ANKYLOSING SPONDYLITIS: NEW INSIGHTS AND NEW TREATMENTS

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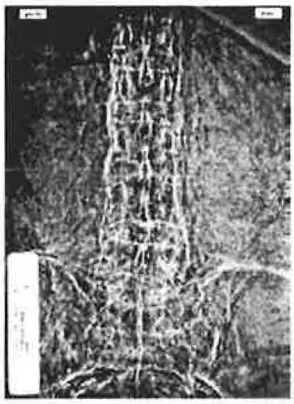

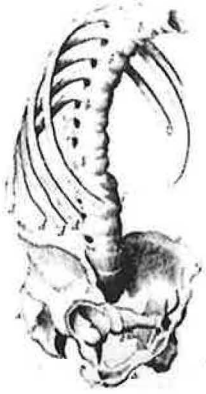

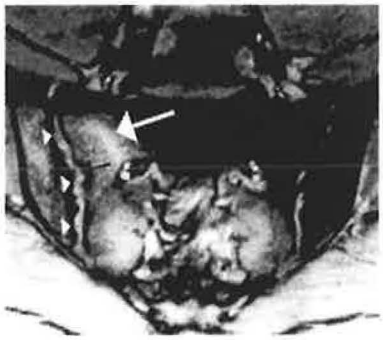

Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center at Dallas

June 10, 2004

This is to acknowledge that Dr. Taurog has not disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Taurog will be discussing off-label uses in his presentation.

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Research interest:
Role of HLA-B27 in the pathogenesis of the spondyloarthropathies

Cover Figures
Left: Xeroradiography of the lumbar spine of the mummy of the Egyptian pharaoh Ramses II, showing changes typical of ankylosing spondylitis. From reference 4.

Center: Skeletal remains described by Bernard Connor in the 1690's. From references 1 and 2.

Right: T1-weighted opposed phase gradient echo sequence 3 minutes after i.v. injection of gadolinium-DTPA (dynamic MRI) showing acute sacroiliitis demonstrated by strong contrast enhancement of the right SI joint (arrowheads), with marked bone marrow edema (white arrow) and erosions (black arrow). From a 23 year old male with AS and severe inflammatory back pain for 3 years, located mainly on the right side. From reference 44.

Summary
Ankylosing spondylitis is a chronic progressive inflammatory disorder of the spine with a strong genetic basis. It is part of the phenotype of the spondyloarthropathies, which overall have an estimated prevalence of 2% in Caucasian populations. HLA-B27, genes predisposing to IBD, and genes predisposing to psoriasis appear to constitute largely independent but interactive risk factors, and other genes are evidently also important. The symptoms are primarily pain, stiffness, and fatigue. These typically start in early adulthood, but can start in childhood. The disease is 2.5 to 3 times more common in males. Many patients suffer attacks of anterior uveitis, and a small minority develop aortic valve disease and heart block. Many patients suffer disability, and mortality is probably increased. In recent years, a variety of useful clinical indices have been formulated for evaluating disease outcomes and response to therapy. Pathogenesis is poorly understood, but the earliest lesions involve significant bone marrow edema seen on MRI, and biopsies show inflammation of entheses, subchondral bone, and synovium. Pathways of innate immunity are probably involved, and TNF is central to disease activity even in advanced disease. Inhibition of TNF represents a quantum leap in terms of therapy, but its use must be tempered by consideration of known side effects and unknown long term effects. New diagnostic criteria, based on genetic insights and specific lesions seen on MRI, are likely to be developed in the next few years.

History of AS to 1973

Anatomic and clinical descriptions (based primarily on (1-3). The disorder that we recognize as ankylosing spondylitis was evidently prevalent in ancient times (4), and probably occurs not infrequently in non-human primates (5), and perhaps even in other mammals (6). However, the first modern description is generally attributed, at least in the English medical literature, to Bernard Connor (1666-1698) an Irishman who studied medicine in France. While studying anatomy, he came across a skeleton that had been found in a graveyard, in which the ilium, sacrum, 15 lowest vertebrae, and ribs formed one continuous bone (cover, center panel). It was an age in which the disciplines of archeology and geological dating were developing, and there was intense interest in the fossil past. Connor surmised that the individual during life must have been almost immobile and would have had predominantly diaphragmatic breathing. Connor described his finding in separate writings in French, English, and Latin (the latter as his medical thesis) between 1693 and 1695. An earlier Italian author, Realdo de Colombo had described two ankylosed skeletons in his book *De Re Anatomica*, published in 1559. However there is an opinion (1) that at least one of Colombo's cases had what is today called fibrodysplasia ossificans progressiva (7), not ankylosing spondylitis.

Over the next century, a number of skeletons were described that were similar to Connors'. Clinical descriptions began to appear during the 19th century. Sir Benjamin Brodie (1783-1862), whose book *Pathological Descriptions of Diseases of the Joints* went through five editions from 1818 to 1850, in the 5th edition described a man with onset of symptoms at age 28. By age 34 he was "completely rigid without pain, a long continued chronic rheumatism of the spine with a hoop-like deformity and occasionally suffering severe inflammation of the eyes." A monograph published in 1857 described in detail the case of an American patient with what was almost certainly AS who progressively developed very severe kyphosis and disability (8). In 1877, Charles Fagge in London described a 34 year old man with ankylosing of the neck and dorsal spine, whose spine post-mortem showed complete ossification of the apophyseal joints, hips, and costovertebral joints. Sir James Paget and several others also described cases during the 1870's and 1880's.

The classical description of the disease as we know it was set forth in papers by Strümpell (Leipzig), von Bechterew (St. Petersburg), and Marie (Paris) in the 1890's. The most comprehensive and accurate description of the disorder was given by Marie. Pierre Marie (1853-1940) was a neurologist, a pupil of the famous French neurologist Jean Martin Charcot, founder of the Ecole Neurologique de la Salpêtrière. Their names are connected in their description of what is now known as Charcot-Marie-Tooth disease. Marie also described acromegaly, hypertrophic osteoarthropathy, and cerebellar heredoataxia. In 1898, Marie presented two cases to the Medical Society of the Hospitals of Paris of what he termed "spondylose rhizomélique." His remarkably complete description included spinal stiffness, rigidity, ankylosis of the hips, dorsal kyphosis, limitation of chest expansion, lack of knee involvement, and progressive onset in young adults. In 1899 and 1906, Marie and his student Andre Léri, reported clinicoanatomic correlative studies based on 12

of their own cases and 15 from the literature that included a description of ankylosed sacroiliac joints. Léri added to the description in a monograph in 1926.

X-rays, discovered by Roentgen in 1896, were first used to study the spine of a living patient with AS in 1906 (the isolated spine was studied as early as 1897), although the radiological picture of the disease was not fully described until the 1930's. More about AS became recognized as a result of the screening of large numbers of young men during the two world wars. It was realized that the disease tends to be familial, affects men more often than women, and is sometimes associated with psoriasis, inflammatory bowel disease, uveitis, and what today is known as reactive arthritis. In the decades following World War II, several large epidemiologic studies confirmed the familial nature of the disease, with a 70-100 fold increased risk to relatives of probands. Exceedingly high prevalence in certain North American Indian tribes was found, along with relative rarity in American blacks (9). Aortic valve disease, first identified in the 1930's, was found to be clearly associated with AS in the 1950's.

