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Ankylosing Spondylitis: A Late Re-evaluation of 92 Cases

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Ninety-two patients who satisfied the criteria proposed by Kellgren for the diagnosis of ankylosing spondylitis were re-evaluated by clinical, radiological and laboratory parameters after an average length of illness of 18.7 years. The following associated clinical lesions were studied: aortic insufficiency 8%, heart block 3%, iritis 11%, and other associated lesions. Long-term effects of x-ray therapy were evaluated by comparing irradiated and non-irradiated patients; no significant difference was noted in the clinical course of these two treatment groups. On serum protein electrophoresis no characteristic dysproteinemia was demonstrated; in no instance was there a marked hypergammaglobulinemia. Test results for rheumatoid factor, antinuclear factor and antithyroglobulin were all within the range expected for a normal population. In addition to bilateral sacroiliitis, several other characteristic radiological lesions, such as anterior spondylitis, were present in a high percentage of cases. It is suggested that the diagnostic criteria proposed by Kellgren, although useful, should be enlarged and refined.

Quatre-vingt-douze malades dont le cas répondait aux critères proposés par Kellgren pour poser le diagnostic de spondylite ankylosante ont été réexaminés d'après les paramètres cliniques et radiologiques et les analyses de laboratoire après que leur maladie eût duré en moyenne 18.7 ans. On a également étudié diverses pathologies connexes (insuffisance aortique 8%, bloc auriculo-ventriculaire 3%, iritis 11% et autres lésions connexes). On a cherché à évaluer les effets à long terme de la radiothérapie en comparant les malades irradiés et ceux qui n'avaient pas été irradiés: on n'a trouvé aucune différence notable dans l'évolution clinique de ces deux groupes traités. L'électrophorèse de la protéine sérique n'a pas permis de mettre en évidence de dysprotéinémie caractéristique; dans aucun cas, il n'y avait d'hyperglobulinémie marquée des globulines gamma. Les tests relatifs au facteur rhumatoïde, au facteur anti-nucléaire et à l'antithyroglobuline étaient tous dans les valeurs normales que l'on s'attend de trouver dans une population. Outre la sacroilliite bilatérale, on constatait, dans un pourcentage élevé de cas, plusieurs lésions radiologiques caractéristiques, comme de la spondylite antérieure. On estime que les critères diagnostiques proposés par Kellgren, bien qu'ils soient utiles, devraient être étendus et précisés.

IN 1962 the American Rheumatism Association adopted the criteria proposed by Kellgren[1] as the diagnostic standards for ankylosing spondylitis. Since a large group of patients with spondylitis was available for study at Queen Mary Veterans Hospital, Montreal, we believed that the application of these criteria to this group would allow for a comprehensive and controlled study of a standardized group of unequivocal spondylitics that would be at once retrospective and prospective. This group also provided an opportunity to observe the late effects of large doses of radiation therapy. The present communication describes the results of the initial survey of this group of patients.

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METHODS

All these patients were attending the Treatment Services of Queen Mary Veterans Hospital, Montreal. The records of 162 patients who had previously been given the diagnosis of ankylosing spondylitis were examined from the first through to the last entry. Records which contained data inadequate for the application of Kellgren's criteria or to which a grossly incorrect diagnostic nomenclature had been applied were eliminated after thorough inspection. Twenty-eight such records were discarded.

When the criteria of Kellgren were applied to the 134 records that remained, it was found that 103 patients satisfied the criteria and could be designated as having "definite" ankylosing spondylitis. In other words, 31 cases (23% of those originally designated as ankylosing spondylitis) did not satisfy the criteria and, accordingly, were excluded. In addition, 11 patients were lost to follow-up. Hence, the 92 patients which remained constitute the basis for this study (Table I).

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TABLE I.—COMPOSITION OF SERIES

	No.	%
Total by recorded diagnosis*	162	
Number with inadequate data, etc†	28	
Number tested by criteria‡	134	
Total confirmed by criteria§	103	77
Total followed up	92	89
Deceased	20	20
Surviving	72	80
—irradiated	50	70
—non-irradiated	22	30

*All patients at Queen Mary Veterans Hospital previously diagnosed as having ankylosing spondylitis.

†Records with inadequate data or grossly incorrect diagnosis—removed from series.

‡Total number of records to which criteria of Kellgren were applied.

§Total number of records which satisfied the criteria of Kellgren for the diagnosis of ankylosing spondylitis.

