Genetics of Ankylosing Spondylitis

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Ankylosing spondylitis, also sometimes referred to as rheumatoid spondylitis or Marie-Strumpell disease, is a chronic arthritis affecting the small joints of the spine, sacro-iliac joints, occasionally the peripheral joints (shoulders, hips, and knees), and sometimes the costovertebral, sternoclavicular, and costosternal joints. The onset is usually before the age of 30. At first the affected joints are painful and there is limitation of joint movement but after several years there is painless ankylosis. The disease is compatible with normal survival except in the small proportion of patients who develop aortic incompetence.

Ankylosing spondylitis occurs in Caucasian populations with a frequency of around 2 per 1000 and is commoner in males than in females (Lawrence, 1963). Summarizing the results of several previously reported studies of the frequency of the disease in relatives, Kellgren (1964) estimated a mean prevalence of 0.1–0.2% in controls and 4% in relatives. Ankylosing spondylitis is therefore much commoner among the relatives of affected subjects than in the general population.

Previous studies, which were based on the familial incidence of overt clinical disease, have suggested that this condition is due to an autosomal dominant gene (Hersh, Stecher, Solomon, Wolpaw, and Hauser, 1950; Stecher and Hersh, 1955; Stecher, 1957; Blécourt, Polman, and Blécourt-Meindersma, 1961; Karten, DiTata, McEwen, and Tanner, 1962). This explanation, however, seems rather unsatisfactory because only about 4% of first-degree relatives have clinical manifestations of spondylitis.

Sacro-iliitis is present in almost all patients with clinical manifestations of ankylosing spondylitis (Scott, 1942). It is one of the earliest manifestations of the disease and is often symptomless (Gofton, Lawrence, Bennett, and Burch, 1966) and only recognizable on x-ray film. In the present investigation the familial incidence of radiographic evidence of sacro-iliitis, with or without other mani-

festations of ankylosing spondylitis, has been studied. The results suggest that it may be multi-genic in causation.

Subjects and Methods

Probands. The probands were patients with ankylosing spondylitis who attended the Christie Hospital in Manchester for radiotherapy during the period 1957–1959 and who lived within 15 miles of the centre of Manchester. Altogether there were 76 probands (63 males and 13 females). Details are given in an Appendix.

Relatives. All first-degree relatives over age 14 who lived in the U.K. were sought. Altogether there were 484 first-degree relatives but only 274 were accessible to study, the remainder being under age, dead, or not traceable. Of the 274 accessible relatives, 250 (133 males, 117 females) co-operated and were investigated. The completion rate was therefore 92% (Bremner, Emery, Kellgren, Lawrence, and Roth, 1967).

Those relatives who co-operated underwent a thorough clinical examination of the musculo-skeletal system and x-ray pictures of the sacro-iliac joints were taken in males over 14 years and in females over 44 years. The combined results of 8 surveys from various parts of the world, involving 1750 subjects (from 15 to 65+), indicate that the incidence of sacro-iliitis in the general population is not affected by age (Gofton *et al.*, 1966).

Controls. A population survey was carried out on an area sample in Watford near London. Subjects in the same age range as the probands and their relatives were examined clinically and had x-ray films taken of the sacro-iliac joints. This gave us 188 controls (122 males and 66 females). Details of this survey have been published previously (Ansell and Lawrence, 1966).

Criteria Used in Diagnosing Ankylosing Spondylitis. Two diagnostic categories have been used.

A. 'Clinical ankylosing spondylitis', as diagnosed on the clinical findings at the time of the survey.

B. 'Sacro-iliitis', in which there was x-ray evidence of bilateral sacro-iliitis of the type encountered in ankylosing spondylitis.

Interpretation of Pelvic X-ray Pictures. All x-ray films were read blind by two observers and those

in which there was disagreement were re-read to give a reconciled grading. The young males were read a third time in order to reduce the probability of misinterpretation due to unfused epiphyses. Only definite and unequivocal involvement of both sacro-iliac joints, in accordance with grades 2-4 in the *Atlas of Standard Radiographs of Arthritis* (C.I.O.M.S., 1963), was accepted as evidence of sacro-iliitis.

