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Rheumatoid Arthritis—Nature or Nurture?

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Since much of the confusion which has arisen on the influence of heredity and environment in rheumatoid arthritis stems from the employment of population samples as a source of index cases, I should like first to say a few words about the parameters used for assessing arthritis in population samples and about the way in which arthritis, encountered in populations, differs from the arthritis which we see in the out-patient clinic or in the hospital ward.

Dr. Sidney Cobb (1970), who was one of the pioneers of the epidemiological study of rheumatism, has discoursed on the 'rheumatic range', the most severe cases at the apex of the mountains and the least severe mingled in the base of the massif, thus producing 'peaks of diagnostic clarity and valleys of indecision'. Unfortunately, in any population sample of feasible dimensions, the peaks of diagnostic clarity are sharp and the valleys of indecision wide. There is thus a temptation, in designing family surveys based on such samples, to include amongst the probands or index cases some who were too close to the base of the massif or even bogged down in the valleys of indecision. This concept of the rheumatic range was elaborated by Prof. J. H. Kellgren in his Bunim Lecture in 1966, but its importance to the theme of my talk warrants, I think, some reiteration.

The classical case of rheumatoid arthritis such as we see in hospital requires no great clinical acumen for its recognition and the diagnosis is confirmed by radiological evidence of erosions and by positive serological tests. This picture, however, is rarely found in population samples, indeed in less than 1 per cent. of adults. On the other hand clinical evidence of inflammatory polyarthritis is found in some 4 per cent. of the population and radiological evidence of erosions in a similar proportion but only rarely in the same individuals or in association with rheumatoid factor. When one compares those with clinical

evidence of inflammatory polyarthritis with those who have radiological evidence of erosions, as Dr. P. H. N. Wood has done in Table I, it becomes evident that the more severe cases (Grade 3+) quite often have both clinical and radiological changes but that the minimal cases (Grade 2) seldom do so, in fact only slightly more often than would be expected to occur by chance. What conclusions can one draw from this? Can it be that the minimal cases of inflammatory polyarthritis are of recent onset and have not yet had time to develop erosions? If so, what of the minimal erosive arthritis without clinical evidence of polyarthritis? To elucidate this point the x rays taken in Leigh and Wensleydale were read by two observers independently and one of the observers re-read them

Table I *Wensleydale sample—Association of inflammatory polyarthritis and erosive arthritis in 646 subjects (Unweighted means of percentage prevalence in the four age groups 35-44, 45-54, 55-64, and 65+ years)*

Grade of polyarthritis	2	3+
Inflammatory poly-arthritis	4.7	2.3
Positive SCAT or LFT	0 per cent.	50 per cent.
Erosive arthritis at any site	12.4	3.4
Positive SCAT or LFT	4 per cent.	78 per cent.
Concordance of inflammatory and erosive arthritis observed	1.2 ^{NS}	1.4*
Expected if random concurrence	0.5 ^{NS}	0.08*

* P $\leq$ 0.05 NS = not significant.
 Note: Grade 2 = minimal, grade 3+ = moderate or severe. For further discussion of criteria and grading in inflammatory polyarthritis, see Lawrence and Wood (1968). Erosive arthritis is graded in accordance with the 'Atlas of Standard Radiographs of Arthritis' (1963).

later. The results bring out very forcibly Dr. Cobb's peaks of certainty and valleys of indecision (Table II). For Grade 4 there was general agreement, and in most of those with Grade 3 arthritis there was agreement between three or at least two observations. For Grade 2 (slight but definite changes) the readings are reproducible in only a few cases. Indeed minimal changes were generally noted by only one observer. The observer who read the *x* rays a second time did so after an interval of some 5 years and during such an interval ideas can change considerably; a very high prevalence of erosions in one

Table II *Observer differences in three readings for erosive arthritis of hands or feet in relation to grade of arthritis in Leigh and Wensleydale in 2,187 subjects*

Concordance		Total subjects	Worst grade		
			2	3	4
Grade 2-4 positive	3 readings	23	4	6	13
	2 readings	25	21	4	0
	1 reading	122	121	1	0
Total positive		170	146	11	13
Total read 3 times		2,187			

survey population, particularly if unassociated with clinical or serological abnormality, tends to result in a more conservative grading of *x* rays read subsequently. In epidemiological studies *x* rays must be read blind, since a knowledge of the clinical findings introduces the possibility of observer bias. In Fig. 1 erosions of the 5th metatarsal head in a Nigerian without and an Englishman with clinical inflammatory polyarthritis are compared and demonstrate the very similar appearances.

A feature of minimal erosions, apart from their lack of reproducibility, is that they are often confined to one joint. Seldom are Grade 2 erosions found in both the hands and feet, though this occurs more frequently than would be expected from random occurrence. In Leigh and Wensleydale, for example, Grade 2 erosions occurred in both hands and feet nine times as often as expected, but Grade 3-4 erosions ninety times as often (Table III, opposite).

Thus the Grade 3-4 group shows a far greater correlation with clinical evidence of inflammatory polyarthritis, with erosions at other sites and with sero-positivity. This suggests that the gradings for erosive arthritis do not describe a continuous distribution, as their numerical sequence infers, but that there may be important qualitative differences

FIG. 1 *Grade 2 erosions in head of 5th metatarsal. left: Healthy Nigerian. right: English patient with clinical evidence of arthritis.*

Table III *Prevalence of erosive arthritis in hands and feet in 646 subjects (Unweighted means of percentage prevalence in four age groups 35-44, 45-54, 55-64, and 65+)*

Grade of erosion	2	2+	3+
Hands	1.7	2.6	0.9
Feet	2.4	3.7	1.3
Coincidence in hands + feet observed	0.7 ^{NS}	1.6**	0.9 ^{NS}
Expected if random coincidence	0.08 ^{NS}	0.1**	0.01 ^{NS}

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

(Wood, 1966). If one uses the ARA Criteria, a similar picture emerges (Table IV). Most of those with three or more ARA clinical criteria had negative x rays and serology, and similarly with the Rome Criteria for Inactive Rheumatoid Arthritis. Moreover, the cases diagnosed by the clinician and those picked out by the ARA criteria are not identical (Table V). Indeed the correlation between the clinician's opinion and the active or inactive criteria is only $r = +0.5$, significant but not very good. There is fairly satisfactory agreement about the 'definite' cases but these are few. If probable arthritis is added, the numbers are greatly increased but the specificity is reduced; in Leigh and Wensleydale less than half of the 'probable' cases were considered by the physician on clinical grounds to have arthritis.

