
How did ankylosing spondylitis become a separate disease?

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ABSTRACT

Individual patients whose disease in retrospect is compatible with a diagnosis of ankylosing spondylitis (AS) began to be described in the 19th century, at a time when “rheumatism” comprised an undefined conglomeration of ailments. In the 1890s, rheumatoid arthritis (RA) began to be extricated from rheumatic fever and gout. But what criteria should delimit the diagnosis of RA? The first assistance came with the introduction of radiology in the first decade of the new century. By the 1930s, objective radiologic distinctions between RA and AS were being made, beginning with the preferential involvement of the sacroiliac joints in AS. The first useful serologic test was developed in the 1950s: “rheumatoid factor” that eventually is present in about three-fourths of cases of RA, but is absent in AS. In the 1970s discovery of clinical associations with specific histocompatibility antigens finalized the distinction between RA and AS with the discovery that one antigen, B-27, is associated ten times as frequently with AS than with RA, while it occurs no more frequently with RA than in the general population. Associations between B-27 and certain radiologic appearances has further been mutually confirmatory of their diagnostic significance.

Introduction

The purpose of this article is to review the development of knowledge about ankylosing spondylitis, how the disease has been defined and has come to be differentiated from rheumatoid arthritis. During this process possible variants of ankylosing spondylitis associated with psoriasis, reactive arthritis and inflammatory bowel disease were discovered and these relationships are also reviewed up to 1974.

No disease has received as many names within one century as has ankylosing spondylitis. Table I is modified from Spencer *et al.*, who listed seventeen (1)! The multiplicity is in part linguistic, in

part because various prominent features of the disease were used to identify it, and resemblances to other diseases that also lacked an acknowledged etiology. Eponymic use has not been strongly nationalistic. While the French use Marie alone or in combinations, the German literature has tended to use the Russian, Bechterew, rather than the German, Strümpell. Bechterew himself came to use Strümpell’s designation.

Paleopathologic evidence

Paleopathologic remains favor the discovery of spondylitic diseases over rheumatoid arthritis (RA) because of the greater likelihood of preservation of the axial skeleton over the extremities (2). The earliest European findings suggestive of RA are two of eleven skeletons in a grave-site on a Swedish island from around 2000 BC (3). The oldest known axial specimen, from the III. Egyptian Dynasty, before 2900 BC, was ankylosed from the 4th cervical vertebra to the coccyx. Absence of a description of the pelvis precludes definite differentiation of diffuse idiopathic skeletal hyperostosis from AS (4). The former diagnosis has been made of a skeleton in the tomb of Thutmose I, circa 1500 BC (5).

Unique in paleopathology is evidence that two identified remains are known to be related. This pertains to the pharaoh Ramses II (13th century BC) and his son, Merenptah, his successor. Radiographic examinations of their mummies makes the diagnosis of ankylosing spondylitis (AS) virtually certain (5).

Early case descriptions

An unearthed partial French skeleton that was described to the Royal Society of London in 1695 is generally accepted as the first convincing instance of ankylosing spondylitis (AS), although lacking any clinical information (6). A few probable cases of this disease were reported during the 19th century prior to the 1880s, for example, a man who

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Table I. (Modified from (ref. 1)
Synonyms for ankylosing spondylitis.

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| Bechterew's disease |
| Chronic ankylosing inflammation of the vertebral column (Strümpell, 1897) |
| Spondylose rhizomélique (Marie, 1898) |
| Spondylitis deformans (Goldthwaite, 1899) |
| Spondylarthritis ankylopoietica (Fraenkel, 1904) |
| Ossifying ligamentous spondylitis, (Knaggs, 1924) |
| Syndesmitte ossifiante (Simmonds, 1931) |
| Spondylitis rhizomelica |
| Marie-Strümpell Disease |
| Morbus Bechterew-Marie-Strümpell |
| Rheumatoid spondylitis (ARA 1941) |
| Pelvo-spondylitis ossificans (Romanus, 1951) |
| Rheumatoid ossifying pelvispondylitis |
| Rhizomelic spondylosis |
| Ankylosing spondylitis (Tichy, 1961; ARA 1963) |
| Atrophic ligamentous spondylitis |
| Atrophic spondylitis |
| Infectious spondylitis |
| Bamboo spine |
| Poker spine |

at 33 “began to stoop a great deal.” When C.H. Fagge (1838-1883) examined him at Guy’s Hospital a year later “His dorsal vertebrae formed one large rounded curve, with little or no movement. He had but slight power of moving the neck; the ribs also seemed to be quite fixed....” He died of pneumonia; the autopsy showed no evidence of tuberculosis. Extensive ankylosis, including the apophyseal joints is described (7). V.O. Sivéń (1868-1918, Helsinki) in 1903 considered this case “without doubt as belonging to the Pierre Marie type” of spondylitis (8).