In order to reduce observer error to a minimum, all patients were examined on at least one occasion by the same physician. Patients were seen by appointment, chronological details of the history were reviewed, and the patient was given a complete physical examination. The following laboratory procedures were carried out: urinalysis, complete hemogram, serum protein electrophoresis, titrated latex test, C-reactive protein, serum anti-nuclear factor (ANF), serum antithyroglobulin (ATG), serum uric acid, an electrocardiogram (ECG), and radiographs of the entire spine, the chest and, where indicated, symptomatic peripheral joints. All radiographs were examined and reported by the same radiologist; the clinical and radiological assessments were carried out independently.

With respect to laboratory procedures, the following techniques were used: erythrocyte sedimentation rate (Wintrobe), serum protein electrophoresis (paper electrophoresis using the Spinco Method B with a Durrum Cell and Analytrol apparatus, Spinco Division, Beckman Instruments Inc., Belmont, Calif., U.S.A.), latex fixation test,[2] serum antinuclear factor (LE-TEST, Hyland Laboratories, Los Angeles, Calif.), serum antithyroglobulin (TA-TEST, Hyland Laboratories, Los Angeles, Calif.).

Except for one patient, all of the irradiated patients received their therapy at the Royal Victoria Hospital, Montreal. The characteristics of the beam were as follows: 200 KVP with HVL of 1 mm. of copper. The focal skin distance was 50 cm. Eight ports were used, as follows: a 15 x 15 cm. port for each sacroiliac joint area and a 10 x 15 cm. port for each lumbar, thoracic and cervical area. The average depth dose at the level of the apophyseal and costovertebral joints was 1000 r per course, delivered within 15 days. Each patient received three courses of therapy. After the first course, a period of three to four months elapsed before the second course was started. After the second course, a period of six to eight months elapsed before the third and final course was given. The total radiation delivered to each area of the spine during the three courses was estimated as 3000 r depth dose. Five patients did not complete the full three courses: three patients withdrew after the first course and two patients after the second course. Two patients received more than three courses: one received four and the other five.

RESULTS AND DISCUSSION

The patients in this series are reviewed under two main headings: the "Entire Group", which includes deceased and living patients, and the "Surviving Group", which includes only those patients who were living at the time of the last follow-up visit; there were 92 patients in the first group and 72 in the second (Table I). There was one female in the entire group.

ENTIRE GROUP

Diagnostic Interval

The diagnostic interval was the time between the onset of symptoms and the assigning of the diagnosis of ankylosing spondylitis. This interval ranged from two months to 17 years, with a mean of 5.7 years.

Duration of Illness

The duration of illness was the time from the onset of symptoms to the death of the patient or to the last follow-up visit. The duration of illness for the entire group ranged from two months to 45 years, with a mean of 18.7 years. If the deceased patients were considered separately, the range of illness was from 11 months to 41 years, with a mean of 12.6 years (Table II).

TABLE II.—DURATION OF ILLNESS IN YEARS, CALCULATED FROM THE YEAR OF ONSET OF SYMPTOMS IN ALL GROUPS

Duration in years	*Deceased*	*Irradiated*	*Non-irradiated*	*Total*
0 - 2	2	0	1	3
3 - 4	2	0	0	2
5 - 9	4	2	5	11
10 - 14	6	3	4	13
15 - 19	2	12	3	17
20 - 24	1	32	8	41
25+	3	1	1	5

Miscellaneous Clinical Lesions

A variety of clinical lesions, frequently and erroneously called "complications", are encountered in patients with ankylosing spondylitis. Table III lists these lesions as encountered in the entire group of patients.

Aortitis and Aortic Insufficiency

For some years now aortitis and aortic insufficiency have been recognized, under the title of "spondylitic heart disease", as distinct accompaniments of ankylosing spondylitis.[3] In the present series eight patients (8%) with aortic insufficiency,

TABLE III.—MISCELLANEOUS CLINICAL LESIONS ENCOUNTERED IN 92 PATIENTS WITH ANKYLOSING SPONDYLITIS

	Deceased		*Surviving*		*Total*	
Lesion	*P.M.**	*No P.M.*	*Irradiated*	*Non-irradiated*	*No.*	*%*
Aortic insufficiency	3	?	2	3	8	8
Heart block	2	?	0	1	3	3
Iritis	2	0	7	2	11	11
Gastrointestinal tract disease	0	0	0	1	1	1
Leukemia	0	1	0	0	1	1
Aplastic anemia	0	1	0	0	1	1
Psoriasis	1	0	0	2	3	3

*P.M.—postmortem examination.

the clinically recognized expression of the aortitis, have been encountered. Additional instances might also have been found in the nine deceased patients on whom no autopsy was performed (Table III). This incidence of aortic insufficiency in spondylitis is slightly higher than that reported elsewhere.[4]

Of the eight with aortitis, three had died and five were living. Only one of the living patients had demonstrable hemodynamic changes due to the valvular lesion—namely, left ventricular hypertrophy, left ventricular failure and coronary insufficiency with angina pectoris. The other four had the classical clinical signs of aortic insufficiency, such as an early diastolic murmur and a wide pulse pressure with a collapsing pulse, but gave no history and had no physical signs of cardiac decompensation. None of the survivors were subjected to cardiac catheterization, and the follow-up has been too short to determine whether a typical course can be defined.