Table IV *Comparison of three sets of clinical criteria in Leigh and Wensleydale*

Criteria	Total subjects	Physician's grading 2+	ARA criteria active 3+	Rome criteria inactive 2
Serology and x ray negative	110	82	61	32
x ray only positive	30	7	8	7
Serology only positive	74	2	7	7
Serology and x ray positive	16	15	14	14
Total	230	106	90	60

Table V *Clinical rheumatoid arthritis in Leigh and Wensleydale*

<i>ARA Criteria</i>		<i>Physician's grading</i>					
		<i>None</i>	<i>Doubtful</i>	<i>Minimal</i>	<i>Moderate</i>	<i>Severe</i>	<i>Percentage with rheumatoid arthritis</i>
None	1,898	1,732	144	20	2	—	1
Possible	191	108	54	26	3	—	15
Probable	73	24	18	26	4	1	42
Definite	25	—	1	4	12	8	96

$r = +0.5$ $P < 0.001$

Note: Only those in whom x rays of hands and feet and the SCAT were done are included.

Table VI *Clinician's diagnosis and ARA criteria 'probable' and 'definite' in Leigh and Wensleydale population sample with x rays and SCAT*

Clinical diagnosis		ARA criteria	
		Probable	Definite
Total		73	25
Rheumatoid arthritis	Grade 2-4 1	31 3	24
Generalized osteoarthritis	Grade 1-4	16	1
Local osteoarthritis	Grade 1-4	18	0
Spondylitis		2	
Bursitis		1	
Past polyarthritis		1	
Undertermined		1	

The remainder had been diagnosed mainly as osteoarthritis, either local or generalized (Table VI), and though it is possible that some of the generalized cases may have been secondary to inflammatory polyarthritis, thirteen of the sixteen were associated with Heberden's nodes and thus belonged to the primary generalized form described by Kellgren and Moore (1952). This is not surprising, since the first three criteria (morning stiffness, pain on movement of a joint, and swelling of a joint) apply equally to rheumatoid arthritis and osteoarthritis.

In 1966, in an attempt to discover criteria which would give a more satisfactory separation of rheumatoid arthritis and generalized osteoarthritis, the symptoms and signs in persons diagnosed as cases of rheumatoid arthritis in the Leigh, Wensleydale, and Watford population samples were reviewed and were compared with those in persons of the same age and sex without arthritis (Lawrence and Wood, 1968b). Two features stood out as being more common in those with rheumatoid arthritis:

- (1) A history of pain in three limb joints in one episode
- (2) The finding of symmetrical swelling, limitation of movement, or subluxation in the PIP or MCP joints of the hands, the wrists, or the lateral MTP joints of the feet.

These two criteria were provisionally adopted as a substitute for the physician's diagnosis of inflammatory polyarthritis. Subsequently it became necessary to amend the second criterion to include three joints, two of which must be symmetrical, one involving a hand or foot joint, since in some populations both wrists were slightly limited without other evidence of arthritis. At a population symposium held in New York in 1966, these amended criteria were adopted and have since been designated the New York Criteria (Bennett and Wood, 1968).

Both criteria were present in 64 persons in Leigh and Wensleydale and 41 of these had been diagnosed as cases of rheumatoid arthritis by the physician compared with only eleven who had osteoarthritis (Table VII). The New York Criteria were thus more selective than the ARA Criteria and gave a more satisfactory separation from osteoarthritis. They were more often confirmed by x-ray examination and serological findings than either the physician's grading for inflammatory polyarthrtiis or the ARA Criteria (Table VIII).

Table VIII *Comparison of three sets of clinical criteria in Leigh and Wensleydale population samples, using confirmed x ray readings*

Criteria	Physician's grading		ARA clinical criteria		New York criteria	
	2+		3+		1 and 2	
	No.	per cent.	No.	per cent.	No.	per cent.
Total polyarthritis	106		90		65	
Confirmed by x ray	22	21 ^{NS*}	22	24 ^{NS}	25	38*
Sero-positive arthritis	17	16	21	23	17	26
Confirmed by x ray	15	14	14	16	12	18
Sero-negative arthritis	89		69		48	
Confirmed by x ray	9	7**	8	9	13	20**

** 0.05 > P > 0.01 * P ≈ 0.05 NS = not significant.
Note: Wensleydale New York criteria based on new sample of 677 adults.

Table VII *Clinician's and New York criteria in Leigh and Wensleydale population sample*

Clinician's diagnosis	New York criteria both positive
Rheumatoid arthritis Grade 2-4 1	42 9
Osteoarthritis	11
Chondrocalcinosis	1
Undetermined	2
Total cases	65

Evidence for a genetic influence

In 1806 William Heberden himself suggested a genetic influence in rheumatic arthritis. In his book of *Commentaries on the History and Cure of Diseases* there is an appendix on 'Chronical Rheumatism'. In this he gives a very lucid description of rheumatoid arthritis, including both the benign, self-limiting forms and the more severe, progressive disease. He ends with a very significant sentence. 'Is this not in some degree hereditary?' Was he the first to pose this question? That I cannot say, but I am quite sure that he was not the last.

