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Rheumatoid factors in families

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Ziff, Schmid, Lewis, and Tanner (1958) first reported that rheumatoid factors reacting with human Cohn fraction II gamma globulins assessed by means of a latex-fixation test (LFT) were aggregated in the families of hospital patients with rheumatoid arthritis. This evidence for familial aggregation was confirmed by Ball and Lawrence (1961) in the urban population sample of Leigh, England, the test system being a sheep cell agglutination test (SCAT) for rheumatoid factor reacting with rabbit gamma globulin. It was further shown that in these sera there was a graded relationship between the titre in the probands and in the relatives. Somewhat unexpectedly, most of the aggregation occurred in the offspring (Lawrence, 1963). Bennett and Burch (1968 a, b) found significant aggregation of rheumatoid factor reacting with human gamma globulin (BFT) by sib-pair analysis in Pima but not in Blackfeet Indians, but showed that the aggregation was related to sibship size and therefore considered it was not genetically determined. Fudenberg and Franklin (1965) observed families in which there appeared to be a genetically-determined basis for both the rheumatoid factor and the reactant 7S gamma globulin.

In view of these conflicting results and the continuing uncertainty as to the significance of familial aggregation, we have made a survey of the first-degree relatives and spouses of persons with positive tests for rheumatoid factor in a rural population sample in Wensleydale in the north of England.

Methods

Throughout this paper titres are given as reciprocals. All persons having a positive SCAT at a titre of 32 or more or a positive latex-fixation test (LFT) at a titre of 640 or more in a population sample aged 15 and over tested in Wensleydale in northern England were included as probands. Their spouses and first-degree relatives aged 15 and over living in the United Kingdom were examined clinically by the two rheumatologists who also examined the population sample with which they were compared. *X* rays of the hands and feet and a blood sample were taken. The serum was examined for rheumatoid factor using the SCAT and LFT. The SCAT was tested in Manchester, the LFT in Leiden.

Probands

Probands were also classified as a relative or spouse if another member of the family was sero-positive provided this other member was in the original population sample.

Both tests were positive in fourteen of the probands, five of whom had rheumatoid arthritis. These probands had forty first-degree relatives, of whom 36 (90 per cent.) have been tested, and seven spouses, all of whom were tested (Table I).

The LFT alone was positive in 36 probands, two of whom had rheumatoid arthritis. They had 113 first-degree relatives, of whom 87 per cent. have been tested,

Table I *Completion rate in relatives and spouses*

Probands with positive tests	*Total Tested*	*Relatives*			*Spouses*		
		Total in sample	*Refused or not available*	*Examined and tested*	*Total in sample*	*Refused or not available*	*Examined and tested*
SCAT and LFT	14	40	4	36	7	0	7
LFT only	36	113	13	100	24	0	24
SCAT only	8	14	2	12	5	1	4

N.B. One individual (W1008) is the parent of a positive SCAT and the husband of a positive SCAT and LFT.

Based on a paper presented at a meeting of the Heberden Society at Bürgenstock, Switzerland, in June, 1968.

and 24 spouses all of whom were tested.

The SCAT alone was positive in eight probands, one of whom had rheumatoid arthritis. They had fourteen relatives, twelve of whom were tested, and five spouses, four of whom had a blood test.

Results

Of the 48 first-degree relatives of SCAT-positive probands who have been tested, four had a titre of 32 or more, whereas 1·3 would have been expected in a sample of the Wensleydale population of this size and age distribution (Table II). The frequency of positive tests was thus roughly three times that in the population as a whole. In view of the small numbers studies this is not formally significant, but is of the same order as in the Leigh family survey. None of the eleven spouses had a positive test. The subgroups of parents, siblings, and offspring were too small to yield significant differences.

The LFT was positive in sixteen persons among the 122 first-degree relatives of LFT-positive probands, more than twice the expected number of relatives, but only the expected number of spouses (Table III). The excess in relatives as a whole is significant. It is also significant in the parents or offspring when these are considered apart, but not in siblings. The prevalence of positive results with either test showed no sex differences.