Table 1. ***Criteria for diagnosis of AS***

New York criteria 1966 (10)

A. Clinical criteria

1. Limitation of motion of the lumbar spine in all three planes – anterior flexion, lateral flexion, and extension
2. History of, or presence of, pain at the dorso-lumbar junction or in the lumbar spine
3. Limitation of chest expansion to ≤ 2.5 cm at the 4th intercostal space

B. Radiological criteria

Grade 3 or 4 bilateral sacroiliitis

Grade 3 or 4 unilateral sacroiliitis or Grade 2 bilateral sacroiliitis

C. Diagnosis

Definite AS with radiological criterion 1 and at least one clinical criterion, or with radiological criterion 2 and clinical criterion 1 or both clinical criteria 2 and 3

Probable AS with radiological criteria 1 and no clinical criteria

Modified New York criteria 1984 (11)

A. Clinical criteria

1. Low back pain > 3 mo improved by exercise and not relieved by rest
2. Limitation of motion of the lumbar spine in frontal and sagittal planes
3. Reduced chest expansion corrected for age

B. Radiological criteria

Grade 2 to 4 bilateral sacroiliitis

Grade 3 or 4 unilateral sacroiliitis

C. Diagnosis

Either radiological criterion and at least one clinical criterion

Disease critieria formulated. Although spondylose rhizomélique (also called spondylitis deformans, morbus Bechterew, morbus Marie-Strümpell, and other names) was considered by European clinicians from the time of its first description to be a distinct and separate disorder, there was a tendency among some influential American clinicians to consider it as a variant of rheumatoid arthritis and to call it rheumatoid spondylitis. In fact, it was not until 1963 that the American Rheumatism Association formally recognized ankylosing spondylitis as a separate disorder distinct from rheumatoid arthritis, and even then the term "rheumatoid variants" lingered on into the 1980's. International consensus criteria for AS (Rome

criteria) were first published in 1963. These were later largely replaced by the 1966 New York criteria (10) (Table 1). These criteria placed heavy emphasis on finding advanced radiographic changes in the sacroiliac joints. This is a highly specific lesion, but as will be seen later it is in many cases a late finding and hence far too insensitive to be used for practical diagnostic purposes. Table 1 also shows the modified New York criteria (11), which have largely replaced to New York criteria.

Description of early histopathology. Another development in the decades following WWII were attempts to define the early histopathology of AS. Since AS typically begins in early adulthood and has little if any early mortality, and since the SI joints and spine are relatively inaccessible to routine investigation, most of the known histopathology of was taken from advanced cases studied at autopsy. In the late 1960's British rheumatologist Eric Bywaters (1910 – 2003, (12)) reported autopsy findings from two early cases (13), and in 1971, the British pathologist John Ball reported on the histology in elective biopsies of focal tender areas over the iliac crest and greater trochanter from patients with AS (14). Ball in particular emphasized the importance of enthesitis, inflammation at ligamentous attachments to bone, frequently with erosion of bone and edema and inflammation in the underlying bone marrow. He hypothesized that this is a fundamental lesion in AS, and that reactive healing of the bone leads to formation of a new enthesis. This process was found at the attachment of the outer fibers of the annulus fibrosus to the vertebral body, bony repair of which evidently leads to syndesmophyte formation and the characteristic bamboo spine. Synovitis, particularly of apophyseal joints, and erosion of bone by subchondral granulation tissue, were found to be common lesions. Histology of the sacroiliac joint will be discussed below.

Relationship to reactive arthritis. During WWII, an outbreak of shigellosis among 150,000 Finnish troops led to a large number of cases of what is now called reactive arthritis (15). One physician, Ilmari Paronen, described 344 cases in a 1948 publication (16). In 1969, a followup examination was carried out on 100 of these individuals, and 32 were found to meet criteria for AS (17). This and other more anecdotal data suggested a pathogenetic link between these two rheumatic conditions.

Therapy. Beginning in the early 20th century, enthusiasm developed for radiation treatment of AS, with X-rays, thorium, and radon. X-ray treatment to the spine became widely used in the 1930's, '40's, and early '50's, despite only one controlled trial, published in 1953. In 1955, a report appeared documenting a high incidence of leukemia is AS patients treated with radiation. In 1965, a study of over 14,000 patients in the U.K. who had received spinal radiation from 1935 onward indicated a significantly increased death rate from leukemia and aplastic anemia (Fig. 1) (18). Thereafter, the use of radiation almost disappeared, although radon therapy is still pursued in central and eastern Europe (19). Meanwhile, the appearance of phenylbutazone in the early 1950's and indomethacin in 1963 marked the beginning of drug therapy that was effective in controlling symptoms in many

patients. The importance of physical therapy and posture control began to be widely recognized during and after World War II (20).

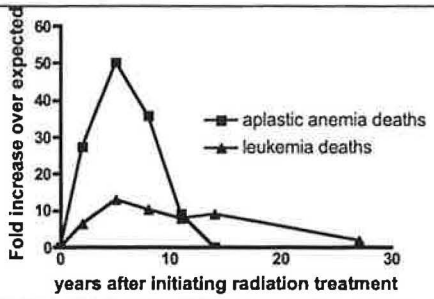


Fig. 1. Marked increase in fatal aplastic anemia and leukemia in AS patients treated with spinal irradiation in the U.K., 1935-1960. Data from 14,554 patients, total of 52 deaths from leukemia (5.5 expected) and 15 deaths from aplastic anemia (0.5 expected) out of 1,582 total deaths (866 expected). From (18).

Advent of HLA-B27

Discovery. In the spring of 1973, two groups, one at Westminster Hospital in London and the other at UCLA, independently reported a striking association of a histocompatibility antigen, then called HL-A 27, with AS (21-24). The antigen became known as HLA-B27 following the 6th International Histocompatibility Workshop in 1975. The association of AS with B27 was rapidly confirmed in AS patients all over the world (25). Moreover, it was soon found that B27 is also associated with reactive arthritis, acute anterior uveitis, and spondylitis associated with inflammatory bowel disease or psoriasis. These associations are summarized in Table 2.

Table 2. ***Prevalence of HLA-B27 in the spondyloarthropathies and related conditions***

Diagnosis	**Prevalence of HLA-B27 (%)**
Ankylosing spondylitis	90
with uveitis or aortic insufficiency	99
Undifferentiated spondyloarthropathy	40–70
Psoriatic arthritis (with axial arthropathy)	40-70
Psoriatic arthritis (only peripheral arthropathy)	<20
Arthritis of IBD (with axial arthropathy)	35-75
Arthritis of IBD (only peripheral arthropathy)	<20
Juvenile onset spondyloarthropathy	>70
Reactive arthritis	30-80
Acute anterior uveitis	>50
Aortic valve insufficiency with 3° degree heart block	80
Caucasian population	8

Based on (26, 27). For B27 and disease prevalence in other populations, see (25, 28).

Impact. The discovery of the B27-disease association led almost immediately to the concept of the spondyloarthropathies as a group of disorders with closely related clinical features and a association with HLA-B27 (29). It also rapidly led to improvements in the diagnosis of early or previously unrecognized cases of AS and other spondyloarthopathies, and to an overall heightened awareness of and interest in these disorders. It provided an impetus for the discovery of other HLA and disease associations. It also had the effect, for better or for worse, that much of the investigation into the etiology and pathogenesis of AS over the next several decades would be directed toward understanding the role of HLA-B27. Despite enormous effort in this regard, the molecular basis for this association remains unknown to this day. The field is divided between those who favor a classic

immunologic hypothesis (i.e., that B27 presents disease-specific peptides to T lymphocytes) (30) and those who favor alternative hypotheses (31). Although B27 typing has played a central role in the advances in the epidemiology of the spondyloarthopathies and it has a legitimate place in clinical diagnosis, most of the advances in the diagnosis and clinical management of AS in recent years have come from areas other than HLA investigation.

The absolute risk of spondyloarthropathy in B27+ individuals. An early question following the discovery of the B27-AS connection concerned the absolute risk of AS to individuals who are B27+. Two early studies published in the mid-1970's, one of blood donors and one of tissue donors, suggested that 20 to 25% of B27+ individuals have symptoms or X-ray findings suggestive of ankylosing spondylitis (32, 33). Many of these individuals had never been diagnosed with any rheumatic disorder. Evaluation of these symptomatic but undiagnosed B27+ individuals led to the recognition that the early back pain of AS, termed inflammatory spinal pain or inflammatory back pain, could be distinguished from other types of back pain on the basis of 5 characteristics: back pain that is insidious in onset, beginning before age 40 years, persisting for at least three months, associated with morning stiffness and improving with exercise (34). This concept of inflammatory back pain has figured prominently in the evaluation of AS and related disorders for several decades. Subsequent broader population studies suggested a lower prevalence, between 1 and 6.7%, but a much higher risk to B27+ 1st degree relatives of probands (35-37).

