

FAMILIAL INCIDENCE OF RHEUMATOID ARTHRITIS

BY

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Several studies of the relatives of patients suffering from rheumatoid arthritis have shown a similar small increase in the incidence of the disease as compared with that found among the relatives of healthy controls. In most of these studies (Empire Rheumatism Council Report, 1950; Barter, 1952; Stecher, Hersh, Solomon, and Wolpaw, 1953; Miall, 1955) the information has been obtained from questionnaires, and few, if any, of the relatives have been seen. However, the most recent survey (Lawrence and Ball, 1958) differs in several respects from previous investigations. The *propositi* were 64 persons with rheumatoid arthritis or a positive sensitized sheep cell test (S.S.C.T.) who were found during surveys of the incidence of rheumatic disease among the population of the town of Leigh in Lancashire. Nearly a third of them had no clinical evidence of disease. 183 parents, siblings, and children of these individuals were examined clinically, radiologically, and serologically. The controls were a group of people matched for age and sex with the relatives seen, taken from a random sample of the population of Leigh. Among the relatives as a group, the incidence of clinical rheumatoid disease was 9 per cent. compared with 2 per cent. among the controls; radiological evidence of the disease was found in 7 per cent. of the relatives and 3 per cent. of the controls; a positive sheep cell test occurred in 13 per cent. of relatives and 5 per cent. of controls. These figures showed an increase in the incidence of the disease in relatives of affected persons of a similar order to that found in other studies, but a striking difference was revealed when the relatives of sero-positive and sero-negative *propositi* were considered separately. The increased incidence of clinical disease in both groups was twice as great among the relatives of those with both clinical disease and a positive sheep cell test (16 per cent. compared with 9 per cent. among sero-negative families). The sero-positive families had four times as much radiological evidence (12 per cent.) and serological evidence (20 per cent.) of rheumatoid disease as the controls, but among the relatives of sero-negative *propositi* the incidence was not increased. These results suggest that the

familial factor is particularly associated with a positive sheep cell test, and that this may be the only manifestation of the disease in a significant number of persons at the time of examination.

It is recognized that the result of the sheep cell test may vary over a period of time in individual patients. In a series of 333 cases of rheumatoid arthritis observed by the authors, in whom the test had been performed on two or more occasions, the results fluctuated between positive and negative in 28 per cent.

Though hospital patients are likely to be among the most severely affected and therefore not representative of the whole pattern of the disease, it was felt that a study of the relatives of such a group, in whom the results of the sheep cell test had been consistently positive or consistently negative over a considerable period, might shed some additional light on the pattern of familial incidence revealed by the work of Lawrence and Ball.

Material

Propositi

The 63 *propositi* were chosen on the basis of the results of two or more sheep cell tests. All had been in-patients in the Rheumatic Unit, and all had been followed for a number of years since discharge. The sheep cell test had been consistently positive in 28 and consistently negative in 35. The composition of the group in respect of clinical severity of disease and the result of the sheep cell test is shown in Table I.

TABLE I
CLINICAL GRADING OF RHEUMATOID ARTHRITIS AND RESULTS OF SENSITIZED SHEEP CELL TEST IN PROPOSITI

Result of S.S.C.T.	Clinical Grading	Sex		Total
		M	F	
Negative	Severe and Moderate	6	14	20
	Mild	8	7	
Positive	Severe and Moderate	8	14	22
	Mild	3	3	
Total		25	38	63

The distribution of the propositi in respect of age and sex is shown in Table II; 35 were resident in Edinburgh, the remainder in different parts of South-East Scotland.

Relatives

The patients had 510 first-degree relatives over the age of 14 years, made up of 126 parents, 246 siblings, and 138 offspring. Of these, 238 (46 per cent.) were accessible and 202 of them agreed to undergo examination. Of the total of 510, 11.9 per cent. of parents, 41.4 per cent. of siblings, and 60.8 per cent. of offspring were seen. The composition of the group by age and sex is shown in Table III.

Method

The majority of the relatives were seen by appointment at the Unit. A history of past or present rheumatic symptoms, previous illness, or injury, and the presence or absence of morning stiffness was obtained. Joints were examined clinically, and a sample of blood was taken for estimation of haemoglobin (100 per cent. = 14.8 g./100 ml.), erythrocyte sedimentation rate, and serological examination. Radiological examination of hands, feet, and cervical spine was carried out in all cases, and if other joints appeared to be involved at the clinical examination these were also x rayed.