Though the occurrence of arthritis in families did not escape the attention of Charcot and of Sir Archibald Garrod, little attention was paid to Heberden's suggestion until Kroner (1928, 1929) reported four generations of rheumatoid arthritis in one family, the disease being apparently transmitted by females. There has, since then, been much argument on the relative importance of *genetic make up* on the one hand and of those influences which the *environment* imposes on the individual on the other. Some workers, particularly in the United States, have claimed that heredity plays no part in the aetiology and that any aggregation of the disease in families depends purely on influences present in the family

environment. Others have felt that genetic influences must play a part.

Familial aggregation

Bearing these points in mind, let us look at some of the results of family studies which have been published to date. Probably the first attempt to obtain statistics on the occurrence of rheumatoid arthritis in families was made by the Empire Rheumatism Council in their enquiry into the aetiological factors associated with rheumatoid arthritis. This study, made in a number of centres, was duly analysed by Lewis-Faning (1950) (Table IX). It was based on a family history taken from patients with arthritis, comparison being made with a similar history taken from controls matched for age and sex without arthritis. It indicated that fathers, mothers, and siblings of arthritic patients had roughly twice as much arthritis as the relatives of controls.

A number of papers on the same lines followed in subsequent years and gave prevalences varying from twice to fifteen times the expected rate in

first-degree relatives.

Around 1958, research workers began to question this technique on the grounds that perhaps patients with arthritis were more likely than those with other diseases to remember episodes of arthritis in their families. To overcome this fallacy the relatives were seen and examined and were compared either with relatives of controls or with random samples of the population. This resulted in a less striking difference between relatives and controls, the relatives having on average only $2\frac{1}{2}$ times the expected amount. The next stage which emerged in 1968 involved the ARA Criteria to assess the prevalence of rheumatoid arthritis. This was associated with a still further reduction in the degree of familial aggregation. The last two surveys mentioned in Table IX were based on area population samples and show virtually no excess of arthritis in the relatives. O'Brien, Burch, and Bunim (1963) have attributed this negative finding to the complete ascertainment in their population. Familial aggregation, they suggest, is due to selection, families in which more than one

Table IX *Familial aggregation in rheumatoid arthritis. Prevalence of clinical or probable and definite rheumatoid arthritis in first-degree relatives*

Authors	Year	Place	Total cases	Criterion	Mode of ascertainment	Percentage with rheumatoid arthritis		
						Observed	Expected	K*
Lewis-Faning	1950	United Kingdom	—	Clinical	History from Proband	7.0	3.0	2.3
Fathers			—	Clinical		15.0	9.0	1.7
Mothers			—	Clinical		3.8	1.8	2.1
Siblings			—	Clinical		12.0	5.0	2.4
Short, Abrams, and Sartwell	1952	New England	—	Clinical		3.1	0.6	5.2
Miall	1955	Wales	354	Clinical		6.1	0.4	15.2
Neri Serneri and Bartoli	1956	Italy	1,163	Clinical		3.4	0.58	5.9
Stecher	1957	Northern USA	1,443	Clinical				
							mean	5.0
Lawrence and Ball	1958	England	131	Clinical	Examination	10.6	4.6	2.3
Bremner and others	1959	Scotland	202	Clinical	Examination	4.9	3.9	1.3
de Blécourt and others	1962	Holland	741	Clinical	Examination	3.4	0.8	4.3
Siegel, Lee, Widelock, Gwon, and Kravitz	1965	USA	154	Clinical	Examination	3.2	0†	
Lawrence and Wood	1968	England	645	Clinical	Examination	7.6	4.9	1.5
							mean	2.3
Veenhof-Garmann and others	1968	Holland	757	definite ARA	Examination	2.8	1.4	2.0
Lawrence and Wood	1968	England	145	ARA probable and definite	Examination	6.2	5.0	1.2
Bennett and Burch	1968	Amerindians (USA)	268		Examination	4.1	3.2	1.3
							mean	1.5

† No rheumatoid arthritis in 154 matched relatives of controls, mainly with cervical and breast cancer.
K* = Observed divided by expected prevalence.

person is affected being more likely to be chosen. There is, however, a second possibility, namely that differences in familial aggregation depend on the criteria used for diagnosis and some criteria are not selective enough to demonstrate familial aggregation. I will deal with the last proposition first. In the population of Leigh and Wensleydale, two methods were used to choose the index cases or probands for a family survey and three methods to assess the prevalence of arthritis in the relatives (Table X). Using the ARA Criteria for both probands and relatives, the latter had little more probable or definite arthritis than expected. Using the physician's grading, they had only $1\frac{1}{2}$ times the expected rate when Grade 2 was included, but Grade 3-4 arthritis was present at four times the expected rate. Radiological evidence of erosive arthritis was twice as common in relatives as in controls and when minimal changes were excluded it was three times as common. Thus it seems likely that the degree of aggregation in families depends greatly on the parameters used both to select probands and to assess the prevalence in relatives. The more severe grades of disease, whether because they provide greater diagnostic clarity, or because of a genetic influence on severity, seem to provide a more profitable field for the investigation of hereditary influences. Since the more severe grades of arthritis are uncommon, random population samples are not a practical source of probands for family surveys of such grades of arthritis. As this may involve errors due to incomplete ascertainment, data from family surveys based on population samples in Leigh and Wensleydale were compared with those from a survey in Manchester in which the probands were patients attending the local hospitals. No significant difference was found in the prevalence of arthritis in the first-degree relatives in these two groups (Lawrence and Wood, 1968a).

Manchester Family Survey

To minimize selection bias in this survey all patients seen by Professor Kellgren during the years 1957-59

who were diagnosed as cases of definite rheumatoid arthritis, and in whom the sheep cell agglutination test (SCAT) was positive at a titre of 1 in 64 or more on at least two occasions, were included as sero-positive arthritic probands. Those having a titre of 1 in 8 or less on all occasions were included as the sero-negative arthritic group. Later an intermediate group having a titre of 1 in 16 or more on at least one occasion was added. To be meaningful a survey of this sort should be completely blind, the investigator having no indication of the type of family he is examining. This was achieved by including the families of patients with ankylosing spondylitis, psoriatic arthritis, psoriasis without arthritis, systemic lupus erythematosus, discoid lupus erythematosus, and a number of less common connective tissue disorders.