Table 3. ***Estimate of prevalence of spondyloarthropathy in B27+ individuals (38)***

Subject characteristics	B27+	B27-	p value
sent questionnaire (n)	161	159	
responded (n)	140	133	
% male	67	68	
age	38.4 ± 10	39.5 ± 10	
suspicion of SpA by history	68	58	
underwent physical exam	46	44	
MRI of SI joints for "IBP" sx	32	26	
sacroiliitis by MRI	15	1	<0.001
dx of spondyloarthropathy	19	1	<0.001
AS (7 males, 2 females)	9	0	
undiff. SpA (5 m, 2 f)	7	0	
psoriatic arthritis (2 m, 1 f)	2	1	
reactive arthritis (1 male)	1	0	

A recent study, again of blood donors, but incorporating MRI, probably provides the best current estimate of the frequency of SpA in B27+ individuals (38). The data are shown in Table 3. Of 20 persons meeting ESSG criteria for SpA, there were 19 out of 140 B27+ (13.6%) and 1 out of 133 B27- (0.7%) subjects. Nine had AS, 7 had undifferentiated SpA, 3 had psoriatic arthritis, and 1 had chronic reactive arthritis. On the basis of a B27 frequency of 9.3% among the population of Berlin, the estimated prevalence of SpA was 1.9%, AS was 0.86%, uSpA was 0.67%, and PsA was 0.29%. The relative risk of developing SpA in B27-positive subjects was calculated as 20.7 (95% confidence interval 4.6-94.2; P = 0.001). Of 58 persons with inflammatory back pain, sacroiliitis was detected by MRI in 15 of 32 B27-

positive (46.9%) and 1 of 26 B27-negative (3.9%) subjects (P = 0.002). Four of these 16 donors did not fulfill diagnostic criteria for SpA. These data suggest that the prevalence of spondyloarthropathy approaches 2% in Caucasians, higher than the prevalence of rheumatoid arthritis.

The concept of the spondyloarthropathies

The concept of spondyloarthropathy (or spondylarthropathy, or spondylarthritis) was put forth in 1974 by the British rheumatologists Moll and Wright (29). Clinical and epidemiologic studies had previously suggested that ankylosing spondylitis, reactive arthritis, psoriatic arthritis and spondylitis, and enteropathic arthritis and spondylitis were interrelated disorders. The discovery of the connection to HLA-B27 confirmed that there was a genetic basis for this interrelatedness and provided the final impetus for developing the concept of spondyloarthropathy. Additional clinical investigation over the next 15 years made it clear that patients often presented with features of one or more of this disorders but not meeting criteria for any of them. This led to the inclusion of an additional diagnosis within this group of disorders termed undifferentiated spondyloarthropathy (39), which was usually manifested by either asymmetric peripheral oligoarthritis or inflammatory back pain without the advanced radiographic changes required by the criteria for AS.

Additional broadening of the concept led the establishment in 1991 of the European Spondylarthropathy Study Group (ESSG) preliminary criteria for the classification of spondyloarthropathy (40) (Table 4), based on 403 patients with presumed spondyloarthropathy and 674 patients with other rheumatic diseases. Patients fulfilling these criteria were said to have spondyloarthropathy as a generic diagnosis with 87% specificity and 87% sensitivity. The criteria were developed more for investigation than for diagnosis, i.e., they are classification criteria, since the sensitivity in patients with ≤ 1 year of symptoms was only 68%. These criteria have been validated in many different populations around the world, and have been widely used in clinical studies for more than a decade.

Table 4. ***Criteria for ESSG diagnosis of spondyloarthropathy (40)***

• Inflammatory spinal pain	***or***	• synovitis that is asymmetrical or predominantly in the lower extremities

Plus one or more of the following:

- Positive family history of SpA
- Psoriasis
- IBD
- Alternate buttock pain
- Enthesopathy
- Radiographic sacroiliitis

Another set of criteria for spondyloarthropathy were proposed in 1990 by the French group of Amor *et al.*, and are often called the Amor criteria (41). These criteria actually perform somewhat better than the ESSG criteria, but they are more cumbersome to use and have not gained wide usage outside of France. In terms of disease frequency, most patients diagnosed with SpA by ESSG criteria either meet criteria for AS or have undifferentiated SpA (38). Among the latter group, some patients have only peripheral arthritis, whereas others have inflammatory back pain (with or without peripheral arthritis) without meeting criteria for AS, usually

because of insufficient evidence of sacroiliitis on imaging studies. A second major distinction between AS and uSpA is the frequency of HLA-B27, which approaches 90% in patients meeting criteria for AS, but is closer to 50% among patients with uSpA in the U.S. and Europe. All of the different forms of spondyloarthropathy can occur in childhood (42), and although spinal symptoms are unusual before late adolescence, axial changes can be detected earlier by MRI. In the wake of the HIV epidemic in sub-Saharan Africa, uSpA in the absence of either B27 or spinal disease, formerly almost completely unknown, is now perhaps the most prevalent rheumatic disease (43).

Radiology of AS

Inadequacy of conventional radiography for early diagnosis. A large number of classic radiographic features have been described in AS, including advanced sacroiliitis, vertebral squaring, vertebral osteopenia, vertebral erosions (Romanus lesion), nondestructive marginal vertebral sclerosis (shiny corners), spondylodiscitis, joint capsule and ligamentous ossification, syndesmophytes, bamboo spine, and vertebral fractures (44). However, many of these lesions occur only in a minority of AS patients. It has long been recognized that sacroiliitis is a cardinal feature of AS and advanced radiographic sacroiliitis was included as a required criteria in the 1966 New York criteria. However, plain films of the sacroiliac joints are often difficult to read, with significant interobserver variation. Moreover, although advanced radiographic sacroiliitis eventually develops in virtually all AS patients, its appearance may take years (45). For this reason, alternative imaging methods have been sought.

Imaging of sacroiliitis by MRI. During the past decade, great usefulness for MRI has been demonstrated in the early diagnosis of sacroiliitis and spondylitis. T1-weighted sequences with fat suppression (T1FS) following gadolinium-DTPA contrast and fast short tau inversion recovery (fast STIR) sequences have proven particularly useful (44). Although CT is usually thought to be superior to MRI in identifying bony lesions, MRI can be comparable to CT in sensitivity and specificity in detecting cortical erosions and subchondral sclerosis in the SI joint (46), and both MRI and CT are far more sensitive in this regard than plain films. Moreover, MRI is able to demonstrate very early acute inflammation that correlates with symptoms, including bone marrow edema and synovitis (44, 47, 48). Subchondral bone marrow edema, in particular, appears to be a specific early lesion of sacroiliitis in the spondyloarthropathies. (See right hand cover figure, with legend on p. 2).

A recent detailed study examined 9 separate structures in the SI joints of 93 patients with SpA and inflammatory back pain (49). T1-weighted, T2*-weighted, STIR, and dynamic Gd-DTPA contrast-enhanced images were examined. Among patients with very early disease, almost half had only unilateral sacroiliitis. Among patients with established AS, 84% had bilateral changes. However, the number of sites with abnormalities was not significantly different between early disease (4.5±3.2 sites) and late disease (5.2±2.3 sites). The dorsocaudal parts of the synovial joint and the bone marrow were the most frequently inflamed structures in early disease.

Imaging of the spine by MRI. MRI has also proved more sensitive than plain radiography for identifying lesions in the spine in AS, including osteitis; syndesmophytosis; discovertebral lesions; certain lesions in the facet, costovertebral, and costotransverse joints; ligamentous calcification; atlanto-axial disease; and complications of injuries (48). T1- and T2-weighted, STIR, and Gd-DTPA contrast enhanced images are all useful in this regard. A scoring system has recently been described for active spinal lesions seen on MRI (50). Significant correlation was observed between lesion activity seen on Gd-DTPA and STIR images on the one hand and clinical disease activity index (BASDAI) on the other. As described below, the acute lesions in the SI joints and spine have been shown to resolve following treatment with anti-TNF agents (50).