The first American clinical description, in 1883, was of a woman examined by E.H. Bradford in Boston (9). She had transient symptoms in her small joints during the three years before she was examined, while a marked kyphosis developed. The New York neurologist Charles L. Dana (1852-1935) published three cases of “chronic stiffness of the vertebral column” in 1899 (10). He first saw these men in 1891, 1894 and 1896. All eventually had completely rigid spines. The one patient who was shown photographically also had severe peripheral arthropathy. In 1884 Adolf Strümpell (1853-1925), the professor of medicine at Erlangen

(Nuremberg) made the following rather casual comment in his textbook of medicine:

We may incidentally mention here a remarkable disease that seems unique to us. This is a type of illness in which, very gradually and without pain, the entire vertebral column and hips become completely ankylosed, so that the head, trunk and thighs are rigidly bound together and entirely stiff, while all other joints retain their normal mobility. That very peculiar modification of posture and gait must result from this is obvious. We have personally seen two identical cases of this peculiar disease (11).

William Osler (1849-1919) in the 1892 edition of his “*Principles and Practice of Medicine*” states that “One of the most interesting forms (of arthritis deformans or rheumatoid arthritis) affects the vertebrae, completely locking the articulations, and producing the condition known as *spondylitis deformans*. When the cervical spine is involved the head cannot be moved up and down, but is carried stiffly. The dorsal and lumbar spine may also be involved, and the body cannot be flexed to the slightest degree. No other joint may be affected (12).”

Vladimir Bechterew (1857-1927, St. Petersburg), a neurologist, in 1892 described three patients: a mother and daughter and a man who had remotely incurred some trauma to his back. These were his conclusions:

Based on these data we may assume that in the cases described we have dealt with a chronic process of the vertebral column that develops independently and leads to ankylosis, and probably also with a diffuse, chronic inflammation of the epidural connective tissue. One must also consider that the presentation of our cases resembles spondylitis deformans. The process, on the one hand leads to expanding intervertebral rigidity, and on the other to pressure on the nerve roots.

This sufficiently explains the rigidity or stiffness of the vertebral column, as well as the sensory symptoms of the spinal nerve roots, the

weakness and mild atrophy of the neck and back muscles, as well as the weakness of the muscles of the upper extremities that is sometimes present (13).

Pierre Marie (1853-1940) described six male cases in 1898 as well as his analysis of costo-vertebral specimens at the Dupuytren Museum (Paris). Photographs to demonstrate the posture of these patients are provided (14).

Another male case, also complicated by a history of trauma, reported in 1897, convinced Bechterew of his original interpretation. Two years later, he presented two more cases in order to compare them with the cases that Strümpell and Marie had published since his first report. Bechterew now emphasized that his recent cases had begun with peripheral arthritis (knee, ankle) (15). He disagreed with Marie’s term *spondylose rhizomélique* and suggested Strümpell’s more descriptive “chronic ankylosing inflammation of the large joints and vertebral column (16).” He conceded that the etiology of his earlier cases may have been obscured by heritable factors, trauma, or syphilis. His two new cases were associated with “so-called rheumatic causes.”

It became customary to speak of the “Bechterew type” and the “Strümpell-Marie type” of arthropathy. The former was characterized in addition to stiffness of the back, with dorsal kyphosis, weakness of various spinal muscle groups, and paresthesias in the cervical, dorsal and arm distribution. In the latter type there was neither kyphosis or paresthesias, but ankylosis of the large joints, specially hips and shoulders, with sparing of small joints. Probably due to Bechterew’s neuropathic interpretation “arthritis deformans of the vertebral column” was cited by Hermann Oppenheim (1858-1919) in his 1894 textbook of neurology (17).

In 1899, Valentini voiced the opinion that “By far the outstanding characteristic of *Spondylose rhizomélique* is that it results in ankylosis of the affected joints.” This may occur in rheumatoid arthritis and osteoarthritis, but not inevitably. He proposed a four item classification: 1. chronic articular rheumatism (*i.e.* rheumatoid arthritis),

2. arthritis deformans (*i.e.* osteoarthritis), 3. Marie-Strümpell spondylose rhizomélique, 4. stiffening of the vertebral column with intercostal neuralgia (Bechterew) (18).

Heiligenthal, another German spa physician, in 1900 summarized 23 published cases and added five from his practice (19). He considered the presence or absence of involvement of small peripheral joints not to be diagnostically significant. "Chronic rigidity of the vertebral column with involvement of the large joints is a syndrome that may develop during the course of various types of arthropathies and does not comprise a disease that is circumscribed by either etiology, course or localization."