All spouses and first-degree relatives aged 15 years and over living in the United Kingdom were approached and 92 per cent. were examined.

By combining this family study with those in Leigh and Wensleydale, it has been possible to assemble an adequate mass of data for detailed analysis, and this shows that clinical evidence of arthritis was present in excess in the sero-positive families (Table XI) but showed no significant aggregation in families of sero-negative probands. Indeed, when the families of probands with psoriasis were removed from the sero-negative group, the actual and expected rate became identical.

When the arthritis in relatives was divided into grades it was found that the excess in the sero-positive families was limited to the more severe forms which were nearly four times as common as in the population samples. In the sero-negative families, both the minimal and severe forms of arthritis occurred with about the expected frequency. Differences between sero-positive and sero-negative families have been reported also by Wilkinson and Torrance (1967), de Blécourt, Boerma, and Vorenkamp (1962), and Bland and Brown (1963).

Table X *Familial aggregation of rheumatoid arthritis in Leigh and Wensleydale, using three different criteria*

Criteria	No. of probands	Total first-degree relatives examined	Positives among first-degree relatives		
			Observed	Expected	K
Probable and definite rheumatoid arthritis	76	145	9	7.3	1.2
Clinical rheumatoid arthritis Grade 2-4	104	257	20	12.4	1.6
	3-4	104	8	2.0	4.0
Erosive arthritis hands or feet Grade 2-4	104	251	15	8.5	1.8
	3-4	104	4	1.3	3.1

Table XI *Clinical inflammatory polyarthritis in first-degree relatives of rheumatoid arthritis probands*

Proband	First-degree relatives						
	Total	Clinical inflammatory polyarthritis					
		Grade 2			Grade 3-4		
		Observed	Expected	K	Observed	Expected	K
Sero-positive rheumatoid arthritis	345	17	14	1.2	16	4.5	3.6**
Sero-negative rheumatoid arthritis	300	12	10.1	1.2	4	3.3	1.2

** $P \approx 0.01$

Note: In this and subsequent Tables the sero-positive families include all those in whom the proband had a SCAT titre of 1 in 16 or more. Expected values are based on a population sample of 2,234 individuals and adjusted for age and sex.

Though the Manchester family survey was performed in such a way as to avoid knowledge of the proband's diagnosis, the physician knew that he was examining a relative and was not dealing with a member of a population sample. In this sort of situation x rays have a unique advantage, since they can be mixed with those from a random sample and a truly blind assessment can be performed. It is therefore of interest that the radiographic assessment gives an even more convincing result, as though the clinicians had fallen over backwards in their attempt to avoid bias. The difference between the relatives of sero-positive arthritics and the population samples was significant even for the minimal grades of erosive arthritis (Table XII). It was, however, much more significant for the moderate and severe grades of erosion, which were seven times as common in the sero-positive families as in the population. There was no excess in the relatives of sero-negative probands.

In American Indian populations as in the English populations, there was little evidence of familial aggregation of 'probable and definite' rheumatoid arthritis using the ARA criteria (Bennett and Burch, 1968a, b). None was found in the Blackfeet Indians and, though there was a slight excess in first-degree relatives of affected Pima Indians, it was limited to the parents and in the group as a whole was at only 1.3 times the expected rate (Table XIII).

When the families were analysed in the same way as the Manchester Family Survey, using the clinician's diagnosis of inflammatory polyarthritis to determine the probands and dividing them into sero-positive and sero-negative cases in accordance with the results of the sheep cell agglutination test, no excess of erosive arthritis was found in the families of probands with sero-negative arthritis. The first-degree relatives of sero-positive arthritis probands on the other hand had 2.6 times the expected amount of inflammatory polyarthritis. The x rays

Table XII *Radiological evidence of erosive arthritis of the hands or feet in first-degree relatives of rheumatoid arthritis probands in Manchester, Leigh, and Wensleydale*

<i>Proband</i>	<i>Total x- rayed</i>	<i>Grade of erosive arthritis</i>					
		<i>2</i>			<i>3-4</i>		
		<i>Observed</i>	<i>Expected</i>	<i>K</i>	<i>Observed</i>	<i>Expected</i>	<i>K</i>
Sero-positive rheumatoid arthritis	342	23	11·1	2·1*	17	2·5	6·8†
Sero-negative rheumatoid arthritis	296	7	9·0	0·8	2	1·7	1·2

* $0.05 > P > 0.01$ † $P < 0.01$

Note: Significance based on 766 controls from Leigh and Wensleydale population samples

Table XIII *Analysis of rheumatoid arthritis in Amerindians, using 3+ ARA criteria (after Bennett and Burch, 1968)*

Type of relative	Total examined	3+ ARA Criteria		
		Observed	Expected	K
Parent	17	3	1.4	2.1
Sibling	154	4	3.68	1.1
Offspring	122	4	3.56	1.1
Total	293	11	8.6	1.3

have been read by three observers, one of whom also read the Manchester family *x* rays. Grade 2-4 erosions were 2.3 times as frequent as expected according to one observer and had 2.9 times using a reconciled grading of the other two observers. The degree of aggregation was thus alike in the Amerindian and English family surveys, the Grade 3-4 erosions being six to seven times as frequent as expected and significantly in excess in both racial groups (Table XIV). Burch (personal communication) has examined the degree of familial aggregation in the Amerindians with sero-positive arthritis by an alternative method, selecting as a control for each proband the next person admitted to the survey who was of the same sex and age group. The control probands selected in this way had 52 first-degree relatives, of whom one had Grade 3-4 erosions in the hands or feet, thus giving a *K* value of 3.6 which is not significant. On the whole it would seem that the difference between family studies of rheumatoid arthritis in English and Amerindian populations depends more on the mode of assessment than on any innate differences in the populations, some 4 per cent. of whom seem to have a predisposition to develop moderate or severe erosions.

