

Scientific Contributions of ankylosing spondylitis patient advocacy groups

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The Spondylitis Association of America has been the driving force behind a major research initiative in the US, having leveraged a substantial amount of money into a \$4.5 million grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The grant last year established the North American Spondylitis Consortium to expedite the search for genes that determine susceptibility to ankylosing spondylitis. The German Ankylosing Spondylitis Society, which has more than 14,000 patient members, initiated in 1996 a professional survey of ankylosing spondylitis patients, with financial support from the German Federal Health Ministry. The results of this survey have recently been published but only in the German language; a part of it is summarized here in English. Following are some of the important findings: The average age at disease onset does not differ significantly between men and women, but there is a significantly longer delay in disease diagnosis among female patients. The average delay in disease diagnosis is getting shorter; there was an average delay of 15 years for patients with disease onset in the 1950s, and it decreased to 7.5 years for patients with disease onset between 1975 and 1979. There was a relatively greater degree of underdiagnosis of the disease among female than male patients in the past; whereas only 10% of the patients in whom the disease was diagnosed in about 1960 were women, this percentage has progressively increased in the subsequent decades to reach 46% among those in whom the disease was diagnosed since 1990. The speed at which spinal ankylosis progresses is slower in female patients, but women are in a significantly worse situation than men in terms of pain and the need for drug therapy, even though the women in the German Ankylosing Spondylitis Society sample are, on average, younger than the men and have a shorter average disease duration. It is possible that the slower and relatively incomplete progression of spinal ankylosis in female patients impedes the occurrence of a decrease in pain with time, compared with that observed in male patients. *Curr Opin Rheumatol* 2000;12:239–247 © 2000 Lippincott Williams & Wilkins Inc.

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Abbreviations

ASIF	Ankylosing Spondylitis International Federation
DVMB	Deutsche Vereinigung Morbus Bechterew
IBD	Inflammatory bowel disease
NASC	North American Spondylitis Consortium
NASS	National Ankylosing Spondylitis Society
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
SAA	Spondylitis Association of America
SVMB	Schweizerische Vereinigung Morbus Bechterew

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The patient advocacy groups, such as the British National Ankylosing Spondylitis Society (NASS) [1–4], the Swiss Schweizerische Vereinigung Morbus Bechterew (SVMB) [5,6], and their international federation, the Ankylosing Spondylitis International Federation (ASIF) [7], have made significant contributions to research in ankylosing spondylitis. The ankylosing spondylitis society in Germany, the Deutsche Vereinigung Morbus Bechterew (DVMB), has more than 14,000 patient members, the one in the US is called the Spondylitis Association of America (SAA). In fact, such societies now exist in 24 countries, including Canada, Japan, Australia, Taiwan, Singapore, and many European countries, with altogether about 40,000 members. Nearly all of these societies distribute quarterly newsletters, many have published guidebooks for ankylosing spondylitis patients in their own national languages, and most have regional branches within their countries where patients gather for weekly group exercises. For instance, there are 377 such groups in Germany, 240 in Sweden, 105 in the UK, and 80 in Switzerland. Many of these patient members have participated in the clinical and immunogenetic studies currently underway in Europe and North America. An international survey initiated by ASIF on disease triggering events contributing to ankylosing spondylitis, and another survey to find the incidence and prevalence of spinal fractures in ankylosing spondylitis, are in preparation. The review highlights some of the major recent achievements of the SAA and summarizes in English the salient results of a comprehensive survey performed in Germany by the DVMB, the results of which have recently been published but only in the German language [8–10, 11•].

The Spondylitis Association of America and the North American Spondylitis Consortium

Over the past two decades there has been relatively little interest in ankylosing spondylitis research in the US

compared with Europe. Although the primary role of the SSA, formerly known as the Ankylosing Spondylitis Association, has been patient education and support, the association has taken on the challenge of helping energize national participation in ankylosing spondylitis research. In less than 3 years, this patient self-help organization has succeeded in this effort by directly encouraging and stimulating individual investigators to carry out patient-based research in ankylosing spondylitis and by lobbying government agencies to increase funding for the disease.