It has been claimed[5, 6] that aortic insufficiency is more likely to develop when the spondylitis is severe and a peripheral arthropathy or the other clinical accompaniments of ankylosing spondylitis are present. Analysis of these eight patients does not support this view; four of the eight had only a mild spondylitis, no peripheral arthropathy and none of the other clinical accompaniments of ankylosing spondylitis.

Heart Block

Cardiac conduction defect of variable degree, with and without aortitis, has been described as an accompaniment of ankylosing spondylitis.[6, 7] In this group, three patients had first-degree heart block and none had second- or third-degree block (Table III). We did not have an opportunity to use the development of a progressive degree of heart block as a prognostic sign in the development or progression of the aortitis.

Iritis

Iritis is a well-recognized accompaniment of ankylosing spondylitis.[8] In the present series 11 patients (11%) had iritis at some time during their illness (Table III). No distinct chronological relationship between the spondylitis and the iritis was recognized, but it should be emphasized that in two patients the iritis preceded the spondylitis by as long as seven years. As has been previously indicated,[9] ankylosing spondylitis would be diagnosed earlier if all patients with iritis had detailed history, physical and radiological examinations of the musculoskeletal system. It has been reported that iritis is more commonly found in spondylitis when peripheral joint involvement and the other "complications" develop.[10] Our findings did not support this hypothesis, since five of the 11 patients did not have peripheral arthropathy or any of the other accompaniments of ankylosing spondylitis.

Gastrointestinal Tract

Ankylosing spondylitis has been reported in association with regional enteritis[11] and ulcerative colitis.[12] Only one patient in our series had unequivocal regional enteritis and none had ulcerative colitis (Table III). There was no apparent chronological relationship between flare-ups in the spondylitis and the enteritis in this patient; the enteritis was recognized five years before the spondylitis.

Hematopoietic System

Other than those abnormalities of the hematopoietic system which could be used as an index of clinical activity—such as elevation of the sedimentation rate (ESR), two other hematological diseases were encountered among these patients, namely, acute leukemia and aplastic anemia (Table III). One patient developed acute leukemia five years and two months after three courses of therapeutic irradiation (estimated total spinal depth dose: 3000 r). Another patient developed aplastic anemia 19 months after five courses of radiation; *in toto* this patient had received 5000 r (estimated total spinal depth dose) over a period of five years. Both of these entities are recognized complications of therapeutic irradiation.[13, 14] The cause of death was not determined in nine patients in this series and it is conceivable that the mortality rate from these complications was actually higher.

Psoriasis

Several recent communications have described the articular manifestations of psoriasis,[15, 16] and it is recognized that an ankylosing spondylitis occurs not infrequently in patients with psoriasis.[17] In the present series three patients (3%) had psoriasis, of whom one was deceased and two were living. In one of the living patients the psoriasis and the spondylitis commonly recurred at the same time.

SURVIVING GROUP

The following data represent the results obtained during a survey of the living patients at the time

of their last follow-up visit. An attempt was made to determine the effects of x-ray therapy on the various parameters studied, and this portion of the study is reported from this point of view; 50 patients had therapeutic irradiation and 22 patients did not.

Articular Lesions

Articular lesions were characterized according to involvement of the spinal and peripheral joints. Because of the apparent intermittency of both spinal and peripheral lesions, it was necessary to place considerable reliance on subjective complaints. This was also necessary because it was difficult to develop objective clinical criteria for the acuteness of changes found in the vertebral column on physical examination. Accordingly, each patient was categorized as "clinically active" or "clinically inactive", depending upon the results of historical enquiry and physical examination. Such arbitrary assessment obviously introduces both subjective and objective bias, but some of this bias was obviated by having the same physician evaluate all patients.

Spinal Lesions

In the present report the vertebral lesions are not isolated anatomically but are considered *in toto*. Table IV shows the breakdown of these lesions and illustrates that in each treatment group approximately 90% were "clinically active" and 10% were "clinically inactive" by both subjective and objective parameters. Table III indicates that these results were not biased by the inclusion of recently diagnosed and, therefore, presumably more "clinically active" cases, since only eight living patients had illnesses of less than 10 years. In other words, the clinical course of the irradiated group did not indicate that they had fared any better than the non-irradiated group.