Results

A total of 76 families has been studied; in 29 of these there was more than one affected person with sacro-iliitis with or without other manifestations of ankylosing spondylitis. There were 50 spouses (8 men and 42 women) of affected subjects, but none had sacro-iliitis with or without other manifestations of ankylosing spondylitis. Among the first-degree relatives there were two pairs of non-identical twins: female twins age 42 neither of whom had spondylitis, and male twins age 16 both with sacro-iliitis.

In calculating the proportion of affected relatives the proband has been omitted from each family (Fisher, 1934). Two male probands were related: a man of 54 was the paternal uncle of a man aged 24. This family was counted twice omitting the proband each time. The proportion of first-degree relatives with clinical ankylosing spondylitis is given in Table I and the results are in good agreement with those of previous studies (reviewed by Kellgren, 1964).

In order to study the mode of inheritance it is necessary to determine the proportions of affected parents, sibs, and offspring separately. This is impracticable when considering clinical ankylosing spondylitis because so few relatives are affected. However, the number of first-degree relatives with sacro-iliitis, with or without other manifestations of spondylitis, is greater and therefore more amenable to analysis (Table I). The proportions of various

relatives affected in this way were as follows: 4 out of 24 fathers (16.67%), 0 of 30 mothers, 13 out of 82 brothers (15.85%), 5 out of 30 sisters (16.67%), and 8 out of 22 sons (36.36%). The proportion of affected sons was significantly greater than the proportion of affected brothers and fathers. This may be due partly to the misinterpretation of the pelvic x-ray pictures in some of the younger males. Autosomal recessive inheritance seems unlikely because the proportion of affected sibs is no greater than the proportion of other affected relatives. If only the data for brothers are considered, and these are the most complete, if ankylosing spondylitis is due to an autosomal dominant gene then penetrance would only be about 32%. If it were an X-linked trait, since it is a fairly common disease, *occasionally* apparent male-to-male transmission might occur because an affected male happened to marry a carrier female. In the present study, in 11 out of 29 families there were instances of male-to-male transmission, which is far more frequent than would be expected even for a common X-linked condition. X-linkage therefore seems unlikely. The possibility remains that the disease is at least partly multigenic in causation.

If a particular trait is due to the cumulative effects of many genes, then a threshold effect may make the distribution of liability appear discontinuous, i.e. so-called quasi-continuous (Grüneberg, 1952). It has been shown that in quasi-continuous variation, if the incidence of a particular trait in the general population is p then the expected incidence in first-degree relatives of probands is approximately $\sqrt{p}$ (Edwards, 1960, 1963). The relevant calculations in the present study are given in Table II. There was fairly good agreement between the expected and observed proportions of affected relatives, though the observed proportions were slightly less than the expected values. This is possibly because the expected proportions ($\sqrt{p}$) are based on the assumption

TABLE I
PROPORTION OF CONTROLS AND FIRST-DEGREE RELATIVES OF PROBANDS, WITH (1) CLINICAL ANKYLOSING SPONDYLITIS, (2) BILATERAL SACRO-ILIITIS WITH OR WITHOUT OTHER MANIFESTATIONS OF ANKYLOSING SPONDYLITIS

	Age	Males			Females			Total		
		Total	Affected	% Affected	Total	Affected	% Affected	Total	Affected	% Affected
(1) <i>Clinical ankylosing spondylitis</i>										
Controls*	15 +	1060	4	0.38	1173	0	0	2233	4	0.18
Relatives	15 +	133	7	5.26	117	2	1.71	250	9	3.60
	30 +	100	7	7.00	94	2	2.13	194	9	4.64
(2) <i>Bilateral sacro-iliitis†</i>										
Controls	—	122	6	4.92	66	1	1.52	188	7	3.72
Relatives	—	128	25	19.53	60	5	8.33	188	30	15.96

* Data from Lawrence (1963).
† Males over 14 years, females over 44 years.