In 1996, when the SAA board of directors made a commitment to facilitate research efforts, the leadership sought advice from the National Institutes of Health and from individual researchers throughout the world. Two outcomes resulted. In 1998, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the SAA cosponsored a 2-day scientific conference at the National Institutes of Health entitled "Ankylosing spondylitis Research: HLA-B27 and Beyond", chaired by Joel Taurog. The conference brought together more than 70 scientists from four diverse basic and clinical research fields: clinical and genetics, immunology and immunogenetics, cartilage and bone, and gut inflammation and microbes. The aims of the conference were to review current work in ankylosing spondylitis; to get critical input from experts in current work; to promote new ideas and approaches to the study of ankylosing spondylitis; and to provide an opportunity to foster new collaborations and sharing of resources and information. By 1998, SAA raised sufficient funds to begin a genetic project. Partnering with John Reveille of the University of Texas-Houston Health Science Center, a DNA repository was established at the university, while recruitment, screening and blood work were coordinated by SAA staff.

North American Spondylitis Consortium

Last year, NIAMS followed with an award of \$4.5 million to establish the North American Spondylitis Consortium (NASC) to expedite the investigation of the genetic basis of ankylosing spondylitis. The project is headed by Dr. Reveille along with investigators at nine other research centers and staff from the SAA. The aim of the NASC is to study in 4 years 400 families in which two or more siblings have ankylosing spondylitis. SAA will play a major role in patient recruitment and maintenance of a central registry of information, including clinical, radiographic and laboratory data, supervised by Dr. Reveille and Dr. David T.K. Yu, who serves as local consultant on the project. The genomic DNA, and frozen lymphocytes and sera from the affected and unaffected siblings and, when available, their parents,

will be banked at the Texas-Houston Health Science Center. The investigators will search for additional alleles within the major histocompatibility complex, besides *HLA-B27*, that may predispose to ankylosing spondylitis. A genomic-wide search will also be conducted, in order to map genes linked to ankylosing spondylitis that reside outside of the major histocompatibility complex. Moreover, once the investigators have mapped the candidate genes, they hope to identify gene mutations and their effect on clinical expression and severity of disease.

Although constructed as an independent effort, the data from NASC will be pooled and analyzed together with data from colleagues in other countries. Readers can obtain more information about the NASC by going to its Internet website at www.asresearch.org. The SAA website is at www.spondylitis.org.

NIAMS has partnerships with various patient advocacy organizations, depending on the needs of the project and the capabilities of the organization. The relation with the SAA is unique in that it is the first time a patient advocacy organization is being funded to become an active partner in a major government funded basic research project. SAA's involvement as a driving force in genetic research led to an invitation to the White House to hear President Clinton announce his support of a proposed bill, HR 306, which would specifically prohibit discrimination against individuals on the basis of genetic testing.

The German ankylosing spondylitis society survey

The German ankylosing spondylitis society, the DVMB initiated a professional survey of ankylosing spondylitis patients in 1996, financially supported by the German Federal Health Ministry. This used a 15-page questionnaire that was prepared in co-operation with German rheumatologists Jürgen Braun, Bernd Frederich, Gerhard Josenhans, and Ernst-Martin Lemmel. This questionnaire had been pilot tested in a large local DVMB branch before being used for the survey. It contained 78 items, including the information on age at diagnosis, age and symptoms at disease onset, misdiagnoses, possible disease-triggering events, family history, associated symptoms, disease activity, functioning ability, effect of ankylosing spondylitis on personal and occupational situations, official recognition of being handicapped, family financial situation, education, labor and employment status, health insurance and pension, age at the starting of pension, doctor consultations, physical therapy, use of medical therapy, home exercises, sports activities, use of special aids and appliances, hospital stays, orthopedic surgery, and the importance of DVMB in managing the disease.

Method and patients:

A total of 3,000 ankylosing spondylitis patients were randomly selected out of the more than 14,000 DVMB patient members, and they were asked by mail to complete the 15-page questionnaire. The response rate within 6 weeks after the distribution of the questionnaire was 54%. The returns corresponded with the general membership of DVMB with respect to age, sex, and federal country. Not all of the questions were answered by all patients, and a patient was ignored in the analysis of a question if the patient did not answer it by not marking one of the proposed positive or negative options (eg. "no associated disease"). Therefore the number of patients responding differs from question to question, and that number is mentioned in the legends used for Table 1 and all figures. For all of the questions using medical terms, we must take into account, of course, that the answers reflect the patients' view, including possible problems with recall and possible misinterpretation of the information they had received from their doctors.

The question on the diseases associated with ankylosing spondylitis, ie, psoriasis, and the inflammatory bowel diseases (IBD), ie, ulcerative colitis and Crohn's disease, was answered by 1499 patients. Ankylosing spondylitis was associated with psoriasis in 17% and with IBD in 9%, and an additional 2% had both psoriasis and IBD; such disease overlap was well established in prior studies [12]. We assume that nearly all of the 72% respondents who marked neither psoriasis nor IBD, have primary ankylosing spondylitis. The term "spondyloarthritis patients" will be used in this report when referring to all respondents, ie, including those with primary ankylosing spondylitis and those who have associated psoriasis or IBD.