The early role of roentgenography

The earliest roentgenographic descriptions were made in conjunction with autopsies or of a skeleton. Fraenkel cites a congress presentation by Rudolf Beneke in which, already in 1897, spondylitis was studied "by means of the Roentgen technique (20)." Joel Goldthwait (1866-1961), a Boston orthopedic surgeon, stated in 1899 that, including his ten cases, about 45 cases of spondylitis deformans had been reported. He mentioned that in one of his cases, a 34-year-old man with a five-year history of skeletal symptoms, whose spine was straight and was ankylosed from the pelvis to the cervical region: "The x-ray picture showed a similar osteo-arthritic process (21)." "Osteo-arthritis" then meant what became rheumatoid arthritis and, presumably "similar" meant "typical (22)." It is surprising that Goldthwait was so casual about what must have been one of the earliest radiographic examinations of such a patient.

In 1902 Goldthwait speculated that pain probably does not result from pressure on nerves by newly formed bone, but "hyperemia which surrounds any irritative or inflammatory process (23)." While he carefully described clinical findings, he now did not mention roentgenographic examinations. Goldthwait believed that due to experience gathered in the last three years the diagnosis can now be made at an earlier stage of the disease, thereby improving the chances of successful treatment.

Based on the "several dozen published cases" Slivén found, contrary to Bechterew, that while women in general are more susceptible to arthropathies, this disease occurs predominantly in men. This can probably not be attributed to the more strenuous work that men perform. A particular feature of anatomic preparations of this disease is the symmetry of the articular involvement, contrary to arthritis deformans. Slivén concluded that this is a chronic inflammatory process of the small intervertebral joints that differs from arthritis deformans. Therefore the term spondylosis deformans is misleading. The best designation is Strümpell's "chronic ankylosing inflammation of the vertebral column." "Nevertheless, we are as yet unable to determine whether this is an entirely distinct disease (7)."

In 1904 H.F. Vickery published statistics about cases of chronic joint diseases that had been seen at the Massachusetts General Hospital during 1893-1903 (24). He commented on "the increasing precision in diagnosis in later years." Of 1977 patients, not divided by gender, the 15 with "osteoarthritis of the spine" were seen in the last two years. This diagnosis appears only to have ruled out a specific infectious cause, such as typhoid.

The German pathologist, Eugen Fraenkel (1853-1925) differentiated AS from osteoarthritis by anatomic dissection, based on the ligamentous calcification of the former versus the osteophytes of the latter (20). He called attention to the involvement of the costo-vertebral and the small posterior articulations, but believed that the disease originates in the inter-vertebral discs. The prognosis of AS is worse than that of spondylitis deformans. Writing in 1903: "In the now highly developed Roentgen procedure we are able to produce sharp images of the vertebral column also in the living, an excellent means for gathering information about the vertebrae." "It would be very desirable if patients after their 5th decade when seen in the hospital would systematically undergo roentgenologic examination of the vertebral column, because it will be easily possible by this method to detect the first signs of deforming spondylitis

and then also to obtain definite clinical indications of accompanying manifestations of the further course of this disease

George R. Elliott, a New York orthopedic surgeon, stated ambiguously in 1906: "As a means of diagnosis the x-ray is of especial value. So far a large number of x-ray examinations have proved only of negative value – great stress having been placed upon finding the intervertebral substance and vertebrae intact. When bony ankylosis is proven through chloroform narcosis examination, such negative evidence tends to support small joint involvement (25)."

The director of the medical clinic in the Tübingen spa stated that 14 patients with marked stiffness of the vertebral column were seen in one year (26). Patients with a history of significant trauma were excluded. Ten were classed "Bechterew type" and four "Strümpell-Marie type." All had an x-ray examination. He concluded that the earliest radiographic changes could be detected 15 months after the onset of symptoms. The two types may be differentiated roentgenographically: the Bechterew type resembled spondylitis deformans (osteoarthritis), while the others were consistent with clinical AS.

Walter Krebs (1869-1939), a German radiologist, in 1934 emphasized the diagnostic importance of the radiologic examination of the pelvis (27). This is more important than the vertebral column whenever a diagnosis of Bechterew's disease is being considered because the earliest abnormalities are shown in the sacro-iliac joints. He also pointed out the frequent occurrence of periosteal new bone formation, especially on the ischium. The significance of sacroiliac changes was next confirmed by Jacques Forestier (1890-1978) in 1939 (28).

Categorization after 1930

The question of whether division of cases into the Bechterew and Strümpell-Marie types was meaningful continued to be discussed into the 1930s. Osler in the 1920 edition of his textbook considered that "Both appear to be forms of arthritis deformans, and should neither be regarded nor described as separate diseases (29)." In England C.W. Buckley

(1874-1955) still described the criteria that defined the two categories. However, "much more evidence is required before it is proved that the two types are distinct. I am therefore adopting the classification of spondylitis into two main groups: spondylitis ankylopoietica or ankylosing spondylitis, which includes both the above varieties, and spondylitis osteo-arthritis, the degenerative or hypertrophic form..." (30) Buckley mentioned no association with rheumatoid arthritis.