The relatives were divided into three groups: those in which the proband had both the SCAT and LFT positive (dual positivity), those, in which only the SCAT, and those in which only the LFT was positive.

The SCAT was positive 4½ times as often as expected in relatives in the first group (Table IV). The second group, in which the proband had only a positive LFT, had less than twice the expected frequency of positive SCAT tests. The third group had no positive SCAT results.

When the LFT results were compared in these three groups, there was a significant excess of positive LFTs in the first and second groups, but greater in the first. Of the eight relatives with a positive LFT (group 1, Table V), four also had a positive SCAT. Thus some 11 per cent. of the Group 1 relatives were

Table II *SCAT in relatives and spouses of SCAT-positive probands in Wensleydale*

Relationship to Proband		*Total tested*	*SCA titre*									*SCA titre 32+*		
			<4	4	8	16	32	64	128	256	521	*Observed*	*Expected*	*K*
Relatives	Parents	13	9	1	0	1	1	0	0	0	1	2	0·4	5·0
	Siblings	25	23	1			1					1	0·7	1·4
	Offspring	14	10	1	1	0	2	0	0			2	0·3	6·7
	Total	48†	39	3	1	1	3	0	0	0	1	4	1·3	3·1
Spouses		11	9	1	0	1						0	0·20	0

†‖ Four individuals (W639; 704; 842; 1628) were related to more than one SCAT positive proband. In the totals each relative is counted only once. Expected values in this and subsequent Tables are based on the total Wensleydale population sample of 1,149 individuals tested by the SCAT and 889 tested by the LFT and are adjusted for age distribution.

Table III *LFT in relatives and spouses in LFT-positive probands in Wensleydale*

Relationship to proband		*Total tested*	*Latex-fixation titre*									*LF titre 640+*		
			<80	80	160	320	640	1,280	2,560	5,120	10,240	*Observed*	*Expected*	*K*
Relatives	Parents	17	10	1	0	1	1	0	2	1	1	5	1·15	4·3*
	Siblings	74	58	4	2	1	5	2	1	1		9	4·09	2·2
	Offspring	35	29	0	1	0	2	1	1	1		5	1·05	3·3**
	Total	122†	96†	5	3	2	7†	2†	4	2†	1	16†	7·01	2·3***
Spouses		29	26	0	0	1	1	0	0	1		2	1·59	1·3

NS = not significant * = $P < 0·05$ ** = $0·05 < P < 0·01$ *** = $P < 0·01$
† Four individuals (W639; 776, 704, 701) were related to more than one LFT-positive proband. In the totals each relative is counted only once. The pair of concordant sero-positive spouses was counted as both probands and spouses.

Table IV *SCAT in relatives of SCAT and LFT-positive probands*

Probands with positive tests	*Total relatives tested*	*Relatives' SCA titre*									*SCA titre 32+*		
		<4	4	8	16	32	64	128	256	512	*Observed*	*Expected*	*K*
SCAT and LFT	36	29	2	0	1	3†	0	0	0	1††	4	0·9	4·5**
LFT only	98	82	8	3	1	2†††	1		0	1††	4	2·4	1·7
SCAT only	12	10	1	1							0	0·4	0

** 0·05 > P > 0·01 † W701, 842, 775 †† W751 ††† W842 and 701

Table V *LFT in first-degree relatives of SCAT and LFT positive probands*

Probands with positive tests	*Total relatives tested*	*Relatives' LF titre*									*LF titre 640+*		
		<80	80	160	320	640	1,280	2,560	5,120	10,240	*Observed*	*Expected*	*K*
SCAT and LFT	35	24	3	0	0	2	1	2	2	1	8	2·0	4·0**
LFT only	91	72	2	3	2	5†	2††	3†††	1	1	12	5·3	2·3**
SCAT only	11	9	0	1	1						0	0·8	0

** 0·05 > P > 0·01 † W1081, 1082, 1278, 1321, 1579 †† W660, 1268 ††† W225, 661, 842

dual positives. Since only 1·6 per cent. of the population sample in Wensleydale had both SCAT and LFT positive (Valkenburg, Ball, Burch, Bennett, and Lawrence 1966), the 11 per cent. of dual positives in the first group is seven times the expected number and the 4·4 per cent. in the second group is 2½ times the expected number.