Age and sex distribution

The average age of the 1614 respondents was 48.8 years (range 20 to 85 years), and 1070 (66%) of them were males. The age distribution in the DVMB sample is shown by the *gray bars* in Figure 1. For comparison, the age distribution of the general population in Germany [13] is shown by *continuous lines*. The percentage of women among spondyloarthritis patients strongly depended on the date of diagnosis, and the observed final female-to-male

ratio of 1:2 is only a result of averaging out these patients in whom the disease was diagnosed over many decades. Figure 2 shows that whereas among the spondyloarthritis patients diagnosed around 1960, only 10% are women, the percentage of female patients increases continuously in the subsequent decades, reaching 46% among those in whom the disease was diagnosed since 1990. It is of interest that van der Linden and Khan [15] reported in 1985 that radiologically detected sacroiliitis is observed almost as frequently in men as in women, even though their disease is diagnosed relatively later than men's. The DVMB survey indicates that this statements apparently also holds true for the fully developed spondyloarthritis, and the male predominance in ankylosing spondylitis that has so often been noted in the literature may be, at least in part, an artifact induced by deficits in the diagnosis of spondyloarthritis among women many decades ago [11,16].

Age at diagnosis

The distribution of the age at diagnosis is shown in Figure 3. The age distribution of patients with diagnosed spondyloarthritis expected on the basis of Figure 3 is shown in Figure 1 by *broken lines*. Up to age 50 years, the age and gender distributions of the patients correspond roughly to those expected, but after that age, women are underrepresented, and both sexes are underrepresented after age 65 years; ie, the numbers do not correspond to those expected if younger and older spondyloarthritis patients were equally represented in the DVMB membership. The observed underrepresentation of female spondyloarthritis patients older than 50 years in the DVMB sample has possibly resulted from underdiagnosis of spondyloarthritis women many decades ago. It is unlikely that older women have spondyloarthritis far less frequently than younger women, or that female spondyloarthritis patients older than 50 years are less interested in joining a self-help group than the male patients.

Age at disease onset and delay in diagnosis in men and women

The distribution of the age at disease onset (occurrence of initial spondyloarthritis symptoms) shown in Figure 3 indicates that the first symptoms occurred before the age of 15 years in 4% of the patients, between the ages of 15 and

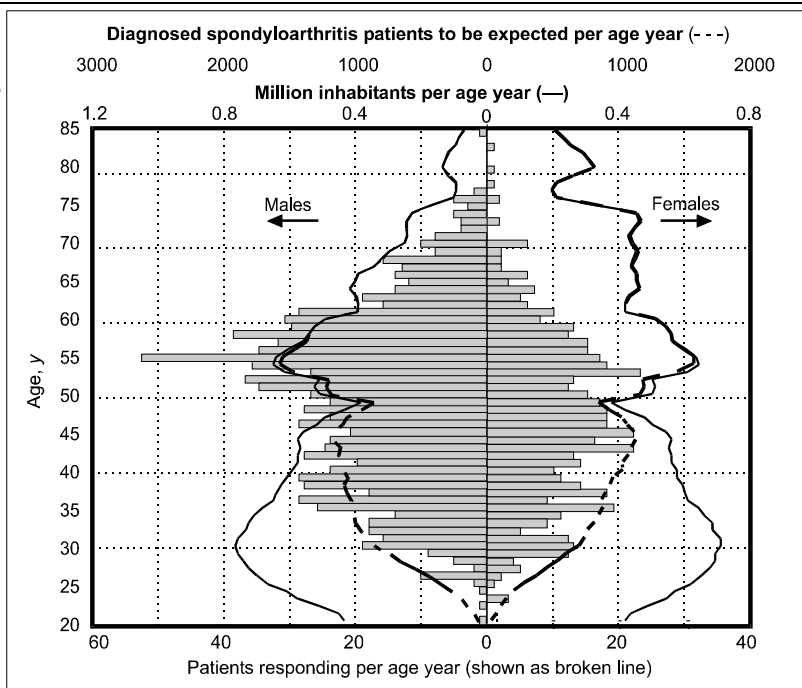
Table 1: The average at occurrence of the first spondylitic symptoms, and at diagnosis