According to a report from the Lahey Clinic (Boston) in 1940, among 1179 cases of arthritis seen in two years, 30% "were of the rheumatoid type," and 6% of these "were of the Marie-Strümpell type," (1.8% of the total). "Presumably it is a form of rheumatoid arthritis usually originating in the sacroiliac articulations, and accompanied or followed by inflammation of the apophyseal joints (31)."

According to E.W. Boland and A.J. Present in 1945, "Whether the disease is an expression of rheumatoid arthritis as it involves the spine or a separate pathologic entity remains disputed." Four factors in favor of a separate disease were 1: ligamentous calcification and ossification, 2: male preponderance versus female in RA, 3: chrysotherapy is ineffective in spondylitis, 4: x-ray therapy may be helpful in spondylitis.

Favoring spondylitis being a form of RA: 1. peripheral arthritis typical of RA frequently co-exists, 2. the ESR is also elevated, 3. pathologic changes in spinal joints resemble those in RA. They conclude "that the evidence favors the concept that the disease is a variant of rheumatoid arthritis (32)." That AS is not a rare disease was realized in military hospitals during the 1940s because of the concentration of young men, the most susceptible age/gender category. Subsequently a cohort of 1043 cases was reviewed at the Mayo Clinic. Ninety per cent were male, with the onset between 15 and 35 in 80%. Contrary to some reports, in only 35% of these cases the first symptoms were in the lumbar area and 12% in the "hips." In 28% of the patients the first symptoms affected peripheral joints, but in one third of these in a single joint (33).

Fifteen years later Boland reiterated the criteria that supported AS to be a separate disease, adding that tests for rheumatoid factor tend to remain negative, while proponents of a unitary disease pointed out that tests for rheumatoid factor may be negative in patients with "otherwise classical rheumatoid arthritis (34)."

According to the classification made by the American Rheumatism Association in 1941, rheumatic diseases were divided into nine categories. Number 3, rheumatoid arthritis included AS and Still's disease (35). Hence the term "rheumatoid spondylitis." Almost simultaneously the New York Rheumatism Association published a more elaborate classification scheme. In it rheumatoid arthritis had four subdivisions: adult, juvenile, AS, and psoriatic arthritis (36). The ARA (now ACR) formally endorsed the term "ankylosing spondylitis" in preference to "rheumatic spondylitis" in 1963 (37). In the same year the five "Rome (from the site of the meeting where they were developed) diagnostic criteria" were promulgated. AS should be diagnosed if bilateral sacroiliitis is present and associated with any of these five symptoms: 1: low back pain and stiffness for more than 3 months, 2: pain and stiffness in the thoracic region, 3: limited motion in the lumbar spine, 4: limited chest expansion, 5: history or evidence of iritis or its sequelae (38).

Extra-articular findings

Recognition of extra-skeletal symptoms has helped to differentiate AS from RA, while suggesting association with other diseases. The most frequent is anterior uveitis (iritis). This association was described several times in the 1930s. In 1933 E. Kunz, a German ophthalmologist, described seven cases with radiographic evidence of the spondylitis. He pointed out that the occurrence of iritis may be an early symptom and is not correlated with the severity of spondylitic symptoms (39). In a study conducted in Helsinki during 1957, 134 patients with diagnosed iritis underwent clinical and radiographic examinations focused on detecting A Sp. This diagnosis was made in 23% of 134 patients (32% of men, 13% of women) (40). In

a similar investigation at a Norwegian hospital iridocyclitis, was found in 36% of 119 male and 20% of 34 female cases (32.6% combined); but in only 4% of 97 cases of RA (41). Kimura *et al.* in San Francisco found that 10% of uveitis patients, children and adults, have an arthropathy. Of these 191 patients 8% had definite RA, compared to 21% definite and another 14% presumptive ank sp. They considered the association of uveitis with RA coincidental, but significantly associated with AS. (42).

While rheumatic fever was common, the myocardial abnormalities of RA were difficult to separate from those of remote RHD. Actually myocardial lesions are rare and pericarditis occurs relatively frequently. In 1936, two perplexing arthritic patients came to autopsy at the Massachusetts General Hospital: Did they have RA and/or rheumatic heart disease? "There was the same type of involvement of the aortic valve and then the queer fibrous growth over the intima of the first portion of the ascending aorta." The possibility of AS was not mentioned, although the history of the second case is at least suggestive of this diagnosis (43). Eric G. Bywaters (1910-2003) in a 1950 article on the differentiation of rheumatic from rheumatoid heart disease mentions that the 27 autopsies on which the investigation was based included three cases of AS and one of psoriatic spondylitis, but he did not differentiate findings in these cases from cases of RA (44). In 1957 Clark, Kulka and Bauer prefaced their study of "rheumatoid aortitis with aortic regurgitation" by stating that a distinction between rheumatoid arthritis and rheumatoid spondylitis is not being attempted... By the usual criteria all but two patients might be said to have rheumatoid spondylitis. The authors have hoped to side-step the controversy as to whether or not the two diseases should be separated." Nine of 22 patients came to autopsy at which an abnormal aortic root was revealed, rather than the destroyed valve leaflets of RHD. This abnormality resembled syphilitic aortitis. Thirteen of the 22 had a history of uveitis, far greater than likely by chance (45). In RA, contra to AS, the most frequent anatomic finding is evidence of pericarditis (46).