Inflammatory Polyarthritis (IP) in relatives

Inflammatory polyarthritis, assessed by the clinician without the aid of *x* rays or serology, was found in three times the expected number of relatives in the dual positive families, in 2½ times the expected number in the LFT+ only families, and in the expected number in the SCAT+ only families. The numbers in the first two groups are significant (Table VI). Only two of the relatives (W751 and W1628) had seropositive arthritis. Erosive arthritis of the hands or feet was also more frequent in the dual positive families and in the LFT+ only but not in the SCAT+ only (Table VII, overleaf).

Discussion

This study confirms the aggregation of rheumatoid serum factor in first degree relatives which was found previously in the urban population in Leigh.

The most important finding to emerge from the Wensleydale family survey is that the familial

Table VI *Clinical RA in SCAT and LFT-positive Wensleydale families*

Probands with positive tests	*Relatives' grade of clinical RA*															*K*
	Male							*Female*								
	No. tested	0	1	2	3	2–4		*No. tested*	0	1	2	3	4	2–4		
						Observed	*Expected**							*Observed*	*Expected**	
SCAT and LFT	18	13	2	2	1	3	0·5	19	15	1	2	0	1	3	1·4	3·2**
LFT only	52	37	10	4†	1	5	1·4	48	36	6	4††	1	1	6	3·1	2·4**
SCAT only	7	5	2	0	0	0	0·2	7	6	0	0	1	0	1	0·7	1·1

* Expected rates assessed from Leigh, Wensleydale, and Watford surveys.
** 0·05 > P > 0·01 † W1588, 1282, 1060, 1631 †† W1150, 1057, 1590, 1628

Table VII *Erosive arthritis in hands or feet in relatives of SCAT or LFT-positive probands*

Probands with positive tests	*Relatives' grade of erosive arthritis hands or feet*							
	Total x-rayed	0	1	2	3	4	2–4	
							Observed	*Expected*	*K*
SCAT and LFT	36	24	8	3	1	0	4	1·4	2·8
LFT only	92	71	15	4†	2	0	6	3·4	1·8
SCAT only	14	10	4	0	0	0	0	0·7	0

† 1060, 1066, 1146, 1172

aggregation is greatest when the proband's serum is positive both by the SCAT and the LFT. In previous studies the possible importance of dual positivity was not recognized and was thus not taken into consideration. The finding of a greater excess of clinical arthritis in the relatives of dual positive individuals adds practical importance to the survey.

There is also significant aggregation when the proband has a positive LFT only. However, in some individuals, rheumatoid factor reacting only with human gamma globulin may be the first to develop, dual positivity appearing later. This is supported by a follow-up study of these probands. After 5 years we re-tested thirty of those in whom only the LFT was positive and found that four (W372, 557, 704, and 893) had become dual positive. Two of these (W557 and 704) had sero-positive relatives (W1082, 1081, 751, 701, 1628). Thus, of twelve sero-positive relatives in Group 2 (Table V), five were in reality relatives of dual positive probands. None of them had sero-positive spouses.

Experiences with the induction of rheumatoid factor in rabbits led Christian (personal communication) to conclude that wide strain differences exist in that species. This evidence for a genetic influence is supported by our Wensleydale survey, in which increased SCAT and LFT titres occurred in relatives but not in spouses. The number of spouses was unfortunately small. To remedy this we have added the Leigh and Wensleydale family surveys together and assessed the number of spouses with a positive SCAT, since the LFT was not undertaken in Leigh. Only two of the 32 spouses had a positive test, whereas 2·9 would have been expected by chance. This confirms the findings of Bennett and Burch (1968) in a much larger group of spouses, using both the SCAT and the Bentonite flocculation test, and argues against the passage of an infective agent within the family. It does not, however, rule out some special relevance for environment in childhood.