TABLE II

INCIDENCE IN GENERAL POPULATION AND IN FIRST-DEGREE RELATIVES OF PROBANDS, OF SACRO-ILIITIS WITH OR WITHOUT OTHER MANIFESTATIONS OF ANKYLOSING SPONDYLITIS

	General Population			Proportion of Affected Relatives			
	Total	Affected	Incidence	Expected	Observed		
				$\sqrt{p}\%$	Total	Affected	% Affected
Males	122	6	0.04918	22.18	128	25	19.53
Females	66	1	0.01515	12.31	60	5	8.33

tion that there is complete genetic determination, i.e. a maximal value for multifactorial inheritance.

The relative incidence (Penrose, 1953) in male and female sibs (for each sex the incidence in sibs divided by the incidence in the general population) has been calculated assuming different modes of inheritance (Edwards, 1960). Again agreement is best when multifactorial inheritance is assumed (Table III).

TABLE III

RELATIVE INCIDENCE IN SIBS OF SACRO-ILIITIS WITH OR WITHOUT OTHER MANIFESTATIONS OF ANKYLOSING SPONDYLITIS

	Incidence in General Population	Observed Relative Incidence in Sibs	Expected Relative Incidence in Sibs		
			Dominant ($\frac{1}{4}p^{-1}$)	Recessive ($\frac{1}{4}p^{-1}$)	Multifactorial ($p^{-1/2}$)
Males	0.04918	3.22	10.17	5.08	4.51
Females	0.01515	11.00	33.00	16.50	8.12

For diseases in which the genetic predisposition is multifactorial, Falconer (1965) has derived formulae for calculating the *heritability*, which is the proportion of the total phenotypic variance due to additive genetic variance. In the present study 7 out of 188 controls compared with 30 out of 188 first-degree relatives had bilateral sacro-iliitis with or without other manifestations of ankylosing spondylitis. From these data the heritability of the liability to sacro-iliitis with or without other manifestations of spondylitis is $72.5 \pm 10.2\%$ (weighted mean). It was not possible to make meaningful comparisons between like-sexed and unlike-sexed relatives because of the wide limits of the sampling errors due to the small sample sizes. With regard to clinical ankylosing spondylitis, 4 out of 2233 controls were affected compared with 9 out of 250 first-degree relatives (Table I). From these data the heritability of the liability to clinical ankylosing spondylitis is $70.0 \pm 9.3\%$.

Discussion

Evidence from several sources suggests that ankylosing spondylitis is hereditary. The inci-

dence in first-degree relatives of affected subjects is some 20 times greater than in the general population, and of the 10 pairs of monozygotic twins recorded in the literature, where one twin had the condition in 7 instances the other twin was also affected (Moesmann, 1960; Julkunen, 1962). Regarding the mode of inheritance, several investigators have suggested that it is due to an autosomal dominant gene (West, 1949; Hersh *et al.*, 1950; Stecher and Hersh, 1955; Stecher, 1957; O'Connell, 1959; Blécourt *et al.*, 1961; Karten *et al.*, 1962). However, families in which the disease is clearly inherited as an autosomal dominant trait through several generations are rare (Riecker, Neel, and Test, 1950; Graham and Uchida, 1957), and it has therefore been assumed that the gene is not always fully penetrant. Assuming that it is due to an autosomal dominant gene it has been estimated that the gene is penetrant (produces the full clinical picture) in 70–80% of males but only in about 10% of females (Hersh *et al.*, 1950; Stecher and Hersh, 1955; Karten *et al.*, 1962). Incomplete penetrance as an explanation for pedigree patterns in common disorders is rather unsatisfactory for a number of reasons, and becomes rather meaningless when a very low penetrance has to be assumed (Edwards, 1960). Further, in arriving at their estimates of penetrance, Hersh *et al.* (1950) and Karten *et al.* (1962) assumed complete ascertainment of cases basing their calculations for the expected number of affected subjects on a truncated binomial (Hogben, 1932, 1946). This method of analysis assumes that every family with at least one affected person is equally certain to be ascertained. However, this is only possible when a defined population has been exhaustively examined (Crow, 1965), and in studies based on the presentation of cases at a hospital, as in the studies of Hersh *et al.* (1950) and Karten *et al.* (1962), this is not true. In the present investigation incomplete ascertainment has been assumed and the proportion of affected individuals determined by omitting the proband from each family.