TABLE IV.—ARTICULAR MANIFESTATIONS IN 72 SURVIVING PATIENTS: COMPARISON OF CLINICAL ACTIVITY OF ARTHRITIS IN SPINAL AND PERIPHERAL JOINTS IN IRRADIATED AND NON-IRRADIATED PATIENTS

Treatment group	*Clinical activity*							
	Spinal joints				*Peripheral joints*			
	Active		*Inactive*		*Active*		*Inactive*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Irradiated (50)								
—subjective.....	44	88	6	12	33	66	17	34
—objective.....	48	96	2	4	23	46	27	54
Non-irradiated (22)								
—subjective.....	20	90	2	10	14	64	8	36
—objective.....	20	90	2	10	12	54	10	46

A characteristic clinical course was readily apparent on reviewing the histories of the patients with active disease. Stiffness of the spine, most severe in the morning and after prolonged immobility, was an almost universal complaint. The most enduring pain was aching in character, localized in some or all segments of the spine, and was present almost daily. Acute exacerbations of more severe pain in the back occurred once or twice a week in very severe cases, and several times a year in less severe cases. These exacerbations ("flares") had an average duration of from three to five days and, in untreated cases, eventually subsided spontaneously. Such patients regularly observed that enforced inactivity—e.g. complete bed rest—prolonged the acute flares by several days or more; conversely, persistence in reasonable and normal activity had an ameliorating effect on the pain.

The results suggest that the course of ankylosing spondylitis is not greatly different from that of many other rheumatic diseases—for example, rheumatoid arthritis; a minority improve spontaneously after a variable period of time, but the majority progress at a variable but inexorable rate. These results also indicate that therapeutic irradiation confers no long-term advantage over other forms of therapy available for ankylosing spondylitis.

Peripheral Joint Lesions

Assessment of peripheral joint involvement in these patients was less difficult, since subjective and objective results could be readily compared. Table IV illustrates the close agreement between the two treatment groups in the percentage of patients who had subjective arthralgia and those who had objective evidence of peripheral joint activity. In brief, approximately 50% of each group had objective evidence of peripheral joint involvement. The shoulders, hands, feet, hips and heels (plantar spurs), in that order of frequency, were the most commonly affected peripheral joints. We could not demonstrate a definite temporal relationship between flares in the spinal arthralgia and flares in the peripheral arthralgia.

LABORATORY RESULTS

Urinalysis

An unexpectedly high percentage of patients (27%) had abnormal findings on urinalysis (Table V). From urinary sediment and other appropriate studies, it was found that eight patients had chronic pyelonephritis, one had chronic glomerulonephritis and 11 had a non-specific urinary tract infection (? non-specific urethritis). The incidence of similar urinary abnormalities in these patients at the time of onset of their symptoms of spondylitis could not be determined.

Hemoglobin

Minor degrees of anemia were common and made interpretation of this index difficult. Accordingly, an arbitrary decision was made to accept a hemoglobin of less than 85% (13 g. %) as evidence of significant anemia. Eleven patients (15%)

TABLE V.—LABORATORY RESULTS IN 72 SURVIVING PATIENTS

Laboratory test	Irradiated No.	%	Non-irradiated No.	%	Total No.	%
Urine (72)						
—normal	37	74	15	68	52	73
—abnormal	13	26	7	32	20	27
HGB (72)						
>85%	44	88	17	78	61	85
<85%	6	12	5	22	11	15
ESR (72)						
—normal	26	52	11	50	37	52
—abnormal	24	48	11	50	35	48
EPP (64)						
$\alpha 2$—normal	27	60	10	52	37	58
—elevated	18	40	9	48	27	42
γ—normal	38	84	15	78	53	83
—elevated	7	16	4	22	11	17
Latex (69)						
—positive	1	2	0	0	1	1
—negative	44	90	20	100	64	93
—doubtful	4	8	0	0	4	6
ANF (41)						
—positive	1	4	1	8	2	5
—negative	26	96	13	92	39	95
ATG (41)						
—positive	1	4	0	0	1	3
—negative	26	96	14	100	40	97

The number in parentheses beside the name of the test represents the number of patients on whom the test was performed. The abbreviations are explained in the text.

had an anemia of this degree (Table V); six were in the x-irradiated group and five were in the non-irradiated group. In these patients the anemia could not be related to manifest blood loss and was either microcytic or normocytic in type. There appeared to be a clear relationship between the severity of the spondylitis and the severity of the anemia; four of five patients in the non-irradiated group and six of six in the irradiated group had active spondylitis, frequently with various clinical accompaniments of ankylosing spondylitis, such as iritis, aortitis and peripheral arthropathy.