	N	All patients responding	Males	Females	p
Average age at disease onset, y	1,424	25.7	25.9	25.4	NS
Percentage with juvenile disease onset under 17 years of age		10.1	9.9	10.5	NS
Average age at diagnosis (years)	1,599	34.7	34.3	35.3	NS
Average delay in diagnosis (years)	1,396	8.9	8.4	9.8	< 0.01

NS, not significant. Data from Feldtkeller [8–10 and Feldtkeller and Lemmel [11•]

Figure 2. Age distribution of responding patients compared with general population

Age distribution of patients who responded to the Deutsche Vereinigung Morbus Bechterew (DVMB) survey (bars, bottom scale), the corresponding section of the age pyramid of Germany's population [13] (—, second scale from top), and the expected age distribution of patients with diagnosed spondyloarthritis under the assumption that in 0.25% of the population a spondyloarthritis is diagnosed during their life-span, and that the distribution of the age at diagnosis corresponds to that shown in Fig. 3 (---, first scale from top) [8, 9]. Prevalence of diagnosed Spondyloarthritis in Germany was estimated on the basis of the German rheumatology database [14. Assuming percentage other than 0.25% does not affect the form of the dotted line, but only the numbers at the uppermost top scale.



40 years in 90%, and after the age of 40 years in the remaining 6%. The distribution of the age at disease onset agrees well with that published for ankylosing spondylitis patients by Schilling [17] in 1969, and by van der Linden *et al.* [18,19] in 1984. This may be taken as an evidence that, in fact, almost all of the patients responding to this

German survey have ankylosing spondylitis or a related spondyloarthritis. No significant difference was noted in the distribution of the age at disease onset for the different forms of spondyloarthritis, *ie*, primary ankylosing spondylitis and ankylosing spondylitis with associated psoriasis or IBD.

Figure 2: Percentage of female patients depending on the year of their disease diagnosis

Altogether 1,577 patients had entered their age at diagnosis as well as their present age, so that the year of diagnosis could be derived. Because fewer than 10 patients came from each diagnosis year before 1962, the percentage was averaged over these years [9]

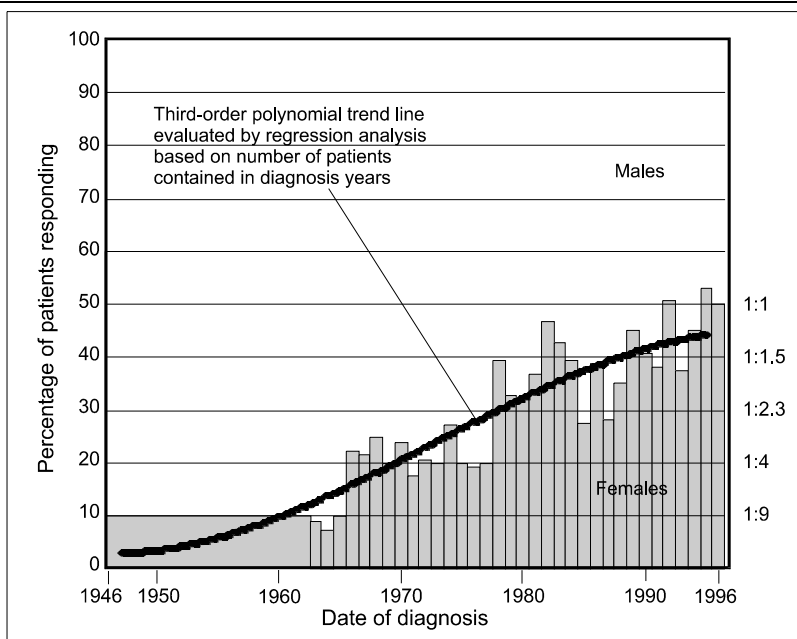
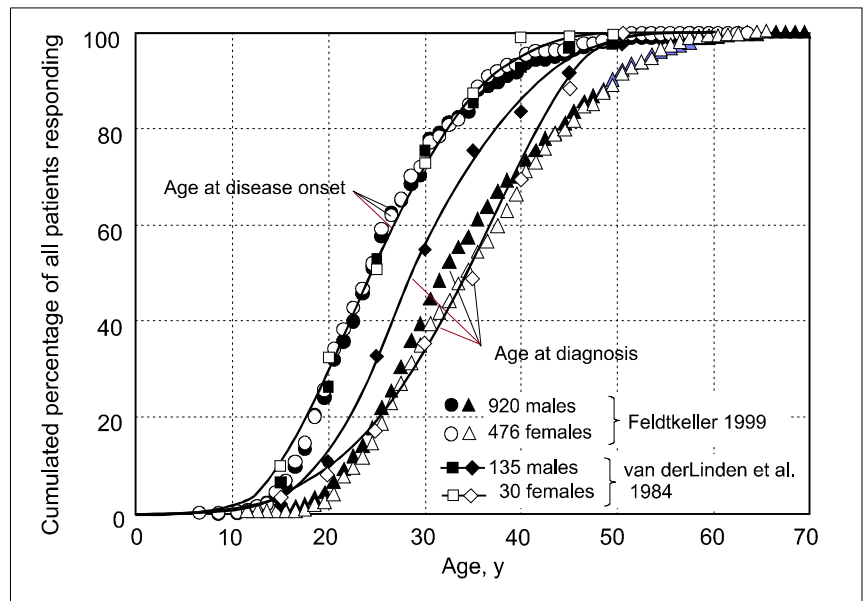