Pathology and pathogenesis of AS

Unlike rheumatoid arthritis, in which much about disease pathogenesis has been learned from synovial biopsy material, AS has been difficult to study. The nature of the primary lesion in AS remains obscure and controversial. As noted above, Ball proposed that enthesitis is a basic lesion. This view has recently been extended by the group in Leeds, U.K., in a series of recent papers (51-54). Ligamentous or tendinous attachments to bone are of two types, one a purely fibrous insertion and the other a fibrocartilaginous insertion. The latter are usually close to articular margins where tendons or ligaments are bent by tensional forces during joint movement. Certain of these fibrocartilaginous entheses can be viewed as part of an "enthesis organ" that serves to reduce shear stress, including the enethesis fibrocartilage at the insertion, adjacent periosteal fibrocartilage covering the bone, and sesamoid fibrocartilage within the tendon (51). Other structures containing fibrocartilage, such as joint capsules at sites where tendons wrap around bone pulleys, can also viewed as functional entheses. In the view of the Leeds group, much of the characteristic pathology of the spondyloarthropathies is explained by inflammation at entheseal sites, including spondylitis, sacroiliitis, and peripheral lesions such as dactylitis and Achilles tendonitis. These lesions are well visualized by MRI and ultrasound, which are more sensitive than physical examination (53-55).

Other studies suggest that enthesitis is not necessarily a primarily lesion, especially in the sacroiliac joints. A recent systematic histologic study of SI joint biopsy and autopsy specimens indicated that synovitis and subchondral bone marrow changes more likely accounted for the widespread joint destruction, rather than enthesitis (56). An earlier histologic study of SI joint biopsies similarly indicated that subchondral bone inflammation may be the earliest identifiable event (57). A detailed MRI analysis of SI joints from 93 patients with SpA and inflammatory back pain also showed that enthesitis within the SI joint is not particularly prevalent in early sacroiliitis (49). Although osteitis with bone marrow edema are clearly the earliest consistent MRI findings in sacroiliitis, the Leeds group have contended that the osteitis is related to adjacent enthesitis (52, 54).

Braun *et al.* (58) carried out CT-assisted biopsy of the SI joint in 5 patients with AS with a mean disease duration of 4.5 years and radiographic stage 2-3 disease. To

characterize the nature of the inflammation they studied the cellular infiltrate and cytokine pattern. Dense cellular infiltrates consisting of CD4+ and CD8+ T cells and macrophages were found in the synovial portion of the SI joints in all 5 patients. High levels of TNFα mRNA were found, and a lower amount of TGFβ mRNA was found near the site of new bone formation. This study provided part of the rationale for the trial of anti-TNF agents in AS.

AS, IBD, spondyloarthropathy, and gut inflammation

Arthropathy in patients with IBD. A relationship between arthritis and inflammatory bowel disease was first described in 1929, but the arthritis was only distinguished from rheumatoid arthritis by the epidemiologic studies in the 1950's and '60's. Both of the common forms of IBD, ulcerative colitis (UC) and Crohn's disease (CD), are associated with spondyloarthropathy. AS and peripheral arthritis are each associated with UC and with CD. Wide variations have been reported in the estimated frequencies of these associations. In three recent European series encompassing almost 2,000 patients with IBD for a median of 5 to 10 years (59-61), overall, AS was diagnosed in 2%, inflammatory back pain in 9%, enthesopathy in 7%, and peripheral arthritis in 10%, with somewhat higher frequencies found in CD than in UC. The combined total frequency of spondyloarthropathy was 18%. These figures are somewhat lower than earlier estimates, probably because they are based primarily on population-based series, not on tertiary center patients. Asymptomatic radiographic sacroiliitis was found in an additional 5%. As shown in Table 5, among these studies, which used different methodologies, there was 10-fold variation in the observed frequency of AS.

Table 5. *Prevalence of IBD in AS and non-AS SpA*

Study site	years of IBD	Dx	Total %	CD	UC
U.K. (59)	10.5	SpA	12.6	91 / 483	93 / 976
		AS	1.0	6 / 483	9 / 976
Belgium (60)	10 ± 8.5	SpA	46.7	35 / 78	15 / 25
		AS	9.7	7 / 78	2 / 25
Norway (61)	6	SpA	18.0	26 / 133	47 / 273
		AS	3.7	8 / 133	7 / 273
composite		SpA	15.6	152 / 694	155 / 1274
		AS	2.0	21 / 694	18 / 1274

SpA = non-AS SpA

It has generally been thought that the peripheral arthritis associated with IBD tends to run a course parallel to the activity of the bowel disease, whereas axial arthropathy and especially AS runs a course independent of the bowel disease. While the latter statement regarding AS is definitely true, one study from the U.K. recently suggested that peripheral arthritis in IBD is of two types (59). Type 1, termed pauciarticular, encompasses fewer than 5 joints, is characterized by acute self-limited attacks of <10 wk, and often coincides with relapses of IBD. Type 2, termed polyarticular, involves ≥5 joints, has symptoms that persist for months or years, runs a course independent of IBD, and is associated with uveitis but not any other extraintestinal manifestations. It remains to be seen whether this classification will be confirmed by others.

Gut inflammation in patients with SpA. The prevalence of overt UC or CD in patients with AS is thought to be 4-10%. However, investigation of unselected spondyloarthropathy patients by ileocolonoscopy has revealed that up to two thirds of these patients have *subclinical* intestinal inflammation that is evident either macroscopically or histologically. These lesions have also been found in patients with undifferentiated spondyloarthropathy or reactive arthritis (both enterically and urogenitally acquired). A great deal of investigation of this phenomenon has been carried out by the rheumatology and gastroenterology groups in Ghent, Belgium, over the past two decades, although the results have been largely confirmed by others. The subclinical histologic lesions tend to be either acute, resembling bacterial enterocolitis (preserved mucosal architecture, PMNs infiltrating ileal villi and crypt epithelial cells, increased inflammatory cells in the lamina propria), or chronic, resembling Crohn's disease (crypt distortion, atrophy of the villous surface, blunting and fusion of villi, increased mixed lamina propria cellularity and basal lymphoid aggregrates, occasional aphthoid ulcers or noncaseating granulomas) (62, 63).

In a large study by the Belgian group (64), 123 patients with SpA underwent serial ileocolonoscopy with biopsy. Three types of gut histology were found initially: normal (32.5%), acute (22.5%), and chronic (45%). Among those with non-AS SpA, 72% had lesions (40% chronic and 32% acute). Among those with AS, 62% had lesions, (52% chronic, 10% acute). Eight of these patients, and another 3 out of 94 SpA patients who had only one initial ileocolonoscopy study, developed IBD after 2 to 9 years of followup (9 CD, 2 UC). All of these individuals eventually developed AS. Only 2 of them were B27+. Ten of the 11 had started with chronic lesions. Of the patients with non-AS SpA, 12 eventually developed AS (all but one started with chronic lesions). Thus, AS was strongly associated with chronic gut lesions, some of which progressed to full blown Crohn's disease.

Genetics and pathogenesis. Both UC and CD have a tendency to familial aggregation, more so for CD. HLA associations have been weak and inconsistent. HLA-B27 is found in 50-70% of patients with IBD and AS, but in 15% or less of patients with IBD and peripheral arthritis or IBD alone (65). A major breakthrough in the genetics of IBD occurred with the observation that certain alleles of the *NOD2/CARD15* gene on chromosome 16 are found in up to half of patients with CD (66-70). Four studies have shown that these CD-prone alleles are not associated with susceptibility to spondyloarthropathy (71-74), either occurring alone or in association with CD. However, one study suggested a relationship between one *NOD2* variant ($Pro^{268}Ser$) and AS disease severity (75), and this linkage was supported by a subsequent genome screen analysis ((76) see below). A recent study from Iceland showed that 41% of 124 asymptomatic 1^{st} degree relatives of 47 AS patients showed evidence of subclinical bowel inflammation, irrespective of B27 status, compared with only 2 of 17 spouses of AS patients (77). Of the relatives with evidence for bowel inflammation, 20% showed SI joint abnormalities on CT scan, vs. only 2% without such evidence. This supports the concept that bowel inflammation in AS has its own genetic predisposition and contributes to the pathogenesis of AS, distinct from the role of HLA-B27.