Erythrocyte Sedimentation Rate

The ESR was elevated in 35 patients (48%) at the time of the last visit; the same percentage was found in both the irradiated and non-irradiated groups (Table V).

If one equates clinical activity solely with elevation of the ESR, surprising variations in the results of this test are seen in this group of patients. However, the clinical course in these patients was one of intermittent acute flares, and a constant elevation of the ESR would not be anticipated. As will be shown later, there was close agreement between elevation of the ESR and abnormalities in serum protein electrophoresis.

Serum Protein Electrophoresis

Serum protein electrophoresis was performed on 64 of the 72 surviving patients at the time of their last follow-up visit. No characteristic changes were found in the albumin fraction but variations from the normal in the α_2 and γ globulin fractions were seen in 33 patients, 51% (Table V). Elevation of the α_2 globulin was found in 27 patients (42%) and elevation of the γ globulin in 11 patients (17%); five patients (7%) had elevations of both fractions. In most instances the elevation of the α_2 and/or γ globulin was only moderate, and in this respect there was no appreciable difference between irradiated and non-irradiated-patients.

As might be expected, there was close agreement between elevation of ESR and elevation of α_2 globulin, namely, 48% and 42% respectively. For this reason, abnormalities of serum protein electrophoresis could not be regarded as exact indicators of clinical activity in ankylosing spondylitis. Furthermore, this group of patients did not display a tendency to marked hyperglobulinemia, a finding recently reported in a small series of cases of ankylosing spondylitis.[18]

Amyloidosis was not encountered in a single deceased or surviving member of this group.

SEROLOGICAL REACTIONS

Several commonly used serological reactions were tested on patients in this series. The latex agglutination test was carried out to determine whether there was any serological relationship between ankylosing spondylitis and rheumatoid arthritis; similarly, the antinuclear factor (ANF) was studied to determine the serological relationship of anklyosing spondylitis to systemic lupus erythematosus. The serum antithyroglobulin (ATG) was determined because this test is said to be positive in a significant number of patients with the various forms of autoimmune illness.[19, 20]

Latex Test

The latex test was performed on 69 (93%) of the 72 patients (Table V). By employing a titration method we hoped that observer error in the slide test could be reduced. Our results confirm the commonly accepted observation[21] that rheumatoid factors are not found in the serum of patients with ankylosing spondylitis. The one patient with an unequivocally positive latex test (it was repeatedly positive—titres of 1/160 to 1/640) had definite rheumatoid arthritis by the criteria of the American Rheumatism Association (A.R.A.) and he had definite ankylosing spondylitis by the criteria of Kellgren. The true significance of the four "doubtful" tests (titres of 1/80) in other patients will only be determined by repeated testing in the future. Our experience is that the rheumatoid factor is almost universally absent in this group of patients with spondylitis.

Antinuclear Factor

This test was performed on 41 (57%) of the 72 living patients and was positive in one patient in each of the treatment groups (Table V). This frequency (5%) is probably not higher than would be expected in a normal population.[22]

Antithyroglobulin

This test was carried out for 41 (57%) of the 72 surviving patients and was positive in one of the

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irradiated patients (Table V). This frequency (3%) is no higher than would be expected in a normal population.

In summary, several of the serological reactions most commonly employed as diagnostic aids in the study of the autoimmune diseases were negative in the vast majority of patients with spondylitis in this series. However, these results do not exclude the possibility that ankylosing spondylitis is an autoimmune type of illness because in several immunological illnesses—for example, rheumatic fever and poststreptococcal glomerulonephritis—serological reactions of this type do not occur.

RADIOLOGICAL RESULTS

At the last follow-up visit all surviving patients had radiographs made of the entire spine and, where applicable, of symptomatic peripheral joints. The types of radiological lesions found in the vertebral column and pelvis are shown in Table VI. The

TABLE VI.—RADIOLOGICAL LESIONS OF THE AXIAL SKELETON IN 72 SURVIVING PATIENTS

Spinal lesion on radiograph	*Irradiated*		*Non-irradiated*		*Total*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Bilateral sacroiliitis	50	100	22	100	72	100
Posterior lumbar joints	44	88	18	82	62	86
Costovertebral joints	40	80	20	90	60	83
Anterior spondylitis	45	90	18	82	63	87
Symphysis pubis and ischium	19	38	6	27	25	35
Osteoporosis	34	68	17	77	51	70
Ligamentous ossification	40	80	17	77	57	79

There are 50 patients in the irradiated group and 22 patients in the non-irradiated group.

sites of the radiological lesions found in the peripheral joints in some of these patients are given in Table VII. A comparative survey of types of lesions was made in irradiated and non-irradiated patients; 72 had complete radiological surveys of the spine, and many had multiple examinations. All the radiographs were reviewed by one observer.