Figure 3. Cumulated distribution of the age at disease onset (occurrence of the first spondylitic symptoms) and of the age at diagnosis for 920 male and 476 female spondyloarthritis patients who responded to these questions

Large steps in the distribution of the age at onset at round numbers (20, 25, 30 years etc.) result from the fact that these numbers are preferably entered in case of uncertainty. Distributions published by van der Linden *et al.* [18,19] in 1984 are shown for comparison.



The average age at disease onset among men and women did not differ significantly, as shown in Table 1, but there was a significantly longer delay in disease diagnosis among women, although the observed difference in the delay of diagnosis is much less than that reported in 1984 by van der Linden *et al.* [18,19]. In Figure 4, the cumulative distribution of the diagnosis delay is shown for different subgroups. Each curve represents a subgroup containing patients with disease onset within the same 5 calendar years. For instance, out of the 87 patients with disease onset between 1955 and 1959, only 45 received their diagnosis within the first 15 years after disease onset. The 1975-to-1979 subgroup was the first in which more than 5% of the patients had entered the same age for the disease onset and for the diagnosis (*ie*, diagnosis delay < 1 year). This subgroup is also the last one for which the completely represented diagnosis-delay-years (*black symbols* in Fig. 4) indicate an approach to saturation, suggesting that the disease has already been diagnosed in most of the patients from these disease-onset years in whom it can be diagnosed with present diagnostics. The data demonstrate that the subgroup with disease onset in 1955 and 1959 experienced a longer average delay in diagnosis than the subgroup with disease onsets in 1975 to 1979.

In order to make a relatively reliable comparison of the average delay in diagnosis for the different years of disease onset, it was assumed that: almost no additional diagnoses will be made in patient subgroups with a disease onset

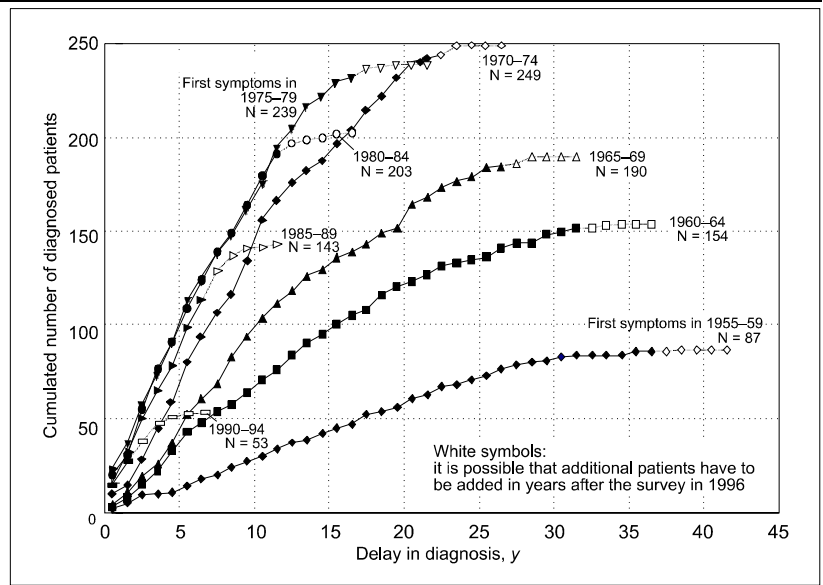
before 1975, and that patients with a disease onset after 1979 (including those whose disease was not yet diagnosed but would be diagnosable according to present standards) have a similar frequency to those with a disease onset between 1975 and 1979. In Figure 5, each subgroup of Figure 4 has been adjusted to a percentile scale with the above-mentioned assumptions.