If a genetic influence is involved in the familial aggregation of rheumatoid factors in Wensleydale, it is clear that it is not a simple Mendelian dominant or recessive. A polygenic inheritance is suggested by the continuous distribution in populations and their families (Ball and Lawrence, 1961). The application of the formula of Edwards (1960) to the present findings produced a K value much below that which would be expected with single gene dominant or recessive inheritance but a close fit for a multifactorial inheritance (Table VIII).

There has been considerable inbreeding in the population of Wensleydale in the past, but there is no evidence that rheumatoid arthritis depends on a recessive inheritance and it is thus unlikely that such inbreeding would influence the gene frequency in the population. In the island of Marken where inbreeding is very high, the prevalence of positive tests for rheumatoid factor is little higher than in the population on the mainland (Steiner, Westendorp Boerma, de Blécourt, and Valkenburg, 1968). It is not proposed to discuss the possible environmental causes in this paper as they will be considered in a later communication.

Table VIII *Possible mode of inheritance of rheumatoid factors reacting with both SCAT and LFT*

Prevalence	*Observed*	*K*	*Theoretical value of K*				
			Single gene inheritance				*Multifactorial inheritance*
(*P*)	(*O*)	*O/P*	*Dominant*	1/2P	*Recessive*	1/4P	$1/\sqrt{P}$
0·016	0·111	6·9	31		16		7·7

Table IX *SCAT and LFT in families*

Series	*Probands*	*Aggregation in relatives*			
		SCAT	*Dual positivity*	*Author*	*Date*
Leigh random sample	SCAT + 80 per cent. without arthritis	3·7 ***		Ball and Lawrence	1961
Edinburgh hospital	SCAT+ All with arthritis	2·4NS		Bremner, Alexander, and Duthie	1959
Manchester hospital	SCAT+ All with arthritis	0·8NS	1·9NS	Unpublished	
Wensleydale random sample	SCAT+ only LFT only SCAT+ LFT+	0 1·7 4·5**	0 2·8 6·9**	Present study	1970

*** $P > 0.01$ ** $0.05 > P > 0.01$ NS = not significant.

Buchanan, Boyle, Greig, McAndrew, Barr, Anderson, and Goudie (1966), in a study of 145 healthy twin pairs, found little difference in the degree of concordance for rheumatoid factor between monozygous and dizygous twins, but dual positivity was not assessed. In any case a purely genetic cause is out of the question because of the relationship of rheumatoid factors to age and the uneven increase which occurs with age (Ball and Lawrence, 1961).

When dual positivity was studied by us in the relatives of hospital patients, a slight increase was found compared with the general population (Table IX). There may thus be a slightly greater tendency to develop rheumatoid arthritis in those carrying a trait related to dual positivity and this is confirmed by the excess of clinical arthritis in the relatives of dual positive individuals in this study.

O'Brien, Bennett, Burch, and Bunim (1967), analysed their data as a continuous variable, using the correlation scores between parent and offspring. By this method r was -0.026 in the Blackfeet and $+0.053$ in the Pima Indians and the coefficient of correlation was not significantly different from zero. They concluded that there was no evidence of any complex or simple hereditary mechanism for rheumatoid factor in their populations. These Indian tribes have been almost decimated on several occasions by infections introduced by European settlers. A trait which influenced immune responses might have had a considerable effect on survival and thus resulted in a population genetically different in this respect from the population of Wensleydale.

Summary

Blood from first-degree relatives and spouses of persons with a positive sheep cell agglutination or latex-fixation test in a population sample in Wensleydale, Lancashire, has been subjected to both tests. In addition, probands and relatives have been examined clinically and radiologically for evidence of rheumatoid arthritis.