In the case of relatives examined at their homes, the haemoglobin level and erythrocyte sedimentation rate were not estimated, but blood was taken for the sheep cell test; arrangements were made for radiological examination to be carried out at local hospitals in all but two instances, men aged 82 and 85, both of whom, clinically, had mild osteo-arthritis; both had negative sheep cell tests. Blood was not obtained from two women, aged 29 and 48, neither of whom had clinical or radiological evidence of rheumatoid disease.

The x rays were read by two observers, five grades being used in respect of rheumatoid arthritis, osteo-arthritis, and disk degeneration:

0 = normal, 1 = doubtful, 2 = mild, 3 = moderate, 4 = severe.

Only Grades 2 to 4 were regarded as positive in the final analyses.

The sensitized sheep cell test was performed by the method of Ball (1950) modified by the use of M.R.C. haemagglutination plates in place of test tubes. Comparison with the results in this laboratory using Ball's original method showed that higher titres were recorded on the plates. In order to retain both the specificity and sensitivity of the original test it was considered advisable to designate a titre of 1/128 as the lowest indicating a positive result.

Results

Of the 202 people examined, 92 were relatives of patients with a consistently positive sheep cell test and 110 were relatives of patients in whom the results had always been negative.

Incidence of Rheumatic Complaints

The over-all incidence of rheumatic complaints is shown in Table IV (opposite).

Relatives of Sero-Positive Patients.—31 (33.7 per cent.) had some rheumatic complaint at the time of examination. Of these, 23 (74 per cent.) had radiological changes in the hands, feet, cervical spine, or other joints which supported the clinical diagnosis. Of the 61 relatives with no complaints, five had

TABLE II
PROPOSITI BY SEX, AGE, AND RESULTS OF SENSITIZED SHEEP CELL TEST

Sex	Male							Female					Total
	15-34	35-44	45-54	55-64	65+	Total	15-34	35-44	45-54	55-64	65+	Total	
Age (yrs)	15-34	35-44	45-54	55-64	65+	Total	15-34	35-44	45-54	55-64	65+	Total	
Results of S.S.C.T.	Negative	1	3	4	3	3	14	1	4	7	8	1	21
	Positive	0	0	2	8	1	11	0	4	2	7	4	17
Total	1	3	6	11	4	25	1	8	9	15	5	38	

TABLE III
AGE AND SEX OF RELATIVES OF PROPOSITI

Sex	Male							Female							Total	
	15-24	25-34	35-44	45-54	55-64	65+	Total	15-24	25-34	35-44	45-54	55-64	65+	Total		
Age (yrs)	15-24	25-34	35-44	45-54	55-64	65+	Total	15-24	25-34	35-44	45-54	55-64	65+	Total		
Result of S.S.C.T. of Propositi	Negative	12	8	9	13	7	3	52	9	10	11	14	6	8	58	110
	Positive	3	15	6	11	5	4	44	7	8	9	8	13	3	48	92
Total	15	23	15	24	12	7	96	16	18	20	22	19	11	106	202	

TABLE IV
INCIDENCE OF RHEUMATIC COMPLAINTS AMONG RELATIVES

Result of S.S.C.T. of Propositi	No. of Relatives	No Complaints or Past Complaints Only				Complaints at Time of Examination			
		No.	Per cent.	X-ray Signs		No.	Per cent.	X-ray Signs	
				No.	Per cent.			No.	Per cent.
Negative ..	110	82	74.5	15	18.3	28	25.5	17	60
Positive ..	92	61	66.3	6	9.9	31	33.7	23	74
Total ..	202	143	70.8	21	14.6	59	29.2	40	67.7

radiological evidence of mild osteo-arthritis or of disk degeneration; one man had minimal radiological signs of rheumatoid arthritis.

Relatives of Sero-Negative Patients.—28 (25.5 per cent.) had rheumatic symptoms at the time of examination, in seventeen (60 per cent.) of whom radiological examination supported the clinical diagnosis. Fifteen of the 82 relatives with no complaints had radiological evidence of mild osteo-arthritis or of disk degeneration.

There is no statistically significant difference between the groups ($p > 0.2$).

Clinical Diagnosis

The diagnoses made on clinical grounds are shown in Table V.

The "undetermined" group included people with minor complaints such as tenosynovitis, capsulitis

of shoulder, ligamentous strain, and ill-defined aches and pains.