The increasing slopes in Figure 5 indicate a decreasing average delay in diagnosis in the decades analyzed. This is the first time that it has been quantitatively demonstrated that the average diagnosis delay for spondyloarthritis patients could indeed be getting shorter in recent decades, at least in Germany. Whereas the average diagnosis delay was 15 years for patients with disease onset in the 1950s, it was about 7.5 years for patients with disease onset between 1975 and 1979. An average delay in diagnosis of less than 7.5 years for patients with a disease onset later than 1979 is not expected on the basis of current data.

The relatively smaller number of female spondyloarthritis patients in whom the disease was diagnosed in former decades (Fig. 2), as well as the longer average delay in diagnosis in female patients (Figs. 3 and 5) may have resulted primarily from the facts that in the past ankylosing spondylitis was wrongly assumed to be very rare among women, and there was a relative lack of adequate knowledge about ankylosing spondylitis on the part of physicians. Moreover, the newer imaging modalities for

Figure 4. Number of spondyloarthritis patients in whom the disease was diagnosed within a certain time after occurrence of their first spondylitic symptoms

Each curve represents a subgroup with disease onset within the same 5 calendar years; eg, of the 87 patients with disease onset between 1955 and 1959, only 45 received their diagnosis within the first 15 years after disease onset. .



detecting early sacroiliitis are more sensitive than roentgenography, and the fact that the ankylosing process progresses more slowly in women, with less radiologic involvement of the spine (see below), may have contributed to former underdiagnosis among women compared with men.

Speed and completeness of ankylosis progression and severity of disease in men and women

Brophy *et al.* [20] have studied outcome differences among 252 male and 51 female ankylosing spondylitis patients in the UK. They divided their patients into two groups according to their radiographic scores and found that the

Figure 5. Percentage of spondyloarthritis patients in whom the disease was diagnosed within a certain time after occurrence of their first spondylitic symptoms

As in Fig. 4, each curve represents a subgroup containing patients with disease onset within the same 5 calendar years. In contrast to Figure 4, each subgroup in this analysis has been adjusted to a 100% scale, with the help of the assumptions that: almost no additional diagnoses will be made in patient subgroups with a disease onset before 1975, and that patients with a disease onset after 1979 (including those whose disease was not yet diagnosed but was diagnosable according to present standards) have a similar frequency as those with a disease onset between 1975 and 1979. The increase of the percentage of patients in whom the disease was already diagnosed among the subgroup with disease onset in 1975 to 1979 (▼ curve), may be approximated fairly well by a function (---) (called E3 by mathematicians and related to the "error function") and may thus be extrapolated to the future.

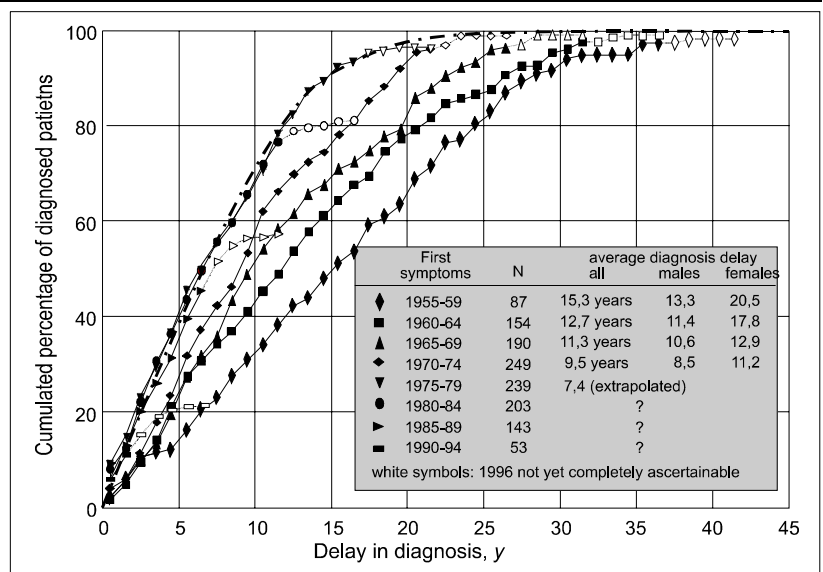
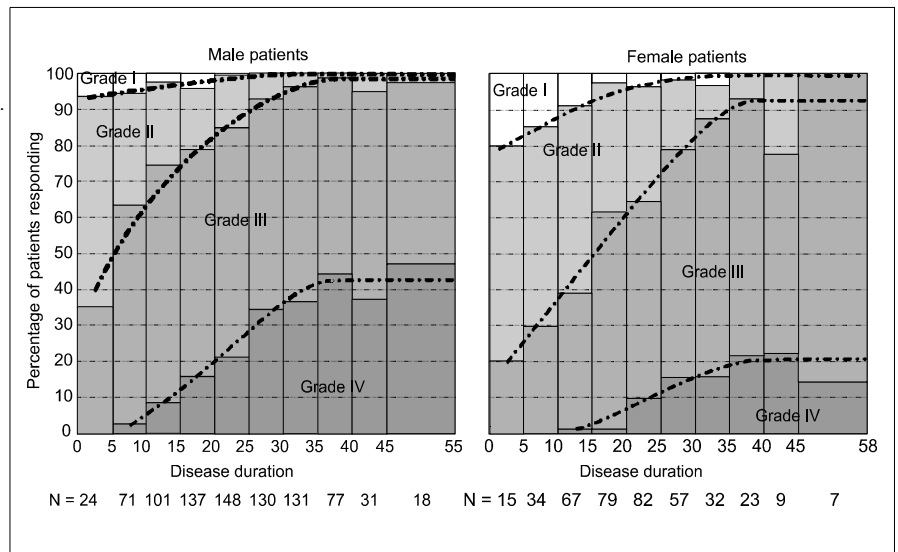