Cause of familial aggregation

Having decided that aggregation of rheumatoid arthritis occurs in families, the next step is to investigate the cause. One possibility is that arthritis results from infections passed around in the family. Concordance in spouses has been reported by Schull and Cobb (1969), but using the Index of Rheumatoid Arthritis which is an interview measure of rheumatoid arthritis. This has not been confirmed by Bennett and Burch (1968a), Hellgren (1969), or Dalakos, MacSween, Whaley, Dick, Boyle, Jasani, Wilson, Buchanan, and Goudie (1969) using the ARA Criteria, or by Lawrence and Wood (1968a) using the physicians' clinical grading. No one has so far collected radiographs of a sufficient number of spouses of sero-positive arthritic patients to give a definite answer, but in the Manchester Survey only one spouse had Grade 3-4 erosions.

Though the evidence for an effect of the home environment in adult life is unconvincing, the possibility that the environment in childhood may predispose to arthritis in later life must be considered. If the operative feature in the shared environment is infection or faulty nutrition, the disease is likely to be more common in large families. Evidence that this is the case in rheumatoid arthritis is forthcoming from the work of Chen and Cobb (1960), Francis and Epstein (1965), and Bennett and Burch (1968b). Using the ARA Criteria, Bennett and Burch found that sibs from large families have a greater chance of developing rheumatoid arthritis than those from small families, but the effect was not such as to cause familial aggregation detectable by the ARA Criteria. In the Manchester Family Survey there were 38 arthritic siblings or offspring of rheumatoid probands (Table XV, opposite). The siblings in these families varied from two to eleven; 25 came from families of five or more siblings. In an age-matched control series of 38 siblings of unaffected offspring of rheumatoid probands, the number of siblings also varied from two to eleven and 22 came from families of five or more siblings. There was thus no significant difference in family size, and it would seem unlikely that factors associated with family size had an important influence on familial aggregation of arthritis in our Manchester sample.

A useful generalization is that, where the environment within the family is responsible for familial aggregation, different generations develop the disease at the same time and thus have the same prevalence, whereas when heredity is responsible different generations develop the disease at the same age and thus have the same value for *K*. In the Manchester Family Survey there was no significant difference in the value of *K* indicating a genetic influence (Table XVI, opposite).

A higher value for *K* in sibs indicates either an influence of the shared childhood environment (Clarke, Price-Evans, Harris, McConnell, and Woodrow, 1968) or a recessive inheritance. A higher value in parents and offspring as in the Manchester survey favours a dominant or polygenic inheritance.

Table XIV *Comparison of English and Amerindian sero-positive rheumatoid families*

Race	Total x-rayed	Grade of erosive arthritis hands or feet					
		2			3-4		
		Observed	Expected	<i>K</i>	Observed	Expected	<i>K</i>
Amerindian	59	3	2.3	1.3	4	0.68	5.9*
English	342	23	11.1	2.1	17	2.5	6.8***

* *P* ≈ 0.05 *** *P* < 0.01
Note: Expected rate for Amerindians based on *x* rays of 2,046 Blackfeet and Pima Indians read by same observer

Table XV Relationship of family size to aggregation of rheumatoid arthritis

<i>Index relatives</i>		<i>Number of siblings in generation of each first-degree relative with rheumatoid arthritis</i>												
		2	3	4	5	6	7	8	9	10	11	5+	<i>Mean</i>	
With rheumatoid arthritis	38	1	7	5	5	9	2	3	1	3	2	66 per cent.	5.8	
Control	38	2	5	9	5	5	4	1	3	3	1	58 per cent.	4.2	

Table XVI Erosive arthritis in parents, siblings, and offspring of sero-positive arthritis probands

Type of relative	Total x-rayed	Grade of erosive arthritis							
		2-4				3-4			
		Observed		Expected K		Observed		Expected K	
		No.	Per cent.			No.	Per cent.		
Parent	27	9	33	1.9	3.5	3	11	0.41	7.3
Offspring	108	3	3	1.5		0	0	0.0	
Sibling	217	28	13	11.9	2.3	14	6	2.2	6.4

Twin Surveys

Another method which may help to separate the influence of environment from that of heredity is the twin study. A greater concordance of arthritis in monozygous than in dizygous twins suggests a genetic influence and has been reported by a number of workers (Table XVII). Taking a mean of these studies it would appear that 32 per cent. of mono-

zygous twins are concordant but only 9 per cent. of dizygous twins. Before we can accept these figures as proof of a genetic influence we must consider certain other explanations. A difference in age or sex distribution between the monozygous and dizygous twins, for example, might account for the greater concordance in the monozygous group, and the proportion of sero-positive and sero-negative arthritis in the index twins could also play a part.

Table XVII Twin studies in rheumatoid arthritis

Source	Authors	Date	Monozygous			Dizygous			MC/DC
			Concordant No.	Discordant Per cent.		Concordant No.	Discordant Per cent.		
General Hospital and Department of Rheumatology	Claussen and Steiner	1938	6	35	11	2	13	14	3
Department of Rheumatism	Edström	1941	4	67	2	1	11	8	6
General Hospital	Brandt and Weihe	1939	2	40	3	2	29	5	1.4
Advertisement	Thymann	1957	3	50	3	1	17	5	3
Birth registrations	Thymann	1957	0	0	8	0	0	9	0
Birth registrations	Harvald and Hauge	1965	16	34	31	10	7	131	4.9
Various	Meyerowitz and others	1968	0	0	8	—	—	—	—
Total			31		66	16		172	
Concordance			32 per cent.***			9 per cent.***			

*** P < 0.001

A still more serious question is the influence of selection. This is illustrated by the study of Thymann (1957), who found that half of the monozygous twins who came in answer to an advertisement were concordant, whereas those obtained from the birth register were all discordant. The numbers studied, however, were small, and in a much larger series obtained from birth registrations by Harvald and Hauge (1965), the concordance was four times as great in the monozygous twins. Unfortunately it was not practicable for these authors to examine the 15,000 pairs of twins on the register and the completion rate in this very ambitious study was only 46 per cent. when the results I have quoted were published. The diagnosis, moreover, was mainly based on a questionnaire so that it is impossible to know how much genuine arthritis was present.