First-degree relatives showed higher titres by both rheumatoid factor tests than the local population after adjustment for age distribution. Spouses showed only the expected titre distribution for their age. Familial aggregation seemed to depend on dual positivity in the proband, it was seven times as common in the relatives of dual positive probands as in the local population.

The prevalence of rheumatoid arthritis was three times as great as expected in the relatives of probands with dual positivity.

A familial predisposition to produce rheumatoid factor reacting with rabbit and human gamma globulin is postulated in a proportion of this population, The part played by heredity in this predisposition is discussed.

Discussion

DR. H. L. F. CURREY (*London*) You have used your results to suggest that both the tendency to develop positive rheumatoid serological tests and the general rheumatic disease are genetically determined. Could the data not apply equally well if both these things were due to perinatal inheritance of virus infections?

DR. LAWRENCE I think, if that were the case, one would expect that the rheumatoid factor tendency would be passed on only by the mother and not by the father. In fact, we found the reverse, the father was slightly more likely to pass on a positive rheumatoid factor test than the mother.

DR. E. N. GLICK (*London*) I am intrigued by the finding that, if one tests the relatives of hospital patients

with positive serology, one does not find an increased incidence, but that one does so in people picked up in population surveys.

DR. LAWRENCE Presumably, in the hospital patients, the disease process eventually gives rise to a tendency to produce anti-gamma-globulins in persons who are not genetically predisposed. This is a more important cause of rheumatoid factor in these patients and it overshadows any genetic factor. We find, looking at the *x* rays of relatives of hospital patients with arthritis, that they have about seven times as much severe erosive arthritis as the population sample. I should imagine that the genetic factors are very complex and that a tendency to produce rheumatoid factors reacting with both human and rabbit gamma globulin is only a small and unimportant factor.

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RÉSUMÉ

Les facteurs rhumatoïdes dans les familles

Le sang des parents au premier degré et des partenaires mariés à des personnes montrant une réaction positive au test d'agglutination aux cellules de mouton ou au test de fixation sur latex dans une population à Wensleydale, Lancashire, a été soumis à ces deux tests. De plus, les sujets examinés et les parents ont été soumis à un examen clinique et radiologique afin d'élucider les signes d'arthrite rhumatoïde.

Les parents au premier degré ont montré des titres plus élevés aux deux tests du facteur rhumatoïde que la population locale après un ajustement fait quant à l'âge. Les partenaires mariés montraient seulement une distribution de titres en accord avec leur âge comme on s'y attendait. L'agrégation familiale semblait dépendre de la double positivité chez le sujet examiné; il était sept fois plus commun chez les parents des sujets à double positivité examinés que chez la population locale.

La présence d'arthrite rhumatoïde était trois fois plus fréquente comme on pouvait s'y attendre chez les parents des sujets à double positivité examinés.

Une prédisposition familiale de produire le facteur rhumatoïde qui réagit avec la gammaglobuline humaine et celui du lapin est postulé dans une proportion de cette population. La part prise par l'hérédité à cette prédisposition est discutée.

SUMARIO

Factores reumatoides en las familias

La sangre de parientes de primer grado y cónyuges de personas con pruebas positivas de Waaler-Rose o de fijación de látex en un grupo de habitantes de Wensleydale, Lancashire, Inglaterra, ha sido sometida a ambas pruebas. Además, *probands* y parientes han sido examinados clínica y radiológicamente, en busca de indicios de artritis reumatoide.

Los parientes de primer grado revelaron, por ambas pruebas del factor reumatoide, títulos más altos que los de la población local, después de haber sido agrupados por edades. Los cónyuges mostraron tan solo la distribución de títulos que se esperaba de su edad. La acumulación familiar parecía depender de la doble positividad del *proband*; era siete veces más común en los parientes de *probands* de doble positividad que en la población local.

La incidencia de artritis reumatoide era tres veces más alta que lo esperado en los parientes de *probands* con doble positividad.

Se supone en una parte de esta población existe una predisposición familiar a producir factor reumatoide que reacciona con globulina gamma de conejo y humana. Se discute el papel que desempeña la herencia en esta predisposición.