Figure 6. Frequency distribution of the spinal X-ray score of 868 male and 405 female spondyloarthritis patients and its dependence on the disease duration

Bony ankylosis progressed – on average – less rapidly and less complete in women than in men [9].



severe group contained 51% of the male patients but only 22% of the females patients and that in the mild group the average disease duration was 6 years longer for women than for men.

To investigate quantitatively the dependence of the degree of spinal ankylosis on the disease duration (defined as the period of time since the occurrence of “first symptoms typically attributable to AS, we used the spinal radiologic grading system developed by Ott and Wurm [21] and subsequently modified by Schilling [22], which has four grades, as follows: grade I, no radiographic changes; grade II, radiographic changes in sacroiliac joints only; grade III, spine only partially ankylosed; grade IV, bony ankylosis in lumbar, thoracic, and cervical spine.

As shown in Fig. 6, bony ankylosis progressed – on average – less rapidly and less completely in women than in men: 12% of the men have reached grade IV at 15 years after the occurrence of their first spondylitic symptom, but only 2% of the women. After a disease duration of more than 30 years, 40% of the men have reached grade IV, but only 18% of the women. The percentage fraction of those still having grade I or II stage after this duration of disease, is correspondingly greater for women, and so is the percentage fraction of never reaching the final (grade IV) stage at the end of life-span.

Disease severity and outcome depend not only on the speed of spinal ankylosis, but also on severity of pain, physical

handicap, peripheral joint involvement, frequent attacks of acute anterior uveitis, and the necessity of orthopedic surgery. To what extent female spondyloarthritis patients are affected by these consequences of their disease, as compared to men, is shown in Table 2. The results show that women are in a better average situation only with respect to the speed of radiologic ankylosis, but when it comes to pain and the need for drug therapy, they are in a significantly worse situation than men.

For the whole sample, the distribution of pain severity did not depend on the disease duration. But if the male and female patients are analyzed separately (Fig. 7), the percentage of male patients with severe pain decreases from 29%, on average, during the first three decades of the disease, to 14% when the disease has lasted for more than 40 years ($P < 0.05$). However, this phenomenon was not observed in female patients, the equivalent percentages being 31% and 42%, respectively (P value insignificant). A similar difference between male and female patients in the percentage with severe pain over time has also been reported by Zink *et al.* [23●].

The question arises whether this apparently surprising result represents an artifact induced by the former diagnostic deficits among females, so that female patients with a high disease activity could be overrepresented among those in whom the disease was correctly diagnosed in former decades. However, the disease severity in female spondyloarthritis patients significantly depends on the

Table 2. Indicators for a severe disease outcome for male and female spondyloarthritis patients.