It was impossible to obtain a clear idea of the mode of inheritance of ankylosing spondylitis from

the proportion of parents, sibs, and offspring with the clinical form because so few relatives were affected. However, the number of first-degree relatives with sacro-iliitis, with or without other manifestations of ankylosing spondylitis, was much greater and therefore more amenable to analysis. The proportions of parents, sibs, and offspring, with sacro-iliitis appeared to fit no simple mode of inheritance. However, the proportion of affected first-degree relatives agreed fairly well with the proportion expected ($\sqrt{p}$) on multifactorial inheritance and the relative incidence in male and female sibs also agreed best when multifactorial inheritance was assumed. If ankylosing spondylitis is multigenic in causation, estimates of the heritability may be obtained, heritability being that proportion of the total phenotypic variance which is due to additive genetic variance. The estimate of heritability based on the data for sacro-iliitis with or without other manifestations of spondylitis ($72.5 \pm 10.2\%$) was in fairly good agreement with the estimate based on the data for clinical ankylosing spondylitis ($70.0 \pm 9.3\%$). Estimates of heritability however are only valid if there is no major gene contributing to the cause of the disease, since this would lead to discontinuity in the distribution of liability. If the condition were due to a dominant gene, then estimates of heritability would be unreasonably high (Falconer, 1965). The estimates of heritability obtained in the present study were not abnormally high. Another important factor to be considered is that relatives may resemble each other because of non-genetic causes, i.e. exposure to the same environmental factors. This is particularly so in the case of sibs, the correlation between whom is also contributed to by non-additive genetic variance (Falconer, 1965). Errors due to environmental causes of resemblance would be much less in second- and third-degree relatives than in first-degree relatives. The incidence of sacro-iliitis in second- and third-degree relatives is being investigated.

An important problem posed by the present investigation is why only a proportion of subjects with radiographic evidence of sacro-iliitis apparently go on to develop the full clinical picture of ankylosing spondylitis. An answer to this question could provide a therapeutic or even a prophylactic approach to ankylosing spondylitis.

Summary

Previous studies, based on the familial incidence of overt clinical disease, have suggested that ankylosing spondylitis is due to an autosomal dominant gene. This hypothesis seems rather unsatisfactory

because penetrance would have to be very low to account for the fact that only about 4% of first-degree relatives are affected with the clinical form.

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

We are grateful to Dr. D. S. Falconer for reading the manuscript and for making several very helpful suggestions.

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Appendix

Details of Families Studied

Numbers refer to age at the time of examination. Radiographic findings are indicated as N (normal), A (abnormal), - (not known); clinical findings as n (normal), a (affected), or - (not known). For each individual the radiographic findings are given before the clinical findings.

Probands			Spouses	Parents		Sibs		Offspring				
Ref. No.	Age	Sex		M	F	M	F	M	F			
No Sib Families												
383	17	M	41Nn	41Nn	43-n							
39	20	M		48-n	52-n							
136	42	M										
2	28	M		37Nn	72-n							
423	48	M		45Nn	78Nn							
591	40	M		27Nn	61Nn							
164	45	M		42Nn								
301	33	F		35Nn	60Na					53Nn		
359	55	M		57Nn								
374	45	F			74Nn							
358	64	F									44Nn	40-n
507	64	F										
336	29	M			75Nn							
321	31	M		63Nn	63Nn							
One Sib Families												
270	24	M	26Nn	56Nn	52Nn	23Nn	21-n					
253	26	M		57Nn	51Nn		39Nn					
529	27	M		67Nn	68Nn							
137	22	M		52An	47Nn		19Nn					
501	31	M		63Aa	61Nn					36-n		
488	33	M		35Nn	57Aa		55Nn			37Nn		
44	36	M		32Nn	65Nn		63Nn			36An		
495	38	M		39Nn						35An		
387	46	M									48Nn	
541	38	M		37Nn	70Na		69Nn			47Nn		
254	55	M		45Nn						53Nn		
337	47	M								46An	20An	
320	61	M	61Nn			56Nn	25An					
							38An	37-n				
							34Nn	22-n				
							31Aa					
154	32	F	39Nn	73Nn	59-n	52Nn	56Nn	17An				
253	35	F		66Nn	61Nn	30Nn						
1	41	F				26An						
547	58	F								41-n		
256	34	M		38Nn		64Nn						
144	36	M		43Nn						40Nn		
302	49	M		46Nn		81Nn				52Nn		
257	29	M			57Nn	56Nn				26Nn		
274	32	M				56Nn				19Nn		
133	24	M			47Nn	44-n				17Nn		
258	20	M			50Nn	48Nn				16Nn		
Two Sib Families												
549	47	M	38Nn		72Nn		42-n					
557	38	M					32-n					
35	44	M	38Nn		46Nn		36-a					
537	50	M	51Nn		59Nn		33-n					
					59Nn		44-n					
382	54	M	52Nn		58An					60Nn		
484	54	M	55Nn		59Nn							
					56Nn						32An	
145	55	M	53Nn		48Aa					50Nn	30Nn	
217	44	M	40Nn		45An					43-n	22An	
393	45	M	43Nn		76-n		76-n			43An	47An	17Nn
41	67	M									58An	18-n
							66Nn					