Clinically osteo-arthritis was mild in most cases in both groups; there was little more than the presence of Heberden's nodes in three cases among the sero-positive families, and in one among the sero-negative.

Rheumatoid arthritis was graded as moderate or severe in three cases in each group.

There is no statistically significant difference between the two groups as a whole ($p > 0.1$) or in respect of the different diagnostic categories, except in the case of osteo-arthritis which is commoner in relatives of sero-positive patients ($p = 0.05$).

Radiological Diagnosis

The results of radiological examination are shown in Table VI.

TABLE V
CLINICAL DIAGNOSIS AMONG RELATIVES

Results of S.S.C.T. of Propositi	No. of Relatives	Undetermined		Disk Degeneration		Osteo-Arthritis		Osteo-Arthritis + Disk Degeneration		Rheumatoid Arthritis	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Negative ..	110	8	7.3	6	5.5	6	5.5	2	1.8	6	5.5
Positive ..	92	5	5.4	7	7.6	12	13	3	3.3	4	4.4
Total ..	202	13	6.7	13	6.7	18	8.9	5	2.4	10	4.9

TABLE VI
RADIOLOGICAL DIAGNOSIS AMONG RELATIVES

Results of S.S.C.T. of Propositi	No. of Relatives X rayed	Disk Degeneration		Osteo-Arthritis		Osteo-Arthritis + Disk Degeneration		Rheumatoid Arthritis	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Negative ..	110	16	14.6	5	4.5	8	7.3	3	2.7
Positive ..	90	12	13.3	8	8.9	5	5.5	4	4.4
Total ..	200	28	14	13	6.5	13	6.5	7	3.5

There is no significant difference between the groups as a whole, nor in respect of any diagnostic category ($p > 0.1$).

Results of Sensitized Sheep Cell Test

Detailed results of the sheep cell test are shown in Table VII. Among the relatives of sero-positive patients the test was positive in four, two of whom had no clinical or radiological evidence of disease. Among relatives of sero-negative patients the test was positive in two, one of whom had no clinical or radiological evidence of disease.

There is no significant difference between the two groups.

Haemoglobin Level and Erythrocyte Sedimentation Rate

Haemoglobin level and erythrocyte sedimentation rate were estimated in 84 relatives of sero-positive patients and in 100 relatives of sero-negative patients.

Sero-Positive Group.—Five persons, all women, had a haemoglobin level below 80 per cent. None had a raised erythrocyte sedimentation rate, and the sheep cell test was negative in each case. Four had had mild rheumatic complaints in the past.

Seventeen people in this group (two men and fifteen women) had an erythrocyte sedimentation rate above 20 mm./1 hr. Three had evidence of intercurrent infection, three had rheumatoid arthritis, five had signs of generalized osteo-arthritis and in six no cause was found. The sensitized sheep cell test was positive in two cases with clinical rheumatoid arthritis.

Sero-Negative Group.—Eight persons (seven women and one man) had a haemoglobin level below 80 per cent. In none was the sheep cell test positive and only one woman had an erythrocyte sedimentation rate above 20 mm./1 hr. Six had had mild rheumatic complaints in the past.

Thirteen people (two men and eleven women) had an erythrocyte sedimentation rate above 20 mm./

1 hr; three had rheumatoid arthritis, two had signs of osteo-arthritis, and in eight no cause was found. One person with clinical rheumatoid arthritis had a positive sensitized sheep cell test.

There is no significant difference between the groups in respect of these characteristics.

Morning Stiffness

Sero-Positive Group.—Eleven persons complained of morning stiffness; four had rheumatoid arthritis, one had generalized osteo-arthritis with a raised erythrocyte sedimentation rate (24 mm./1 hr), one had evidence of degenerative disk lesions, four gave a history of ill-defined joint pains without objective clinical or radiological signs, and one had no rheumatic complaint. All except two people with definite rheumatoid arthritis had negative sensitized sheep cell tests.

Sero-Negative Group.—Twelve persons complained of morning stiffness; five had rheumatoid arthritis, two had generalized osteo-arthritis with a normal erythrocyte sedimentation rate, two gave a history of mild, ill-defined, joint pains with no objective signs, one had tenosynovitis, one gave a history of backache and had a positive sensitized sheep cell test (1/128), and one had no complaints.

The incidence of this symptom does not differ significantly in the two groups.