Laboratory findings

The erythrocyte sedimentation rate proved to be a failure in the differential diagnosis of AS, although some investigators still used it to evaluate this disease (47). Tests for the "rheumatoid factor," first using the sheep erythrocyte agglutination technic, were more helpful. Currier McEwen (1902-2003) and associates in 1958 obtained a positive reaction in all but five of 140 cases of RA, while all but one of 119 cases of AS were negative regardless of peripheral joint involvement, as were all but one of 76 cases of psoriatic arthropathy (48). In a study that employed the latex fixation test 84.2% of 291 cases of RA had a positive reaction versus none of 30 with AS (49).

The relationship with human lymphocyte antigens (HLA), even before refinement of the detection method, became the final clue to differentiate AS from RA. Simultaneously in April 1973 Schlosstein *et al.* (from Carl Pearson's laboratory at UCLA) and Derek Brewerton *et al.* in London reported unequivocal differences in the association of one particular antigen (W-27) with AS. In Los Angeles W-27 was found in 8% of control subjects, in 8% of cases of RA and 9% of cases of gout, but in 88% of 40 cases of AS (50). In London this antigen was detected in 4% of controls but in 96% of 75 cases of AS (51), but also in 76% of 33 cases of Reiter's disease (52), and in 52% of 50 cases of anterior uveitis. (53). The relationship of this antigen to AS is also demonstrated epidemiologically: It is uncommon in the Afro-American population, correlating closely with the scarcity of AS in this population. In a survey conducted in four VA Hospitals comprising 1.5 million men with a White: Black proportion of 3.5:1, the W:B ratio of cases of AS was 9.4:1 (54). In a French study HL-A27 was found in 7% of cases of psoriasis, which was insignificantly fewer than in their controls, and in none of four cases of psoriatic spondylitis (55).

Analogues of ankylosing spondylitis

Wilkinson and Bywaters in 1958 concluded their report of 222 cases of AS

stating their belief that AS is distinct from RA because of its male predominance, absence of rheumatoid nodules, frequency of uveitis and absence of rheumatoid factor. Four per cent of their cases had psoriasis, but they could not be differentiated from those without skin lesions. Furthermore, "it appears possible for ankylosing spondylitis to follow colitic, psoriatic, "Reiter's", rheumatoid, or "Jaccoud's" disease of the apophyseal joints, just as it may follow local brucellar involvement. We have not felt in this comparatively limited survey that we could distinguish any such sub-types, either on radiological, or on clinical grounds" (56).

While uncertainty about whether AS is a variant of RA persisted, the question began to become more complex in that diseases other than RA were being discovered to sometimes display spondylitic symptoms. The first of these was psoriasis. The first comprehensive review of psoriatic arthritis was published in 1903 by a physician in Strassbourg, encompassing 81 cases (57). He found several cases of "deforming inflammation and ankylosis" of vertebral joints. However, the first cases of psoriatic spondylitis were described in 1928 (58) and 1931 (59).

Back complaints were first described with Reiter's syndrome (reactive arthritis) in 1953 in London as four cases of ankylosing spondylitis among 21 cases of Reiter's disease of longer than five years of symptoms. In each case, back symptoms were preceded by peripheral arthropathy (60). George W. Csonka at the same clinic a decade later found 17% of 260 cases of Reiter's syndrome had radiologically proven sacroiliitis, but only four developed spondylitic changes (61). Armin E. Good (Ann Arbor, MI) in 1962 found sacroiliitis in 13 of 27 cases of Reiter's disease of at least two years duration, and in 20% diagnosed AS (62).

The third analogue is the association with ulcerative colitis and regional enteritis, The occurrence of peripheral arthropathy during the course of these diseases became known in the 1930s. However, it was McEwen *et al.* who in 1958 diagnosed seven cases of spondylitis among 22 whose ulcerative colitis

was associated with arthritic symptoms. Subsequently, of 45 men and 42 women with either ulcerative colitis or regional enteritis plus arthritis 18 men and two women (23%) had spondylitis (48). In an extension of this study the authors were surprised in 1962 to find that as many as 28% of their patients with either ulcerative colitis or regional enteritis had AS rather than RA. "The association with ulcerative colitis of both peripheral arthritis and spondylitis with a frequency that excludes coincidence has obvious interest from the standpoint of the possible relationship between rheumatoid arthritis and ankylosing spondylitis.... However, there is growing agreement among American rheumatologists with their colleagues in other parts of the world that the two are distinct diseases (63)."