Both IBD and the spondyloarthropathies are immune mediated, but the specific pathogenetic mechanisms are poorly understood, and the connection between the two is obscure, consisting largely of a series of disconnected observations. IBD is a common phenotype in a number of rodent lines with transgenic overexpression or targeted deletion of genes involved in immune processes. Arthritis is an accompanying prominent feature in two of these IBD models, HLA-B27 transgenic rats (78, 79) and mice with constitutive overexpression of TNF-α (80, 81), and immune dysregulation is prominent in both. Several lines of evidence indicate trafficking of leukocytes between the gut and the joint. Mucosal leukocytes from IBD patients have been shown to bind avidly to synovial vasculature through several different adhesion molecules (82), and T cells with identical antigen receptor sequences have been isolated from both the gut and the synovium in the same patient (83). Macrophages expressing CD163 are prominent in the inflammatory lesions of both gut and synovium in the spondyloarthropathies (84). The complex interaction between AS, SpA, and IBD is summarized in Table 6.

Table 6. ***Summary of interaction between AS, SpA, and IBD***

- Peripheral arthritis occurs in 10 – 50% of patients with IBD, and in some patients parallels the activity of bowel disease.
- AS occurs in 1 – 10% of patients with IBD and runs a course independent of the bowel disease.
- Frank IBD occurs in 4-10% of patients with AS. AS associated with IBD is phenotypically similar to AS alone, except for the sex ratio (M = F) and age of onset (can be older than 40).
- Subclinical inflammatory lesions (macroscopic or microscopic) are found in 70% of patients with non-AS SpA, and in 60% of patients with AS. In the former, the lesions can be either acute or chronic, whereas in AS they are usually chronic.
- Chronic subclinical lesions in SpA patients can progress to frank IBD, usually Crohn's. Non-AS SpA patients with chronic lesions are more likely to develop AS.
- HLA-B27 is found in 50 – 70% of patients with IBD and AS, compared with >90% with AS alone. B27+ individuals with IBD almost inevitably also have AS.
- NOD2/CARD15 alleles associated with Crohn's disease are not associated with SpA. So far, no common predisposing genes have been found for IBD and SpA, but there is evidence that gut inflammation in SpA results from a distinct genetic contribution.
- Both SpA and CD respond to infliximab. SpA but not CD responds to etanercept. UC does not respond to either anti-TNF agent. A variety of experimental phenomena suggest a link between arthritis and bowel inflammation.

Psoriasis and AS

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis. Estimates of its prevalence in patients with psoriasis range from 7 to 42%. A variety of different patterns of joint involvement occur, and these have been organized in several different classification schemes by different authors. Axial arthropathy (sacroiliitis and spondylitis) constitutes one of the forms, and represents 6 to 36% of the total in different series [reviewed in (85)]. Dactylitis, nail involvement, and enthesitis are common in all forms. As noted above, patients who meet criteria for AS who have associated psoriasis have a lower prevalence of HLA-B27 than those with AS unassociated with psoriasis or IBD. Patients with only peripheral psoriatic arthropathy show a nearly normal prevalence of HLA-B27, but tend to have other associated HLA alleles. Unlike isolated AS or AS associated with IBD, the AS associated with psoriasis tends to have more asymmetric sacroiliitis, syndesmophytes that are coarse, nonmarginal, nonconsecutive. Back and neck

fusion are less common in psoriatic spondylitis, and there is also a higher prevalence of associated peripheral joint arthritis. In a recent study, 38% of patients with psoriatic arthritis had sacroiliitis detected on MRI (86). There was no correlation with HLA-B27, but the findings correlated with back symptoms. In most recent series, approximately 10-20% of patients with AS have had associated psoriasis. A large number of genome wide scans have been carried out in familial psoriasis, with linkage well established to a region of the HLA complex and a region on chromosome 17q24-25 thought to contain two susceptibility genes, and with suggestive linkage to many other chromosomal regions (87). So far, there is no strong evidence for the sharing of a susceptibility locus between psorasis and AS.

Uveitis and AS

In recent series, approximately 30-40% of patients with AS have also had uveitis (88-90). The uveitis associated with the spondyloarthropathies is highly associated with HLA-B27 and has a characteristic clinical phenotype, acute anterior uveitis (AAU). It is typically manifest by acute, anterior, unilateral attacks, characterized by pain, photophobia, and intense redness of vessels around the limbus. (Anterior uveitis is also called iritis or iridocyclitis). Recurrences are frequent, often affecting the opposite eye. The intraocular pressure is reduced in the affected eye. The pathology is nongranulomatous. Posterior synechiae are common, and hypopyon, iris bombe, and fibrin in the anterior chamber are rare but characteristic findings. An estimated 75-85% of B27+ individuals with this type of uveitis have, or will develop, a spondyloarthropathy. In most cases the spondyloarthropathy precedes the uveitis, and the prevalence of uveitis increases in proportion to the duration of SpA. Uveitis that is bilateral or chronic or posterior or global (panuveitis) is much less likely to be associated with either HLA-B27 or spondyloarthropathy, although these can occasionally occur with psoriatic or enteric spondyloarthropathy. B27-associated uveitis accounts for an estimated 40-70% of all anterior uveitis. A recent genome wide scan of familial B27+ AAU found significant linkage to a region on chromosome 9p that was not linked with AS or other spondyloarthropathy in the same families (J.T. Rosenbaum, personal communication). Since most patients with B27+ AAU also have SpA, this finding suggests that this 9p locus plus B27 plus the other genes predisposing to SpA are all susceptibility genes for AAU.

Clinical assessment and course of AS

New instruments for disease assessment. Assessment of disease activity in AS has historically been difficult. Pain, stiffness, and fatigue have been difficult to quantitate. Symptoms from active inflammatory disease have been difficult to distinguish from those of fixed deformities. Laboratory data other than ESR and CRP has been found to be of little value, and in a sizeable minority ESR remains normal. During the past decade, significant advances have been made in the development of questionnaires and other clinical assessments of AS that have proven their worth in clinical trials. The most widely used assessment systems in use today were developed in the early 1990's by the group headed by Dr. Andrei Calin at the Royal National Hospital for Rheumatic Diseases at Bath, U.K. These include the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis

Metrology Index (BASMI), the Bath Ankylosing Spondylitis Radiology Index (BASRI), and Bath Ankylosing Spondylitis Global Score (BAS-G) (91-95).

The BASDAI has proven to be particularly useful, and has been validated in a variety of cultural settings. It consists of six questions pertaining to the past week at the time of the test. Patients are typically able to complete all six questions in less about 1 minute. Each question is answered on a visual analog scale from NONE to VERY SEVERE for the first 5 questions, and for 0 to ≥2 hr for duration of morning stiffness. The questions relate to: (1) fatigue; (2) neck, back, or hip pain; (3) pain or swelling in joints other than the neck, back, or hip; (4) discomfort from any areas tender to touch or pressure; (5) level of morning stiffness from the time of awakening; and (6) duration and intensity of a.m. stiffness (≤ 120 min). Items 5 and 6 averaged, giving 5 items scored 0 to 2, for an overall score of 0 to 10. The BASFI has also proved useful. It consists of 10 questions concerning the ability to perform specific activities during the previous week. Scoring is by visual analog, from EASY to IMPOSSIBLE. The mean of the 10 scales gives a score of 0 to 10. The application of these scales is shown below under the discussion of therapy.