Rheumatoid Disease

The incidence of rheumatoid disease among the relatives is shown in detail in Table VIII (opposite).

Seven people in each group had some evidence of this condition. All were siblings of the propositi; the cases came from eleven families, six in the sero-positive group and five in the sero-negative group. Their ages ranged from 35 to 61 years.

The three individuals with a positive sensitized sheep cell test as their only evidence of disease were:

(1) A woman aged 61 (titre 1/128) who gave a history of an episode of painful knees lasting several months, 3 years previously, but who had no residual clinical or radiological signs;

TABLE VII
SENSITIZED SHEEP CELL TEST BY TITRE AMONG RELATIVES

Result of S.S.C.T. of Propositi	No. of Relatives Tested	Negative				Positive				Per cent. Positive
		<1/16	1/16	1/32	1/64	1/128	1/256	1/512	1/1024	
Negative ..	109	87	12	7	1	1	0	0	1	1.8
Positive ..	91	71	12	4	0	1	0	0	3	4.4
Total ..	200	158	24	11	1	2	0	0	4	3.0

TABLE VIII
INCIDENCE OF RHEUMATOID DISEASE AMONGST RELATIVES

Result of S.S.C.T. of Propositi	No. Examined	Clinical and Radiological Signs		Clinical Signs only	Radiological Signs only	S.S.C.T. Positive Only	Total	Percentage
		S.S.C.T. Positive	S.S.C.T. Negative					
Negative ..	110	1	2	3	—	1	7	6.4
Positive ..	92	2	1	1	1	2	7	7.6
Total ..	202	3	3	4	1	3	14	6.9

(2) A man aged 60 (titre 1/1024) who had no history nor clinical or radiological signs of disease.

These two people were among the sero-positive families.

(3) A man aged 34 (titre 1/128) who complained of mild morning stiffness and gave a history of mild backache in the past but who had no objective clinical or radiological signs of disease. He was the brother of a sero-negative propositus.

The incidence of clinical, radiological, and serological evidence of disease is constant in the sero-positive group (4.4 per cent.), but in the sero-negative families the incidence of clinical evidence of disease (5.5 per cent.) is higher than that of radiological (2.7 per cent.) or serological (1.8 per cent.) signs.

Discussion

The results in the present study of relatives of patients suffering from rheumatoid arthritis show no statistically significant difference between the relatives of sero-positive and sero-negative propositi in any of the diagnostic categories considered, except in the incidence of clinical osteo-arthritis which is higher among the sero-positive families.

The two groups of relatives are well matched for age and sex. There is a slightly higher proportion of young people than would be found in the general population, but this applies equally to both groups. The proportion of offspring is higher in the sero-positive (49 per cent.) than in the sero-negative (36 per cent.) families.

The incidence of rheumatic complaints as a whole is higher among the sero-positive families, but the difference between the two groups is not significant. There is little difference in the incidence of minor complaints or of disk lesions.

The incidence of clinical osteo-arthritis is significantly higher among the sero-positive families, but there is little difference between the two groups in the incidence of radiological signs of osteo-arthritis. All the people in whom a clinical diagnosis of osteo-arthritis was made and who were x-rayed had definite, though usually minor, radiological signs of

osteo-arthritis and no radiological signs of rheumatoid arthritis; in all except two (titres 1/16), the result of the sensitized sheep cell test showed no agglutination in the lowest titre used (1/16). These facts, combined with the clinical picture, make it unlikely that confusion has arisen between the two conditions in these cases.

Comparison of the two groups in respect of rheumatoid disease does not show any striking difference between them. However, such differences as there are follow a similar pattern to that found by Lawrence and Ball. The incidence of clinical, radiological, and serological manifestations of the disease is the same (4.4 per cent.) among the sero-positive families, but among the sero-negative families the incidence of clinical disease (5.5 per cent.) is higher than that of radiological (2.7 per cent.) or serological (1.8 per cent.) signs. The numbers involved are so small that these differences depend on one or two people in each case, so that it is impossible to draw any significant conclusions from them.