Comparative roentgenologic studies

A systematic comparison of radiologic findings in AS and RA was published by McEwen's group in 1962 (64). Abnormalities were found to differ in frequency and severity, rather than in kind. While 100% of AS cases had bilateral SI joint abnormalities, they were found in 19% of cases of RA, but there were usually slight and often unilateral. Lumbar apophyseal joint abnormalities were found in 84% of AS versus 15% of RA and cervical in 63% versus 25%, but again the greater difference was in the greater severity in AS than in affected cases of RA. There was no significant difference in involvement of hips or shoulders between the two diseases. Pelvic periostitis was more frequent in ank spond, while calcaneal periostitis was more frequent in RA. The authors concluded that their findings support "that ankylosing spondylitis and rheumatoid arthritis are distinct diseases."

In 1971, McEwen *et al.* extended their comparative radiologic studies of AS to the other "sero-negative spondyloarthropathies": the association with psoriasis, Reiter's disease, and inflammatory bowel disease (65). Sacroiliitis appeared the same in all four groups. They were unable to distinguish the findings in cases of IBD from AS. Furthermore, the abnormalities associ-

ated with psoriasis and reactive arthritis were indistinguishable from each other, but the latter two differed from the former two, with some overlap. The clearest difference was in the location and appearance of syndesmophytes. In group 1, the para-vertebral ligaments that ossify to become syndesmophytes usually are symmetrically placed, extending from a corner of the vertebral body to the adjacent corner, with squaring of the vertebral bodies. In about a quarter of group 2 cases there are bulkier "teardrop" syndesmophytes that originate at a mid-vertebral level. The authors concluded that there are two distinct types of spondylitis, clinically and roentgenographically

Conclusion

This review of how ankylosing spondylitis has come to be differentiated from rheumatoid arthritis demonstrates the complexity of defining a rheumatic disease based only on clinical findings, without a proven pathogen, or additional relevant technique. Great hope is placed in new diagnostic procedures that, at best, are found to have statistical but not absolute discriminatory value, but may, furthermore, reveal unexpected additional associations. Rheumatoid factor in the 1950s had been found in about 80% of RA patients and to be absent in patients with AS. While this appeared to be a clear differentiation from RA, it did not elucidate the clinical syndromes in which the rheumatoid factor also was absent. Two decades later, in the early years of histocompatibility antigen research, AS was found to be unusual in the extraordinary prevalence of its association with one parameter, antigen B-27. This was present ten times as frequently in patients with AS as in either patients with RA or healthy control populations. This remarkable difference has been accepted as final proof that AS and RA are different diseases, while also initiating research into associations between AS and other syndromes in which a greater than normal frequency of this antigen were found. It is hoped that the recounting of this history may prove instructive for future efforts to sub-classify other rheumatic diseases.