TABLE VII.—SITE OF PERIPHERAL JOINT INVOLVEMENT AS DETERMINED IN 23 PATIENTS WITH SYMPTOMATIC PERIPHERAL JOINTS

Acromio-clavicular	8
Glenohumeral	7
Hips	6
Hands	10
Knees	4
Feet	7
Os calcis	5

The radiological appearance of the sacroiliac joints was graded as follows: Grade 1—subchondral demineralization of bone with minimal erosive changes; Grade 2—sclerosis of bone on either the iliac or sacral side of the joint with definite erosive changes; Grade 3—partial to complete fusion of the joint.

For simplicity, any patient who had any of these radiological changes was considered to have sacroiliitis. The earliest finding in these patients was, commonly, bilateral sacroiliitis. This change was present in some degree in all 72 surviving patients at the last follow-up examination (Table VI). As a matter of interest it should be noted that one patient had radiological evidence of regression of these changes during his illness (Patient H.R., Table VIII); another patient had no evident radiological progression during his follow-up, approximately 20 years. All other surviving patients in this series had unequivocal evidence of radiological progression of the spondylitis over the follow-up period.

Next to sacroiliitis, the most common radiological finding was anterior spondylitis (Table VI). The earliest features of anterior spondylitis are small erosive changes, seen in profile in the vertebral bodies close to the superior or inferior margins and near the disc space. They may be seen on the anterior surface in lateral views, on the anterolateral surface in oblique views, and on the lateral surfaces of the vertebral bodies in anteroposterior views. These were commonly seen in the region of T 11, T 12, L 1 and L 2. Sixty-three (87%) of the patients developed an anterior spondylitis at some time during the course of their illness. The frequency was similar in both treatment groups.

Table VI lists the other radiological lesions seen in the vertebral column in patients with ankylosing spondylitis. Of particular note is the high rate of involvement of the posterior lumbar and costovertebral joints, namely, 86% and 83% respectively. These findings indicate that the radiological diagnosis of ankylosing spondylitis need not be made solely on the appearance of the sacroiliac joints when the sacroiliitis is equivocal. A careful survey of the spine and pelvis will often yield supporting evidence in the form of other changes, particularly anterior spondylitis, as demonstrated in these patients.

Involvement of peripheral joints was demonstrated radiologically in 23 patients; the distribution of this involvement is noted in Table VII. The joints in the region of the shoulder (i.e. glenohumeral and acromioclavicular joints) were most commonly involved. In five patients the radiological changes in the hands were indistinguishable from those of rheumatoid arthritis.

The overriding radiological impression in this group of patients was one of relentless progression. Only two of the 72 had no evidence of progression, and in one of these there was definite regression of the original radiological features of spondylitis; in both of these patients the original radiological findings were limited to the sacroiliac joints. In several other patients the spine became solidly fused but the disease, as determined radiologically, continued to progress in the peripheral joints.