Cont'd overleaf

Probands			Spouses	Parents		Sibs		Offspring	
Ref. No.	Age	Sex		M	F	M	F	M	F
Two Sib Families Cont'd									
50	32	M	29Nn	58Nn	57Nn	30An	21-n		
500	60	M	57Nn			55Nn			
554	40	F	42Nn	64Nn	63Nn	61Nn		19Nn	15-n
499	48	M	50Nn	74Nn	72Nn	32Nn			27-n
508	48	M	46Nn			27Nn	36-n		
273	29	M	33Nn	64Nn		38Nn	34-n	17Nn	19-n
						41Nn	50Nn		
5	32	M				26Nn			
381	23	M			45Nn		34-n		
							25-n		
						24Nn			
						22Nn			
Three Sib Families									
34	43	M				53Nn			
						51Nn			
275	67	M	66Nn			48Nn			
506	33	F	40Nn			62An	65Nn		32-n
272	56	F	58Nn			40Nn	51Nn		
107	44	F	47Nn		70Nn		41-a	21Nn	
555	49	F	49Nn			46An	34-n		
498	38	M	38Nn	69Nn	65Nn	47An	53Nn	24Nn	22-n
543	39	M	33Nn			39Nn	45-n		16-n
						37Nn			
						43Nn	53Nn		
						49Nn			
						35Nn	32-n		
							29-n		
						41Nn	42-n		
						37Nn			
Four Sib Families									
418	58	M	61Nn			59Aa	54Nn	30Nn	
						55Nn			
303	54	M				53-n			
						59Nn	43-n		
						47Nn	63Nn		
Five Sib Families									
269	26	M	26Nn	53Nn	52Nn	26Nn	33-n		
						24Nn	27-n		
138	46	M	47Nn	71Nn	70Nn	22-n			
						32Nn	42-n		21-n
155	48	M	41Nn		87Nn	53-n	42-n		18-n
							41-n		
357	55	M	54Nn			46Nn	60Nn		17-n
394	52	M	56Nn				58An		
							57Nn		
							52Nn		
						65Nn	50An	18Nn	
						50Nn	70Nn		
						55Nn	57Nn		
						47Nn	56Nn		
							38-n		
Six Sib Families									
43	48	M				40Nn	54Nn		
						55Nn	49Nn		
3	45	M	33Nn			42An	47Nn		
						64Nn	50Nn		
304	52	M	51Nn			58Nn	42-n		
						56Nn			
571	37	M	36Nn			52Nn		17Nn	22-n
						59Nn	56Nn		
						54Nn	48Nn		
						46Nn			
						55Nn			
						39Nn	28-n		
						37Nn	24-n		
						36Nn			
						30Nn			
Seven Sib Families									
271	35	M	36Nn			34Nn	41-n		
						39Nn	39-n		
						40Nn	29-n		
						41Nn			