In 1959 Dr. Allan Dixon suggested to the Arthritis and Rheumatism Council that a twin study of rheumatic disease based on unselected rheumatic patients be undertaken. A committee was formed under his chairmanship to undertake this task, and rheumatism centres in the United Kingdom and the Netherlands were asked to co-operate by asking every patient attending their clinics or occupying their hospital beds the question 'Are you a twin?' If the answer was 'yes' and the co-twin still living, the names and addresses of the twins were obtained and forwarded to the Council. Altogether 23 centres in the United Kingdom and four in the Netherlands agreed to take part, and the collection of twins continued up to 1963. Between 1962 and 1967 the twins were examined blind by Dr. Dixon and members of the Field Unit staff, x rays being taken of the hands, feet, and cervical spine, and samples of blood for blood grouping and for tests for rheumatoid factors in Manchester and Leiden. Zygoty was determined clinically and by means of eight blood groups by Drs. R. Sanger and F. Stratton. The x rays were read mixed with those from population samples in Leigh, Wensleydale, Watford, and Brabant, and from the Manchester Family Survey, the same observer reading them all.

The United Kingdom sample contained 428 twins with live co-twins, one set being triplets (Table XVIII). Before they could be examined 21 index and twelve co-twins had died, 34 had emigrated or could not be traced, and 35 refused to cooperate. Of the available index twins 98 per cent. and of their

co-twins 94 per cent. were examined. Since dizygous twins share a more comparable environment than sibs of dissimilar ages, it follows that, if the childhood environment is important in determining predisposition to arthritis, dizygous co-twins of sero-positive rheumatoid patients should show a greater prevalence of arthritis than other sibs, but this was not found to be so when the twin and family studies were compared (Table XIX, opposite), the excess over the expected rate being almost identical in the two groups.

On an environmental hypothesis, it would further be expected that *like-sexed* dizygous twins, sharing, as they must, an even closer environment, would show an even greater divergence from other sibs. This also is negated by the Twin Survey. In both groups the prevalence was just over six times that which would be expected. Monozygous twins have, in addition to a similar environment, an identical genetic background and here there is a difference, the prevalence of Grade 3-4 erosive arthritis being 33 times the expected rate. This is confirmed by the clinical findings, which indicate that the concordance of sero-positive arthritis is six times as great in monozygous as in dizygous twins (Table XX, opposite). No concordance was observed in twins with sero-negative polyarthritis, thus confirming the evidence from family studies. The concordance of sero-positive arthritis in this ARC Twin Survey is thus of the same order as that in published twin studies listed in Table XVII, and indicates that the aggregation of arthritis in families does not depend on the shared environment.

Mode of Inheritance

We have already seen, from the prevalence in sibs, parents, and offspring, that a recessive inheritance is unlikely. With a monogenic dominant inheritance one would expect an approximate halving of the prevalence, passing from monozygous co-twins, who must of course possess the predisposing gene, to dizygous co-twins or first-degree relatives, half of whom should possess it. The sharper fall from 25 to 5 per cent. which we have found in the prevalence of Grade 3-4 arthritis would be expected from a polygenic inheritance with a threshold (Carter, 1965, 1968). Since polygenic traits such as height are distributed in the population in a normal or

Table XVIII *Completion rate in twins in United Kingdom survey (ARC Twin Survey)*

<i>Twins</i>	<i>Total in sample</i>	<i>Died</i>	<i>Untraced or emigrated</i>	<i>Refused</i>	<i>Examined</i>	<i>Completion rate (per cent.)</i>
Index twins	428	21	16	9	382	98
Co-twins	429	12	18	25	374	94

Table XIX *Erosive arthritis in co-twins with sero-positive rheumatoid arthritis (ARC Twin Survey)*

Index twins		Co-twins				Siblings			
		Total examined	Grade 3-4 Erosive arthritis			Total examined	Grade 3-4 Erosive arthritis		
			Observed	Expected	K		Observed	Expected	K
Sero-positive arthritis	Monozygous	19	6***	0.18***	33.3*				
	Dizygous	67	4	0.61	6.5*	217	14	2.2	6.4 ^{NS}
	Like-sexed	37	2	0.30	6.7				
	Unlike-sexed	30	2	0.31	6.5				
Sero-negative poly-arthritis		58	0	0.3					

* 0.05 > P > 0.01 *** P < 0.01

Note: Expected rates assessed from 2,759 persons x-rayed in Leigh, Wensleydale, and Watford.

Table XX *Inflammatory polyarthritis in co-twins 33333f twins with polyarthritis (ARC Twin Survey)*

Index twins with arthritis		Co-twins				
		Total examined	Percentage inflammatory polyarthritis in co-twins			
			Grade		Confirmed	
			2-4	3-4	Radiologically	Serologically
Sero-positive	Monozygous	20	40*	25	30*	30
	Dizygous	73	11*	5	4*	5
Sero-negative	Monozygous	18	0	0	0	0
	Dizygous	51	0	0	0	0

* P ≈ 0.05

Note: Figures for dizygous twins are adjusted to age and sex of those for monozygous

Gaussian manner (Fig. 2), first degree relatives, with half their genes in common with the proband, have a distribution of the underlying genetic predisposition, about a mean half-way between that of the index patients or the monozygotic co-twins and that of the general population. Thus, if the average patient with sero-positive arthritis or his monozygous twin has eight predisposing genes, if there are on average four such genes in persons in the general population and at least seven must be present for arthritis to develop, the number in first-degree relatives and dizygous co-twins will vary about a mean of six. Thus, whereas only some 4 per cent. of the population carry the predisposition, this applies in nearly 20 per cent. of first-degree relatives or dizygous co-twins.