	Male patients	Female patients	p
Significantly more favorable values are shown on white background, and significantly less favorable values on dark background.			
NS, difference statistically not significant.			
Average age at time of survey, y	49.6	47.0	< 0,001
Average disease duration at time of survey, y	24.0	21.3	< 0,001
Subjective health state less good or bad	54%	55%	NS
Pain during past 4 weeks severe or very severe	27%	33%	< 0,05
Rather or very much impaired in everyday life	30%	34%	NS
X-ray spinal changes of grade IV [21, 22]	23%	9%	< 0,001
Regular pharmaceutical drug therapy necessary	41%	41%	NS
No medication necessary in the past 12 months	18%	12%	< 0,01
NSAIDs used regularly or occasionally	65%	69%	NS
Gastrointestinal ulcers	10%	9%	NS
Corticosteroids used regularly or occasionally	12%	22%	< 0,001
Sulphasalazine used regularly or occasionally	8%	13%	< 0,01
Experienced at least one iritis attack	42%	36%	< 0,05
Average number of iritis attacks	3.1	3.1	NS
Average number of iritis attacks per disease year	0.13	0.16	NS
Hip or knee involvement	56%	58%	NS
Underwent hip surgery	4%	2%	NS
Underwent surgical kyphosis correction	1%	1%	NS

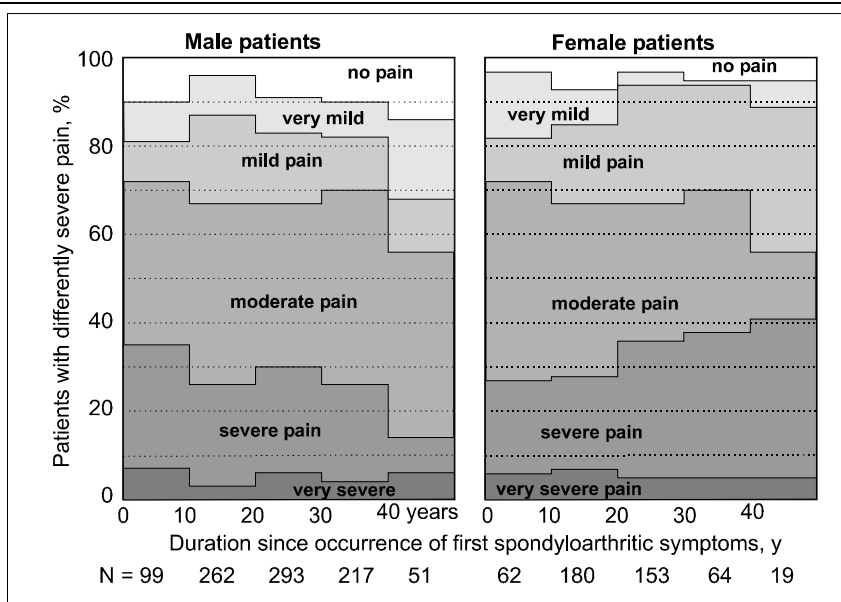
disease duration but not on the date of diagnosis [11●], indicating that the observed increase in the frequency of severe pain with increasing disease duration in female patients (Fig. 7) does not represent a diagnostic artifact but a fact due to natural differences between men and women. Apparently, the slower and less complete ankylosing spinal ossification in female spondyloarthritis patients (Fig. 6)

impedes the occurrence of a decrease of pain with time, as compared to that observed in men.

The percentage with complete painlessness in male patients increases to 14% after the fourth decade of disease, but it stays at about 5% among female patients, independent of the disease duration. A similar pattern is noted for the need

Figure 7. Dependence of frequency distribution of pain severity in 922 male and 478 female spondyloarthritis patients on the disease duration

A similar difference between male and female patients in the percentage with severe pain over time has also been reported by Zink et al [23].



for anti-inflammatory drug therapy with passage of time [10]. The percentage of male patients having severe difficulty in performing everyday functions does not change significantly with time, but it increases significantly among women (from 31% in the first 30 years of disease duration to 60% after 40 years of disease duration) ($P < 0.01$) [10].

In conclusion, the salient results of the German survey of spondyloarthritis patients are as follows: The average age at disease onset among men and women does not differ significantly; but there is a significantly longer delay in disease diagnosis among female patients. The average delay in disease diagnosis is getting shorter, *eg*, there was on average a 15-year delay for patients with disease onset in the 1950s, and it is down to 7.5 years for patients with disease onset between 1975 and 1979. There has been a relatively greater degree of underdiagnosis of the disease among female than male patients in the past, because whereas only 10% of the patients in whom the disease was diagnosed about 1960 were women, this percentage has progressively increased in the subsequent decades to reach 46% among those in whom it was diagnosed since 1990. The speed of spinal ankylosis progression is slower in female patients, but in terms of pain and the need for drug therapy, female patients are in a significantly worse situation as compared with men. It is possible that the slower and relatively incomplete progression to spinal ankylosis in female patients impedes the occurrence of a decrease of pain with time.

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