References

1. SPENCER DG, STURROCK RD, BUCHANAN-WW: Ankylosing spondylitis: yesterday and today. *Med Hist* 1980; 24: 60-9.
2. ACEVES-AVILA FJ, MEDINA F, FRAGA A: The antiquity of rheumatoid arthritis. A reappraisal. *J Rheum* 2001; 28: 751-7.
3. LEDEN I, PERSSON E, PERSSON O: Aspects of the history of rheumatoid arthritis in the light of recent osteo-archeologic finds. *Scand J Rheum* 1988; 17: 341-52.
4. MOODIE RL: *Paleopathology. An Introduction to the Study of Ancient Evidences of Disease*. Urbana, IL, Univ. of Illinois Press, 1923; p.403-4.
5. FELDTKELLER E, LEMMEL E-M, RUSSELL AS: Ankylosing spondylitis in the pharaohs of ancient Egypt. *Rheumatol Int* 2003; 23: 1-5.
6. BLUMBERG BS: Bernard Connor's description of the pathology of ankylosing spondylitis. *Arthritis Rheum* 1958; 1: 553-63.
7. FAGGE CH: A case of simple synostosis of the ribs to the vertebrae, and of the arches and articular processes of the vertebrae themselves, and also of one hip-joint. *Trans Path Soc London* 1877; 28: 201-6.
8. SIVÉN VO: Zur Kenntnis der sogenannten chronisch ankylosierenden Entzündung der Wirbelsäule. *Ztschr f klin Med* 1903; 49: 343-76.
9. BRADFORD EH: Anchylosis of the spine: three cases following rheumatism, two being of gonorrhoeal origin. *Ann Anat & Surg (Brooklyn)* 1883; 7: 279-84.
10. DANA CL: Chronic stiffness of the vertebral column. *Med News* 1899; 75: 673-9.
11. STRÜMPELL A: *Lehrbuch der speziellen Pathologie und Therapie der inneren Krankheiten*. Leipzig, Gogel, 1884. 2: 457.
12. OSLER W: *The Principles and Practice of Medicine*. New York, D. Appleton, 1892; p.286.
13. BECHTEREW W: Von der Verwachsung oder Steifigkeit der Wirbelsäule. *Neurol Ctrbl* 1893; 12: 426-34.
14. MARIE P: Sur la spondylose rhomélisque. *Rev de Méd (Paris)* 1898; 18: 285-315.
15. BECHTEREW W: Neue Beobachtungen und pathologisch-anatomische Untersuchungen über Steifigkeit der Wirbelsäule. *Deut Ztschr f Nervenheilk* 1899; 15: 45-57.
16. STRÜMPELL A: Bemerkungen über die chronische ankylosierende Entzündung der Wirbelsäule und der Hüftgelenke. *Deut Ztschr f Nervenheilk* 1897; 11: 338-42.
17. OPPENHEIM H: *Lehrbuch der Nervenkrankheiten*. Berlin, S. Karger, 1894. 210-1.
18. VALENTINI: Beitrag zur chronischen ankylosierenden Entzündung der Wirbelsäule und der Hüftgelenke. *Deut Ztschr f Nervenheilk* 1899; 15: 239-49.
19. HEILIGENTHAL: Beitrag zur Kenntnis der chronischen ankylosierenden Entzündung der Wirbelsäule. *Deut Ztschr f Nervenheilk* 1900; 16: 275-305.
20. FRAENKEL E: Über chronische ankylosierende Wirbelsäulenversteifung. *Fortschr a d Geb d Roentgenstr* 1903; 7: 62-90.
21. GOLDTHWAIT JE: Osteo-arthritis of the spine: spondylitis deformans. *Trans Am Orthop Assoc* 1899; 12: 103-26.
22. BENEDEK TG: When did "osteo-arthritis" become osteoarthritis? *J Rheum* 1999; 26: 1374-6.
23. GOLDTHWAIT JE: Osteo-arthritis of the spine; spondylitis deformans. *Boston Med & Surg J* 1902; 146: 299-304.
24. VICKERY HF: Chronic joint disease at the Massachusetts General Hospital. *Boston Med Surg J* 1904; 151: 536-7.
25. ELLIOTT GR: Rigid spine. A study with report of five cases. Autopsy. *Am J Orthop Surg* 1906; 3: 305-33.
26. SCHLAYER: Über chronische Wirbelsäulenversteifung. *Fortschr a d Geb d Roentgenstr* 1906; 10: 261-70.
27. KREBS W: Das Röntgenbild des Beckens bei der Bechterewschen Krankheit. *Fortschr a d Geb d Roentgenstr* 1934; 50: 337-42.
28. FORESTIER J: The importance of sacro-iliac changes in early diagnosis of ankylosing spondylarthritis; Marie-Strümpell-Bechterew disease. *Radiology* 1939; 33: 389-402.
29. OSLER W, MCCRAE T: *The Principles and Practice of Medicine*, 9th ed. D. Appleton & Co., 1920; p.1128-9.
30. BUCKLEY CW: Spondylitis deformans. *Brit Med J* 1931; 1: 1108-11.
31. HARE HF: The diagnosis of Marie-Strümpell arthritis with certain aspects of treatment. *N Eng J Med* 1940; 223: 702-5.
32. BOLAND EW, PRESENT AJ: Rheumatoid spondylitis. A study of one hundred cases with special reference to diagnostic criteria. *JAMA* 1945; 129: 843-9.
33. POLLEY HF: The diagnosis and treatment of rheumatoid spondylitis. *Med Clin N Am* 1955; 509-28.
34. BOLAND EW, PRESENT AJ: Rheumatoid spondylitis. *JAMA* 1945; 129: 843-9.
35. HENCH PS, BAUER W, BOLAND E *et al.*: Rheumatism and arthritis (Eighth Rheumatism Review). *Ann Intern Med* 1941; 15: 1001-108. 1003.
36. HENCH PS, BAUER W, BOLAND EW *et al.*: Rheumatism and arthritis (Ninth Rheumatism Review. *Ann Intern Med* 1948; 28: 66-168. 68-69.
37. BLUMBERG BS, BUNIM JJ, CALKINS E *et al.*: Nomenclature and classification of arthritis and rheumatism (tentative) accepted by the American Rheumatism Association. *Bull Rheum Dis* 1964; 14: 339-40.
38. KELLGEN JH, JEFFREY MR, BALL J: *The Epidemiology of Chronic Rheumatism*, Oxford, Blackwell, 1963. 1: p.326-7.
39. KUNZ E: Ueber das Vorkommen von Iritis bei chronisch-entzündlicher Wirbelsäulenversteifung (Spondylarthritis ankylopoetica). *Klin Monatsheft f Augenheilk* 1933; 91: 153-63.
40. LAITINEN H, PELTOLA P, SARAJAS-KYL-LÖNEN S: Spondylarthritis ankylopoetica associated with iritis. *Ann Med Intern Fenn* 1959; 48: 87-103.
41. Haarr M: Rheumatic iridocyclitis. *Acta Ophthalmol* 1960; 38: 37-45.
42. KIMURA SJ, HOGAN MJ, O'CONNOR GR *et al.*: Uveitis and joint diseases. *Arch Ophthalmol* 1967; 77: 309-16.
43. MALLORY TB: Case records of the Massachusetts General Hospital, 22141, 22142. *N Eng J Med* 1936; 214: 690-8.

