared to B27 positive and B27 negative healthy controls. A rabbit antiserum to Klebsiella 427 was found to lyse lymphocytes from B27 positive patients with ankylosing spondylitis, but not those of B27 negative individuals with active disease. By contrast the lymphocytes were B27 positive and B27 negative unaffected individuals were not lysed by the antiserum to Klebsiella 427. Furthermore the cytotoxic activity of the antiserum was removed only by absorption with lymphoid cells from B27 positive patients with ankylosing spondylitis, but not

by lymphocytes from B27 positive or B27 negative normal controls.

(133) Geczy, A.F., Alexander, K. and Bashir, H.V., Edmonds, J., A factor(s) in Klebsiella culture filtrates specifically modifies an HLA-B27-associated cell-surface component, Nature 283:782-784, 1980.

Author's summary:
We have previously shown that a serum raised against certain isolates of Klebsiella pneumoniae lyses the lymphocytes of HLA-B27-positive paitents with ankylosing spondylitis (AS) but not of B27-positive or B27-negative healthy controls. These observations suggested that some Klebsiella antigens cross-react with a gene product intimately associated with B27 or possibly with 'modified' B27 in patients with AS. It seems likely therefore, that some Klebsiella antigens play a role in the pathogenesis of AS, perhaps by specifically modifying a B27-associated cell-surface marker. We have now examined the influence of culture filtrates from three Klebsiella isolates on lymphocytes from B27-positive and B27-negative healthy individuals. We report that 24-h culture filtrates of Klebsiella K43 (previously Klebsiella F19) contain a factor(s) capable of specifically modifying the sensitivity to anti-Klebsiella K43 serum of B27+AS- lymphocytes (that is, cells not lysed by anti-Klebsiella K43 serum): 'modified' B27_AS- lymphocytes are now serologically similar to the cells of B27-positive patients with AS (B27_AS_). The failure of anti-Klebsiella F10 and of anti-Escherichia coli sera to lyse lymphocytes, which have been incubated with the corresponding culture filtrates, excludes a nonspecific lysis by the anti-bacterial sera of target lymphocytes bearing bacterial antigens randomly distributed on their surface. Therefore, the data are compatible with a specific transformation by a Klebsiella K43-derived soluble factor of a B27-associated lymphoid cell component.