An international group of experts termed the ASAS (ASsessments in AS Working Group), formed in 1995 to develop a core set of endpoint measures in AS. Variables assessing disease-controlled antirheumatic therapy, symptom modifying antirheumatic drugs, physical therapy, and clinical record keeping were eventually published (96). These, together with the Bath indices, have proven particularly useful in the recent studies of anti-TNF agents described below.

Course and outcome in AS. Most patients with AS suffer pain, stiffness, and fatigue over years with periods of exacerbation. Sleep disturbance, disability, depression, sexual dysfunction, diminished social function, financial difficulty, and drug side effects can all affect quality of life (97). The average age of onset of symptoms in many studies is 23 years, so this translates into symptoms persisting over most of a lifetime. In a survey of 52,444 patients with RA and 8,776 patients with AS seen in 21 German tertiary rheumatological care centers, age and sex matched groups of patients with RA and AS showed similar amounts of disability, pain, and reduction in well being (98). Younger age of onset, early hip disease, smoking, higher disease activity, failure to perform back exercises, and lack of social support are associated with a poorer prognosis (99, 100). Severe postural deformities that once were common have become much less frequent because of the widespread use of physical therapy (101). Radiographic progression is linear over at least a 30 year period (102). Employment rates in AS are higher than in RA (71% vs. 50% in the German study mentioned above, and 53-85% in 9 other studies (97)), but progressive work disability and/or change in occupation is common, particularly in men doing manual labor (97, 103). There are conflicted data as to whether AS confers increased mortality. Several studies have shown an increased mortality even in patients not receiving irradiation (104-106). One study of Canadian WWII veterans claimed normal survival in those not treated with irradiation (107), but this may have been a group with an initially milder prognosis.

Genetics of AS

Early studies. AS was shown to run in families long before the discovery of the association with HLA-B27. In 1961, DeBlècourt *et al.* reported that the frequency of AS in siblings of AS probands (recurrence risk) was 6.0, 6-fold higher than the risk for 2nd degree relatives and 8.6-fold higher than the risk for 3rd degree relatives (108). Following the discovery of the association with B27, it was observed that the risk to B27+ 1st degree relatives of B27+ probands, estimated at 15-21%, was higher than the risk to unselected B27+ individuals in the general population (36). (Although, as noted above, estimates of the absolute risk of AS to unselected B27+ individuals have ranged from 1 to 25%. Still, whatever the true risk to unselected B27+ individuals, the risk to B27+ 1st degree relatives is probably several fold higher). These data suggested that genes other than HLA-B27 are involved in AS susceptibility.

Genetic relationship between AS and other SpA. What is the relationship between AS and undifferentiated SpA? Do some cases of the latter represent early AS that has not met the arbitrary criteria of advanced radiographic sacroiliitis? One study (cited above) suggesting that this might be the case was published by a German group in 1988 (45). Eighty-eight patients with possible AS where identified with normal or at most suspicious radiographic findings of the SI joints. After 10 years 54 patients were available for followup. Of these, 32 patients (59%, 36% of the original 88) had definite AS, and 10 still had possible AS or undifferentiated spondyloarthropathy. Radiographic sacroiliitis took a mean of 9±6 years to develop, and spinal changes took 11±6 years.

To examine the genetic interrelationship of the spondyloarthropathies, the French group of Breban et al. (109) recruited 115 families with at least two 1st to 3rd degree relatives with some form of SpA by either ESSG or Amor criteria, amounting to 329 affected individuals, B27+ and axial symptoms were present in 97%. They carefully phenotyped them with regard to diagnosis and disease features. Age at onset was virtually identical to other published series (11, 110). Advanced radiographic sacroiliitis (and hence a diagnosis of AS) was found in both men and women in proportion to disease duration: 40% in those with disease <10 yr, 70% in those with disease of 10-19 yr, and 86% in those with disease ≥20 yr. It was also found not to cluster in families. IBD, psoriasis, and peripheral enthesitis also did not cluster, whereas some clustering was seen for uveitis (consistent with the finding of genetic linkage for uveitis, cited above) and peripheral arthritis. It thus appears that AS represents a final common pathway for spondyloarthropathy, at least in B27+ individuals with axial symptoms, and hence the genetic substrate for these conditions is likely to be similar.

Genome wide scans. During the past 6 years, three groups have carried out genome wide scans in multiplex families. One of these groups, based in Oxford U.K., has also analyzed the data on recurrence risk among monozygotic twins, siblings, and other relatives, in an attempt to model to the inheritance of AS susceptibility and estimate the number of polymorphic loci involved. Table 7 shows data from their analysis of 7 publications addressing the recurrence risk for AS

among different types of relatives of probands. They concluded that the data best fit a model in which there is multiplicative interaction among 5 loci. The 63% concordance rate for MZ twins with AS is among the highest for any rheumatic disease. The recurrence risk for siblings (including DZ twins) and parent-child relations were almost identical, and are in close agreement with the data cited above regarding B27+ 1st degree relatives. In a previous study of a subset of MZ and DZ twins (111), they concluded that additive genetic effects contribute >90% of the population variance with regard to AS, and that the contribution of HLA-B27 is less than half of the total genetic contribution. In fact, they estimated that the *non-HLA* genetic contribution to AS is comparable to the entire genetic contribution to insulin-dependent diabetes mellitus, and significantly greater than the entire genetic contribution to rheumatoid arthritis.

Table 7. ***Recurrence risk of AS in different degrees of probands of affected subjects – composite of 7 studies between 1961 and 2000 (112)***

	MZ twins	Siblings	Parent-child	All 1st degree	2nd degree	3rd degree
Number affected	17	404	37	441	8	7
Number studied	27	4924	466	5390	834	997
Recurrence risk (%)	63	8.2	7.9	8.2	1.0	0.7
(95% CI)	(42-81)	(7.4-9.0)	(5.6-10.7)	(7.4-8.9)	(0.2-1.7)	(0.1-1.4)
Recurrence risk ratio	630	82	79	82	10	7

The genome scans have been carried out on subjects in the U.K. (PI in Oxford) (113, 114), North America (North American Spondylitis Consortium, NASC, PI in Houston) (115), and France (PI in Paris) (116). The most significant results are summarized in Table 8.

Table 8. ***Results of genome scans for AS/SpA susceptibility genes***

	U.K./Canadian (114)	NASC (115)	French (116)
Pedigrees	185	180	120
Affected/unaffected	445/373	423/178	348/535
Diagnoses	AS dx'd by referring MD	AS by mod. NY criteria	all SpA
Male:female	1.7	1.5	1.2
Caucasian	100%	94%	100%
IBD	9%	10%	3%
Psoriasis	16%	11%	20%
Uveitis	44%	40%	29%
HLA-B27	100%	97%	100%
Linkage analysis	2-point & multipoint NPL	2-point & multipoint NPL, TDT, PDT	multipoint NPL
LOD/NPL score for HLA	15.6	20.5	5.3
Non-HLA loci showing "suggestive" or stronger linkage	1p, 2q, 6p, **9q**, **10q**, **16q**, **19q**	1q, 3p, 4p, 5q, 6q, **10q**, 11q, **16q**, 17p, **19q**	**9q**, others

Bold figures indicate regions found in more than one study; underlined figures indicate significant linkage (LOD ≥ 3.6)

All three studies confirmed the extraordinary linkage to HLA. The U.K. and French studies identified loci qualifying for significant linkage by the criteria of Lander and Kruglyak (117) (LOD ≥ 3.6) and additional non-HLA loci qualifying as suggestive linkage (LOD ≥ 2.2). The U.K. study identified a region on chromosome 16p with LOD 4.7 at 101 cM. The NASC study showed weak suggestive linkage near this region and also near other regions shared with the U.K. study, shown in bold in the

table. However the two strongest non-HLA loci found in the NASC study, with suggestive linkage on chromosomes 6q and 11q, were not found in the U.K. study. The French study found significant linkage to a locus on 9q (LOD 5.15), near a region of suggestive linkage found in the U.K. study. All three studies confirmed that the strong linkage to HLA constitutes less than half of the genetic contribution to AS, and that a number of loci with comparatively weaker contributions constitute the remainder of the heritability. Whether the differences in the loci found represent genetic variation among populations, disease heterogeneity among the subjects, or other factors remains to be determined.