There are certain differences between this study and that of Lawrence and Ball (1958). In particular, among the Scottish propositi there was none whose only manifestation of rheumatoid disease was a positive sensitized sheep cell test. However, the difference between the sero-positive and sero-negative families in Lancashire remains, even if the relatives of those with only a positive test are excluded from consideration. Among the relatives, the age distribution is similar among the sero-negative families in both studies, but in the Scottish study there are fewer people in the older age groups among the sero-positive families than was the case in Lancashire. Lawrence and Ball found that the incidence of a positive sheep cell test rose with age in all groups and that it was markedly higher among those over 65 in the sero-positive families (38 per cent. compared with 13 per cent. among the controls). In the present study none of the seventeen relatives over 65 had a positive sensitized sheep cell test, so that the reason for the difference in the results is not likely to lie in the age distribution of the families.

It is impossible at present to offer a satisfactory explanation for the difference between the results of this investigation and that of Lawrence and Ball, but it is of interest to note that in Lancashire the incidence of a positive sensitized sheep cell test is higher than that of signs of clinical disease, both in the control population and among the relatives, whereas among the Scottish families the reverse is true. 4.9 per cent. have clinical rheumatoid arthritis and 3 per cent. have a positive sheep cell test. It is known that the incidence of a positive sensitized sheep cell test may vary in different populations (Lawrence, 1959) and it is possible that this variation may influence the familial pattern of the disease.

Summary

(1) 202 relatives (parents, siblings, and children) of 63 patients suffering from rheumatoid arthritis, in whom the results of the sensitized sheep cell test had been consistently positive or consistently negative, were examined clinically, radiologically, and serologically.

(2) Clinical, radiological, or serological evidence of rheumatoid arthritis was found in 7.6 per cent. of the relatives of patients with a positive sheep cell test and in 6.4 per cent. of relatives of those with a negative test. The incidence of each kind of evidence was equal (4.4 per cent.) among the sero-positive families, but the incidence of clinical disease (5.5 per cent.) was higher among the sero-negative families than that of radiological (2.7 per cent.) or serological (1.8 per cent.) signs.

(3) No significant difference was found between the two groups in respect of haemoglobin level, erythrocyte sedimentation rate, morning stiffness, or the radiological or clinical evidence of other rheumatic complaints, except in the case of clinical osteo-arthritis which was seen more frequently in the sero-positive families.

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Fréquence familiale de l'arthrite rhumatismale

RÉSUMÉ

(1) 202 parents (ascendants, descendants et latéraux directs) de 63 malades atteints d'arthrite rhumatismale, chez qui la réaction d'agglutination des globules rouges sensibilisées de mouton avait été régulièrement positive ou régulièrement négative, furent examinés du point de vue clinique, radiologique et sérologique.

(2) Signes cliniques, radiologiques et sérologiques d'arthrite rhumatismale furent trouvés chez 7,6% des parents des malades à réaction d'agglutination positive et chez 6,4% des parents des malades à réaction d'agglutination négative. La fréquence des signes de chaque type fut égale (4,4%) dans les familles séro-positives, mais la fréquence de la maladie clinique (5,5%) fut plus grande que celle des signes radiologiques (2,7%) ou sérologiques (1,8%) dans les familles séro-négatives.

(3) On ne trouva pas de différence appréciable entre les deux groupes en ce qui concerne le taux d'hémoglobine, vitesse de sédimentation globulaire, enraidissement matinal ou des signes radiologiques ou cliniques d'autres maladies rhumatismales, sauf dans les cas d'ostéo-arthrose clinique, rencontrée plus souvent dans des familles séro-positives.

Incidencia familiar de la artritis reumatoide

SUMARIO

(1) 202 parientes (padres, hermanos e hijos) de 63 enfermos con artritis reumatoide, en los cuales la reacción de aglutinación de eritrocitos sensibilizados de carnero fué sistemáticamente positiva o sistemáticamente negativa, fueron examinados clínica, radiológica y serológicamente.

(2) Signos clínicos, radiológicos y serológicos de artritis reumatoide fueron encontrados en un 7,6% de parientes de los enfermos con reacción de aglutinación positiva y en un 6,4% de parientes de los enfermos con reacción de aglutinación negativa. La frecuencia de cada tipo de signos fué igual (4,4%) en las familias sero-positivas, pero la frecuencia de la enfermedad clínica (5,5%) en las familias sero-negativas fué mayor que la de signos radiológicos (2,7%) o serológicos (1,8%).

(3) No se encontró diferencia apreciable entre los dos grupos en las cifras de hemoglobina, velocidad de sedimentación eritrocitaria, rigidez matinal o signos radiológicos o clínicos de otras enfermedades reumatoides, con excepción de osteo-artrosis clínica, encontrada más a menudo en familias sero-positivas.