TABLE VIII.—MATCHED SERIES OF 28 CASES OF ANKYLOSING SPONDYLITIS

Patient	Therapy	Year of birth	Year of onset	Clinical accompaniment	Articular lesion		Laboratory test				Radiological status	
					Spinal	Peripheral	HGB	ESR	α2 glob.	γ glob.	Prog.	Reg.
A.S.	NXR	1903	1945	Psoriasis	+	0	N	E	N	N	+	
F.V.G.	XR	1901	1942	None	+	0	D	N	E	N	+	
F.B.	NXR	1904	1943	None	0	+	N	E	E	E	+	
H.G.	XR	1906	1944	None	+	0	N	E	E	N	+	
K.P.	NXR	1908	1944	None	+	0	D	E	N	N	+	
W.W.	XR	1908	1944	Iritis	+	0	N	E	E	N	+	
L.M.H.	NXR	1911	1943	None	+	+	N	N	E	N	+	
W.B.	XR	1911	1943	None	+	0	N	E	N	E	+	
S.I.	NXR	1913	1944	Aortic insufficiency	+	0	N	E	N	N	+	
C.A.V.	XR	1918	1943	Aortic insufficiency	+	0	N	N	N	E	+	
R.M.	NXR	1914	1952	Psoriasis	+	+	N	E	E	N	+	
G.G.	XR	1912	1955	None	+	+	N	E	N	N	+	
R.J.D.	NXR	1916	1941	None	+	0	N	E	N	N	+	
R.A.E.	XR	1916	1941	None	+	0	N	N	E	N	+	
R.B.	NXR	1917	1952	None	+	0	N	N	E	N	+	
H.R.	XR	1917	1949	None	0	0	N	E	N	N		+
R.L.	NXR	1918	1943	None	+	+	N	N	N	E	+	
E.G.	XR	1918	1941	None	+	+	N	E	N	E	+	
A.B.	NXR	1919	1942	Iritis	+	0	N	N	N	E	+	
G.G.	XR	1919	1943	Iritis	+	0	N	E	E	E	+	
H.A.M.	NXR	1921	1942	Iritis	+	+	N	E	E	N	+	
A.M.	XR	1921	1940	None	+	+	N	N	E	N	+	
R.G.R.	NXR	1921	1944	None	+	0	N	N	N	N	+	
J.P.P.	XR	1920	1945	None	+	0	N	E	E	N	+	
B.S.G.	NXR	1931	1953	None	+	0	N	N	N	N	+	
W.W.B.	XR	1928	1952	None	+	+	D	E	N	N	+	
D.A.M.	NXR	1933	1954	None	+	+	N	N	N	N	+	
R.J.N.	XR	1933	1954	None	+	+	D	N	E	N	+	

Therapy—XR and NXR mean therapeutic and no therapeutic irradiation, respectively.
Articular lesion—+ means active disease and 0 means inactive disease.
Laboratory test—HGB means hemoglobin (N is more than 85% and D is less than 85%).
α2 glob. and γ glob. mean α2 and γ globulin, respectively (N is normal and E is elevated).
Radiological status—Prog. means radiological progression and Reg. means radiological regression.

THERAPEUTIC RESULTS

The patients in this series had many kinds of therapy during the course of their illness(es). Acetylsalicylic acid, adrenal corticosteroids, physiotherapy, therapeutic irradiation and phenylbutazone, alone or in various combinations, were commonly employed. The results of these various forms of therapy were not assessed in controlled studies and, therefore, only minimal useful information was gained in this respect. However, several comments can be made about the response to phenylbutazone and x-ray therapy.

Phenylbutazone

Our personal observations support those of Furber[23] and others[24] that this drug has an almost specific effect on the acute flare-ups of ankylosing spondylitis. The response of the arthralgia of ankylosing spondylitis to phenylbutazone is rapid (24 to 48 hours), particularly if the drug is given early in the flare-up and if doses of 600 to 800 mg./day are used initially. We were not impressed with the ability of phenylbutazone to decrease the frequency of acute flare-ups or to relieve the morning stiffness of the spine and, accordingly, do not usually use this drug in long-term "prophylaxis".

Therapeutic Irradiation

As previously mentioned, many of these patients received x-ray therapy in high doses, the estimated depth dose being 3000 r administered in three series over a period of 11 to 13 months. In the last four or five years, however, we have virtually abandoned this form of therapy because acute leukemia and aplastic anemia developed in two of our patients; this change has been recommended elsewhere.[25] To determine the long-term therapeutic effect of irradiation in this group of spondylitics we made up a retrospective "controlled" series in which 14 irradiated and 14 non-irradiated patients were matched by year of birth (± 3 years) and/or year of onset of symptoms (± 3 years). In addition, these same patients were matched according to the various clinical accompaniments of ankylosing spondylitis in order that the comparison would be more valid (Table VIII).

From this comparison (Table IX) it can be seen that there was no evident decrease in the activity of the disease in the irradiated patients on the basis of the patient's subjective responses and physical examination; the two groups had virtually identical laboratory results and similar indices of radiological progression. On the basis of this small and highly selected group, we can only say that the irradiated group did not appear to follow a different clinical course from that of the non-irradiated group over the period of the follow-up. However, although these 28 patients are a highly selected group, it can be seen from the various clinical, laboratory and radiological indices in Tables IV-VI and Table IX that they closely resemble the

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TABLE IX.—COMPARATIVE SERIES—28 MATCHED PATIENTS WITH ANKYLOSING SPONDYLITIS