The Oxford group more recently has reanalyzed data from their cohort (454 affected individuals in 188 families), looking for loci linked to specific disease manifestations: age at symptom onset, BASDAI, and BASFI (76). All three of these traits were found to have significant heritability [0.33 (95% CI 0.04-0.62), 0.49 (0.23-0.75), and 0.76 (0.49-1.0), respectively]. Significant linkage (LOD 4.0) was seen between BASDAI and a region on chromosome 18p, and suggestive linkage was seen between age of symptom onset and chromosome 11p, and between BASFI and chromosome 2q (LOD 3.3 and 2.9, respectively). Strikingly, there was almost no significant linkage of these traits to HLA, demonstrating that HLA-B27 is overwhelmingly a susceptibility gene and not a severity gene. (Older studies attempting to identify whether B27 homozygotes have more severe disease than B27 heterozygotes have yielded conflicting results). Age at symptom onset and BASFI also showed suggestive linkage to the region on chromosome 16p found to show significant linkage to susceptibility.

Weak linkage to candidate genes has also been shown in some studies, including genes in the IL-1RA family and the recently described ANKH gene (118-121).

Advances in Therapy for AS

Conventional therapy. For the past 4 decades, management of AS has depended primarily on therapy with NSAIDs and exercises (122, 123). COX-2 inhibitors appear to be as effective as the commonly available conventional NSAIDs (124). Although recent evidence suggests that continuous NSAID therapy exerts a significant restraining effect on the radiographic progression of AS (125), the effect is incomplete and for many patients NSAIDs provide insufficient symptomatic relief or cause unacceptable toxicity.

"DMARD" therapy. Many of the agents that have been used in rheumatoid arthritis have also been tried in AS, although there have been few controlled trials (122). Gold is generally agreed to be of no benefit, corticosteroids are dangerous with regard to aggravating spinal osteoporosis and provide relatively little symptomatic benefit, and immunosuppressive drugs have not been studied. The most extensively studied agent is sulfasalazine, which has also been widely used for inflammatory bowel disease and rheumatoid arthritis. In most studies, this agent has shown significant efficacy in reducing peripheral arthritis, both in AS and in other spondyloarthropathies, but having little effect on axial disease (126, 127). Recent assessments of methotrexate have shown it to be of little benefit (128-131).

In general, then, the conventional DMARD agents used for RA have shown little benefit for the axial arthropathy of AS.

Pamidronate and thalidomide. The prominence of bone marrow edema in the early lesions of AS seen on MRI (discussed above), and the finding that osteoporosis occurs early in the course of the disease (132, 133), provided the rationale for studying bisphosphonate therapy in AS. A Canadian group showed evidence for efficacy of pamidronate in two open studies, and then compared the effect of 60 mg vs. 10 mg of the drug i.v. monthly for 6 months in 84 patients with AS (134). (The 10 mg dose served as a placebo surrogate, since the i.v. infusion of any drug causes transient arthralgias). Significantly greater improvement was seen in the 60 mg group in BASDAI, BASFI, BASGI, and BASMI, but inflammatory markers were unchanged. Side effects were tolerable. An open study of 12 patients by the Berlin group showed less impressive benefit (135), and more study is necessary before this therapy can be recommended.

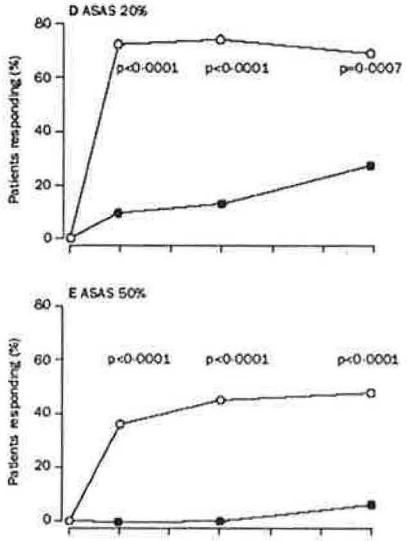
Uncontrolled studies have shown a fairly dramatic effect of thalidomide in approximately 50 patients with severe AS, including reduction in inflammatory markers (136-138). Since this drug exerts an anti-TNF effect, it merits further study in AS.

The dramatic effect of anti-TNF therapy. Treatment with a monoclonal antibody TNF was shown to be beneficial in Crohn's disease and in rheumatoid arthritis in the mid-1990's. In 2000, the Belgian group that had been studying the gut in patients with spondyloarthropathy reported remarkable amelioration of axial and peripheral joint symptoms in 4 patients with SpA being treated with infliximab for Crohn's disease (139), and in 21 patients with a variety of different spondyloarthropathies treated with three infliximab infusions specifically for their arthropathy (140).

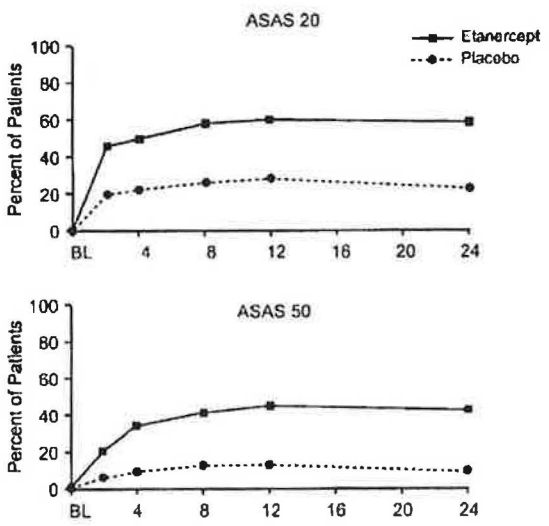
Simultaneously, the Berlin group reported dramatic improvement in 10 AS patients treated with three infusions of infliximab, with documented resolution of spondylitic lesions on MRI (141). In both of these 12 week studies, there was dramatic reduction in BASDAI, BASFI, CRP, ESR, and other subjective and objective assessments of axial and peripheral arthritis, beginning within days of the first infusion. Psoriatic skin lesions also improved dramatically in 8 out of 8 patients. Subsequently, additional open label and placebo-controlled trials were carried out with infliximab and also with etanercept, a soluble p75 TNF-receptor-IgG fusion protein, with similar results. By the end of 2003, by my tabulation 13 separate studies had been published examining anti-TNF therapy in groups of patients with AS [ten with infliximab, three with etanercept; eight open label, five randomized controlled trials (142-145); duration 8 to 54 weeks], plus several anecdotal cases. The median reduction in BASDAI in these studies was around 60% (range 41-93%, vs. 3-12% in the five placebo groups). The results with infliximab and etanercept were comparable. For example, the Berlin group reported a 53% reduction in BASDAI with infliximab and 57% reduction in BASDAI with etanercept in two separate placebo-controlled trials (142, 145). Fig. 2 shows a graphic comparison of the ASAS response criteria in two controlled trials. With both drugs, relapses are seen by 6-12 weeks after withdrawal in most patients (145, 146). Significant

resolution of acute spinal lesions on MRI, compared with placebo, was reported by the Berlin group in their infliximab controlled trial (50) (Fig. 3). A multicenter controlled trial of a third anti-TNF agent, adalimumab, is currently enrolling patients.