In the twin study 30 per cent. of the monozygous co-twins had so far developed sero-positive arthritis but all were genetically predisposed, so the disease was fully expressed in just under one-third of them.

FIG. 2 *Theoretical distribution of predisposing genes in polygenic inheritance (after Carter, 1965).*

Of the dizygous co-twins, 5 per cent. had sero-positive arthritis so that some 17 per cent. were probably carrying the genetic predisposition. These are represented by the hatched area in Fig. 2.

The mode of inheritance has been assessed in another way by using the formula of Edwards (1960) on data from the Manchester Family Survey. This also indicates that the inheritance of sero-positive arthritis is polygenic (Lawrence and Wood, 1968a).

A number of other tests for multifactorial inheritance are available. For example, if relatives of more severely affected patients show a higher prevalence of the disease, a multifactorial inheritance is indicated (Carter, 1965). This is reflected in the relationship to sero-positivity in the proband to which I have already referred, since sero-positive arthritis is, in general, more severe than the sero-negative forms. When the relatives were divided according to the severity of the proband's arthritis, regardless of the SCAT titre, there was in fact a graded relationship between the severity in the proband and the excess prevalence in the relatives (Table XXI).

Heritability of rheumatoid arthritis

From the concordance of 40 per cent. in monozygous twins it is clear that nurture as well as nature must play a part. To cope with this problem, Dr. Wood has estimated the proportion of phenotypic variance which is due to additive genetic variance, in other words the degree of heritability. For this he has used the formula of Falconer (1960, 1965). Using Grade 3-4 erosive arthritis as the parameter, the heritability of sero-positive rheumatoid arthritis was 60 per cent. with a standard error of ± 12 per cent. (Lawrence and Wood, 1968a). This figure is based on the Manchester Family Survey, but the twin data give a similar result. Using like-sexed dizygous twins, the heritability was 58 per cent., with unlike-sexed twins it was 61 per cent, and with monozygous twins 70 per cent. These figures are well within the standard error and it may be con-

cluded that the heritability of the sero-positive disease is between 60 and 70 per cent. These figures may be compared with those deduced for congenital pyloric stenosis which has a heritability of 79 per cent., for club foot 70 per cent., and for peptic ulcer 37 per cent.

Genetic mechanism

Genetic markers

Of the nature of the genetic mechanism there is so far little evidence. There is no way of quantitating the number of genes involved in polygenic inheritance or the threshold at which a predisposition to the disease arises, and the predisposing genes must thus be identified one by one. No convincing gene markers have so far been identified. The ABO, MN, and Kell blood groups have shown no association with rheumatoid arthritis, and though rheumatoid arthritic patients have shown a diminished proportion of Rh negative individuals (Cohen, Boyd, Goldwasser, Cathcart, and Heisler, 1963; Stoia, Ramneantu, and Poitas, 1967), the difference in patients studied by Baxter, Izatt, Jasani, and McAndrew (1968) was slight and not significant. In populations examined by Kirkpatrick, Miall, and myself in the Rhondda and Jamaica, there was less clinical evidence of poly-arthritis in the Rh negative group, and similarly in a group of Rh negative blood donors examined by Boffi Boggero in Buenos Aires, but sero-positive erosive arthritis occurred at the expected rate. Haptoglobin 2-2 is more common in patients with rheumatoid arthritis than in the general population and haptoglobin 1-1 has a diminished frequency (Nettelblad and Sundblad, 1965, 1967). The Hp-2 gene which is thus associated with arthritis is however more common in sero-negative arthritis.

Genetic abnormalities

Possible abnormalities which might be involved in the aetiology of rheumatoid arthritis must next be considered.

Table XXI *Relationship of grade of rheumatoid arthritis in proband to prevalence in relatives*

<i>Grade of rheumatoid arthritis in proband at time of survey</i>	<i>First-degree relatives</i>			
	<i>Total x-rayed</i>	<i>Erosive arthritis hands or feet (Grade 3-4)</i>		
		<i>Observed</i>	<i>Expected</i>	<i>K</i>
4	119	11	0.98	11*
3	215	6	1.08	5.5*
2	264	7	1.52	4.6
0-1	20	0	0.11	0.0
Not graded	20			

* 0.05 > P > 0.01

(1) ABNORMAL MOLECULAR STRUCTURE OF COLLAGEN OR GROUND SUBSTANCE

The heterogeneity of protein polysaccharides in articular cartilage has been emphasized by Brandt (1968) and must surely depend to some extent on genetic control. The increased prevalence of the more severe grades of erosive arthritis which has been the most striking feature of the family studies and of the twin survey, suggest some molecular change in one of the elements of articular cartilage in rheumatoid families. A defect in collagen is suggested by the work of Steven (1964), who found that two peptides present in gelatin derived from the normal Achilles tendon were entirely absent in rheumatoid gelatins. Survival to adult life would be unlikely if they had been lacking from the original collagen, but Steven has further shown that rheumatoid collagens are deficient in certain cross-linkages and are more readily depolymerized by alkali or by exposure to pronase, which causes appreciable digestion in 10 minutes though with normal collagens there is no increase in gelatin formation with pronase even after 24 hours (Steven, 1965, 1966).

A feature which I have noted in rheumatoid families is that many first-degree relatives, who have not developed arthritis, show hypermobility. This could well reflect changes in cross-linkage of collagen or of ground substance. It occurs equally in sero-positive and sero-negative families and is thus not related to the severity of the arthritis (Table XXII). This would suggest a single gene defect and indeed joint laxity is often dominantly inherited in this way (Carter and Sweetnam, 1958). This could account for one of the additive genes which contribute to rheumatoid predisposition.