44. BYWATERS EG: The relation between heart and joint disease including "rheumatoid heart disease" and chronic post-rheumatic arthritis (type Jaccoud). *Brit Heart J* 1950; 12: 101-31.
45. CLARK WS, KULKA P, BAUER W: Rheumatoid aortitis with aortic regurgitation. *Am J Med* 1957; 22: 580-92.
46. BONFIGLIO T, ATWATER EC: Heart disease in patients with seropositive rheumatoid arthritis. *Arch Intern Med* 1969; 124: 714-9.
47. OKSALA A: Rheumatoid arthritis, spondylarthritis ankylopoietica and focal infection in acute anterior uveitis. *Acta Ophthalm* 1960; 38: 322-9.
48. MCEWEN C, ZIFF M, CARMEL P *et al.*: The relationship to rheumatoid arthritis of its so-called variants. *Arthritis Rheum* 1958; 1: 481-96.
49. ROTHERMICH NO, PHILIPS VK: The serologic diagnosis of rheumatoid arthritis. *JAMA* 1957; 164: 1999-2004.
50. SCHLOSSTEIN L, TERASAKI PI, BLUESTONE R *et al.*: High association of an HL-A antigen, W27, with ankylosing spondylitis. *N Eng J Med* 1973; 288: 704-6.
51. BREWETON DA, HART FD, NICHOLLS A *et al.*: Ankylosing spondylitis and HL-A27. *Lancet* 1973; 904-7.
52. BREWERTON DA, NICHOLLS A, OATES JK *et al.*: Reiter's disease and HL-A27. *Lancet* 1973; 996-8.
53. BREWERTON DA, NICHOLLS A, CAFFREY M *et al.*: Acute anterior uveitis and HL-A27. *Lancet* 1973; 994-6.
54. BAUM J, ZIFF M: The rarity of ankylosing spondylitis in the Black race. *Arthritis Rheum* 1971; 14: 12-8.
55. SEIGNALET J, CLOY J, GUILHOU JJ *et al.*: HL-A antigens and some immunologic factors. *Tissue Antigens* 1974; 4: 59-68.
56. WILKINSON M, BYWATERS EG: Clinical features and course of ankylosing spondylitis. *Ann Rheum Dis* 1958; 17: 209-28.
57. ADRIAN C: Ueber arthropathia psoriatica. *Mitt a d Grenzgeb d Med u Chir.* 1903; 11: 237-83.
58. ZELLNER E: Zur Kenntnis der Arthropathia psoriatica. *Munch med Wchnschr* 1928; 75: 903-4.
59. BAUER J, VOGL A: Psoriasis und Gelenkleiden. *Klin Wchnschr.* 1931; 37: 1700-95.
60. FORD DK: Natural history of arthritis following venereal infection. *Ann Rheum Dis* 1953; 12: 177-97.
61. CSONKA GW: Reiter's syndrome. *Ergeb d inn Med u Kinderheilk.* 1965; 23: 125-89.
62. GOOD AE: Involvement of the back in Reiter's syndrome. *Ann Intern Med* 1962; 57: 44-59.
63. MCEWEN C, LINGG C, KIRSNER JB: Arthritis accompanying ulcerative colitis. *Am J Med* 1962; 33: 923-41.
64. DILSEN N, MCEWEN C, POPPEL M *et al.*: A comparative roentgenologic study of rheumatoid arthritis and rheumatoid (ankylosing) spondylitis. *Arthritis Rheum* 1962; 5: 341-68.
65. MCEWEN C, DITATA D, LINGG C *et al.*: Ankylosing spondylitis and spondylitis accompanying ulcerative colitis, regional enteritis, psoriasis and Reiter's disease. *Arthritis Rheum* 1971; 14: 291-318.

Original studies of heart disease in ankylosing spondylitis included six cases of aortic incompetence, but this was attributed to probable antecedent rheumatic fever. However, association between ankylosing spondylitis and aortic incompetence occurred serendipitously in 1956, when the first 100 patients into whom Charles W Hufnagel had inserted a prosthetic aortic valve were reviewed, and it was found that 10% had ankylosing spondylitis, a frequency which was recognised to be far greater than could be attributed to chance (Schilder et al. *How did ankylosing spondylitis become a separate disease?* Clin Exp Rheumatol. 2009;27 Suppl 55:S3-9).