Figure 2. ***Comparable results with infliximab and etanercept in AS***

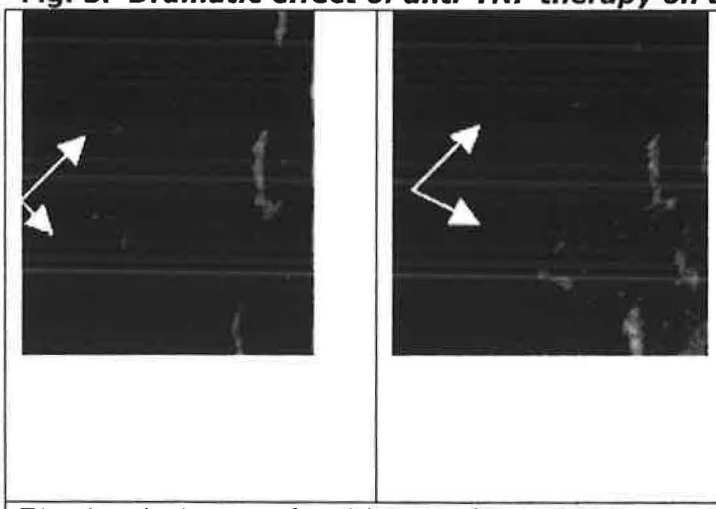


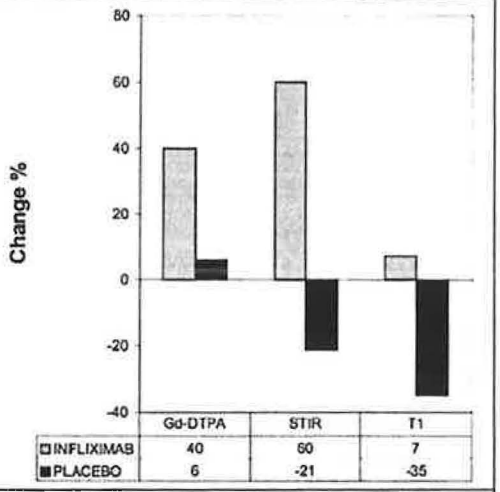
Percentage of AS patients achieving ASAS20 and ASAS50 scores treated with infliximab 5 mg/kg or placebo i.v. at wks 0, 2, and 6. Open circles: infliximab (n=34), closed circles: placebo (n=35) at 0, 2, 6, and 12 wk. From (142).



Percentage of AS patients achieving ASAS20 and ASAS50 scores treated with etanercept 25 mg 2x/wk s.q. or placebo for 24 wk. Etanercept (n=138), placebo (n=139). From (144).

Fig. 3. ***Dramatic effect of anti-TNF therapy on active AS lesions seen on MRI (50)***





T1-spin echo images after Gd-DTPA of L1 and L2 in a patient with AS, before (L) and 12 wk after starting infliximab therapy (R), showing resolution of inflammatory anterior lesions.

Relative changes in activity (Gd-DTPA and STIR) and chronicity (T1) scores in 20 AS patients treated with infliximab.

Similar dramatic responses to anti-TNF therapy have been reported in psoriatic arthritis, undifferentiated spondyloarthropathy, acute anterior uveitis, and at least some reactive arthritis (147-152). It appears that this therapy affects a process that is central to the pathogenesis of all of the spondyloarthropathies. Improvements in bone mineral density in the spine and hip have been observed in patients with SpA treated with anti-TNF agents (153, 154). A few studies have addressed alterations in cytokine patterns during anti-TNF therapy, but the results to date are inconclusive (155-157).

Emerging observations of anti-TNF therapy in AS and SpA. Continuing and expanding observation of patients treated with anti-TNF agents has shown that these drugs maintain continued efficacy. These recent studies have also provided some perspective on the risks and side effects, and have given some indication of which patients are most likely to respond. The Berlin group reported a 54 week extension study (158) of their 3 month placebo-controlled trial of infliximab (142). At week 54, 78% of the patients remained on the drug. (At 2 year followup, 70% remain on the drug – J. Braun, unpublished). By intention-to-treat analysis, about half achieved at least a 50% improvement in BASDAI score. Of 16 patients who discontinued the drug, 11 were for adverse events. Serious events included allergic granulomatosis, tuberculosis, leukopenia, hepatitis, arthritis with positive ANA, and lupus like rash. A fourth of the patients developed a positive ANA, and 4 developed anti-dsDNA antibodies. The infection rate was about 0.5/patient. They also reported that AS patients responding to either infliximab or etanercept with at least a 50% reduction in BASDAI score had significantly shorter disease duration, younger age, lower initial BASFI, and higher initial BASDAI and CRP, compared with BASDAI50 nonresponders (159).

The Belgian group also reported followup of 107 SpA patients treated with infliximab a mean of 1.79 years (160). Continuation rate was 92%. They described 20 serious and/or treatment-related adverse events, including 2 patients with disseminated TB, 13 bacterial infections including 3 patients with retropharyngeal abscess, 2 patients with infusion reactions, 1 patient with skin cancer, and 3 AS patients who developed palmoplantar pustulosis. Although the infection rate and adverse event rate are similar to those reported for RA and CD patients treated with infliximab, retropharyngeal abscess and palmoplantar pustulosis have not been previously reported in patients treated with anti-TNF therapy. The authors speculated that these may reflect a fundamental immune defect in SpA patients. The Belgian group has also compared the SpA and RA patients treated with infliximab in regard to induction of antinuclear antibodies (161). In 62 patients with RA, 52% were ANA+ at baseline vs. 82% at 30 weeks of treatment. In 35 SpA patients, 17% were ANA+ positive at baseline, vs. 89% at 34 weeks. IgM or IgA anti-dsDNA antibodies appeared in 7 RA patients and 6 SpA patients. No patients developed clinical manifestations of SLE.

Whereas infliximab is effective in CD, etanercept has been found not to be, and neither agent is effective in UC (162). Anecdotal cases have been reported of serious flares of CD (163) and UC (S. Kazi, personal communication) in patients with AS treated with etanercept. Since IBD can be occult in patients with AS, this

unexplained phenomenon may be at least a theoretical reason for preferring infliximab in patients with AS.

Deciding whom to treat. The ASessments in AS (ASAS) Working Group has recently published a consensus statement regarding anti-TNF therapy in patients with AS (Table 9). These guidelines would restrict treatment to patients with relatively advanced disease (modified NY criteria, which require grade II radiographic sacroiliitis) and definitely active disease, and would require expert opinion for initiation and assessment. These guidelines will no doubt undergo evolution as the long term risks and benefits of anti-TNF treatment become clearer in the coming years.

Table 9. *ASAS consensus for anti-TNF therapy* (164)

Patient selection	
Diagnosis	AS by modified NY criteria
Active disease	Active ≥ 4 wk; BASDAI ≥ 4; expert opinion favoring treatment
Treatment failure	Failed 2 NSAID. For arthritis or enthesitis:, failed SSZ, local steroids
contraindications	Pg or breastfeeding; TB; hi risk of infection; SLE or MS; cancer in past
Assessment of disease	
ASAS core set for daily practice	
BASDAI	
Assessment of response	
Responder criteria	BASDAI decreased by ≥50% or absolute change of 2 on 10 pt scale Expert opinion favoring continuation
Time of evaluation	Between 6 and 12 wk

Summary

Ankylosing spondylitis is a chronic progressive inflammatory disorder of the spine with a strong genetic basis. It is part of the phenotype of the spondyloarthropathies, which overall have an estimated prevalence of 2% in Caucasian populations. HLA-B27, genes predisposing to IBD, and genes predisposing to psoriasis appear to constitute largely independent but interactive risk factors, and other genes are evidently also important. The symptoms are primarily pain, stiffness, and fatigue. These typically start in early adulthood, but can start in childhood. The disease is 2.5 to 3 times more common in males. Many patients suffer attacks of anterior uveitis, and a small minority develop aortic valve disease and heart block. Many patients suffer disability, and mortality is probably increased. In recent years, a variety of useful clinical indices have been formulated for evaluating disease outcomes and response to therapy. Pathogenesis is poorly understood, but the earliest lesions involve significant bone marrow edema seen on MRI, and biopsies show inflammation of entheses, subchondral bone, and synovium. Pathways of innate immunity are probably involved, and TNF is central to disease activity even in advanced disease. Inhibition of TNF represents a quantum leap in terms of therapy, but its use must be tempered by consideration of known side effects and unknown long term effects. New diagnostic criteria, based on genetic insights and specific lesions seen on MRI, are likely to be developed in the next few years.

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