	Irradiated		*Non-irradiated*		*Total*	
Comparative index	*No.*	*%*	*No.*	*%*	*No.*	*%*
Clinical						
—active	13	93	13	93	26	92
—inactive	1	7	1	7	2	8
HGB						
>85%	11	78	13	93	24	85
<85%	3	22	1	7	4	15
ESR						
—normal	5	36	7	50	12	43
—elevated	9	64	7	50	16	57
α_2 globulin						
—normal	6	43	9	64	15	53
—elevated	8	57	5	36	13	47
γ globulin						
—normal	10	71	11	78	21	75
—elevated	4	29	3	22	7	25
Radiological						
—progression	13	92	14	100	27	96
—regression	1	8	0	0	1	4

Fourteen patients in each group were matched by year of birth (± 3 years) and/or year of onset (± 3 years) and by as many of the clinical accompaniments of ankylosing spondylitis as possible. Of 72 surviving patients, all who satisfied the matching criteria were included in this comparison.

entire group of surviving patients. In addition, in order to decrease bias, every patient who met the requirements for "matching" was included in this comparative review.

In reviewing the entire group of irradiated patients we observed a characteristic response to x-ray therapy. Almost all patients who could tolerate the initial radiation sickness experienced symptomatic relief of spinal arthralgia which lasted, on the average, for two years. Following this period, symptoms directly attributable to the spinal arthritis recurred and continued during the remainder of the follow-up.

Because objective studies of therapy were not done during the course of illness in these patients with spondylitis, only the beneficial effects of phenylbutazone during acute flare-ups and a retrospective analysis of the long-term effect of therapeutic irradiation in a matched group of 28 patients have been presented. Phenylbutazone is valuable in the management of acute exacerbations of ankylosing spondylitis; however, therapeutic irradiation does not appear to alter significantly the natural course of this illness.

CONCLUSIONS

One of the principal objectives of this study was to assess the validity of the criteria proposed by Kellgren for the diagnosis of ankylosing spondylitis. If allowance is made for the fact that the patients in this series were chosen in a highly selective manner, it can be concluded that these criteria are useful in establishing the diagnosis of ankylosing spondylitis in a high percentage of cases.

From our experience with this group of patients, as well as with others, we believe that the criteria proposed by Kellgren should be enlarged and, at the same time, refined in the manner of the A.R.A. criteria for rheumatoid arthritis. Although the basic criteria should be retained, more exact designations, such as "classical" where a complete "bamboo spine" is evident, and "definite"—with an appropriate grade of severity, would greatly facilitate long-term studies on the natural course of this illness. We also suggest that, as in the diagnostic criteria for rheumatoid arthritis, certain pathological entities should be accepted as "diagnostic exclusions"; that is, the diagnosis of ankylosing spondylitis should not be applied in a given case in the presence of such lesions as rheumatoid nodules, a history of Still's disease, the presence of psoriasis, ulcerative colitis or regional enteritis and, perhaps, even a fully developed and classical Reiter's syndrome.

There may be valid objections to these proposals, but they are advanced in the hope that more detailed analysis of the course and clinical accompaniments of ankylosing spondylitis will provide some insight into the etiology of this disease and establish whether or not it is a single disease entity.

With respect to clinical course and therapy in this series, we believe that it is unusual for ankylosing spondylitis to "burn out", spontaneously or after radiation or other forms of therapy. In respect of radiation therapy, it appears that only temporary palliation of symptoms is obtained before the disease resumes its usual course. However, the danger that fatal hematopoietic disease may follow therapeutic irradiation is so great that it should be used only after this possibility has been discussed with the patient.

Recent reports[26, 27] have indicated that phenylbutazone may also cause leukemia. Although, at present, the frequency with which leukemia develops after phenylbutazone therapy appears to be very low, further studies are required before the place of this drug in the treatment of spondylitis and other disorders can be ascertained. Phenylbutazone, as noted above, appears to be beneficial only in the acute flare-up of spondylitis—morning stiffness being influenced minimally or not at all; for this reason we do not usually administer phenylbutazone on a long-term basis. The possible relationship between this drug and leukemia is another reason for intermittent administration.

For all practical purposes, it is almost impossible to diagnose ankylosing spondylitis in the absence of radiological evidence of bilateral sacroiliitis.[1] However, several other radiological lesions are encountered in spondylitis, although none of them are diagnostically specific. Despite this, the fortuitous or inadvertent demonstration of these lesions in a patient should prompt radiological assessment of the sacroiliac joints.

In this group of patients no single laboratory test was diagnostically specific for ankylosing spondylitis. The diagnosis of this disease still rests with the clinician and the radiologist.

The results of the various serological tests for the so-called autoantibodies (in this instance, rheuma-

toid factor, antinuclear factor and antithyroglobulin) were those that would be encountered in a normal population.

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