(2) PERMEABILITY OF LYSOSOMAL MEMBRANES

An inherited flaw leading to increased permeability of lysosomal membranes was suggested by Weissmann (1964). This has been confirmed by Bitensky, Poulter, Scott, and Chayen (1969) who have shown that, in association with a change of the redox state of the tissues, the lysosomes of rheumatoid synovia have an increased permeability for proteolytic en-

zymes. Increased permeability for acid phosphatase has been demonstrated by Wegelius, Klockars, and Vainio (1968). This is not a transient phenomenon. Goldfischer, Smith, and Hamerman (1967) found increased activity of lysosomal hydrolases in the lining cells of rheumatoid membranes even after sub-culture for 7 months in nutrient medium. The increased lysosomal permeability in rheumatoid synovia, moreover, persists after a stimulus such as mechanical injury has ceased. A genetic influence on the structure of the lysosomal membrane or on the redox balance which controls permeability could thus predispose towards persistent cartilage and bone erosion triggered by trauma or some other initiating event.

(3) AUTOIMMUNITY

It is known from animal experiments that susceptibility to infections and the capacity to react to different antigens with production of humoral antibody or cell-mediated immunity is inherited, and that the response of animals to injection of antibody against specific organs varies (Allison, 1968, 1970). This may depend on a single dominant gene as in malaria or on a recessive gene as in Aleutian mink disease or on multiple additive genes as in myxomatosis. The tendency to autoimmunity also appears to be inherited, for example in NZB mice (Bielschowsky, Helyer, and Howie, 1959; Hahn and Shulman, 1969; Friou, Teague, and Myer, 1968).

Evidence of cell-bound antibody to antigens in synovial fluid or synovial tissue in rheumatoid arthritis is forthcoming from the work of (1964), Duthie, Alexander, and Stewart (1965), and Multz, Kamin, McDowell, and Butler (1968) using skin tests, and from that of Hedberg and Kallen (1964), Sukernick, Hanin, and Mosolov (1968), and Loewi and MacLennan (1969), using the culture of synovial cells exposed to lymphocytes from rheumatoid patients. It is perhaps significant that it is only in sero-positive arthritis that Loewi and MacLennan (1969) found cytotoxic lymphocytes and that Sukernick and others (1968) found none in mild cases. Scheiffarth and Warnatz (1968), using a lymphocyte transformation test with homogenized synovial

Table XXII *Hypermobility in relatives of rheumatoid probands. Based on ARC Family Survey, excluding Leigh and Wensleydale Families.*

Probands with rheumatoid arthritis	Relatives	Grade 2-4 Hypermobility		
		Total examined		
		Observed	Expected	K
Sero-positive	369	32	13.8	2.3***
Sero-negative	229	25	10.0	2.5***

*** P < 0.01

tissue as antigen, have also produced evidence that rheumatoid lymphocytes are programmed to react to synovial antigens.

Evidence of a humoral antibody capable of inducing arthritis when injected into the unaffected joints of rheumatoid subjects is forthcoming from the work of Hollander, Fudenberg, Rawson, Abelson and Torralbi (1966) in Philadelphia, and rheumatoid serum has been shown to inhibit the growth of fibroblasts in tissue culture (Castor, Wright, and Buckingham, 1968). Antibodies to collagen have been discovered in both serum and synovial fluid from patients with rheumatoid arthritis by Steffen and Timpl (1962) and Steffen (1969) using an anti-globulin consumption test, and antibodies to synovial cells and small blood vessels adjacent to the synovial surface have been found by Ogawa, Tsujo, Namba, Hamaya, Okamoto, and Miwa (1965), using an indirect immunofluorescent technique; Norton and Ziff (1966), however, concluded from their electron microscope studies that the antibody was produced locally in the deeper layers of the synovium and was directed against an antigen in the connective tissue space rather than against the synovial cells themselves. It is not known whether these autoantibodies occur in other members of the family.

Inherited differences in the immune response to certain organisms might also play a part. Duthie, Stewart, Alexander, and Dayhoff (1967) have suggested that intracellular diphtheroids may constitute the antigenic stimulus. Apart from the diphtheroids, infecting organisms have been found mainly in the sero-negative forms of polyarthritis in which heredity appears to play a very minor role.

(4) INHERITED TENDENCY TO PRODUCE RHEUMATOID FACTOR

Though rheumatoid factor is present in many tissues, including the liver and bone marrow, in rheumatoid arthritis the concentration is greatest in the synovium and, as it is present in plasma and lymphoid cells, it is presumably being produced by those cells. The cells contain factors active against both human and rabbit gammaglobulin or predominantly against the latter (Bonomo, Tursi, and Gillardi, 1968). Rheumatoid factor reacting with altered human gammaglobulin is seldom aggregated in families. This has been amply proved in the Blackfeet Indians by Bennett and Burch (1968a, b) and would appear to apply also to Caucasians (Lawrence, Valkenburg, Bremner, and Ball, 1970). It has been confirmed in a twin study by Buchanan, Boyle, Greig, McAndrew, Barr, Anderson, and Goudie (1966). Indeed, it would seem that all members of the human species have the ability to produce this substance in equal measure, though it occurs with greater frequency in certain cohorts and is more common in individuals

from large families, possibly through greater exposure to infections in such families.

Rheumatoid factor reacting with rabbit gamma-globulin on the other hand is aggregated in families, and it appears that the members of some families are predisposed to produce rheumatoid factor capable of reacting with both human and rabbit gamma-globulin. Dual positivity, as so defined, occurs in eight times as many relatives of dual positive probands as in the population (Lawrence and others, 1970). Families of hospital patients with sero-positive arthritis, however, do not have significantly more rheumatoid factor than expected nor do they have more than the families of hospital patients with sero-negative arthritis (Bremner, Alexander, and Duthie, 1959; Veenhof-Garmann, Steiner, Westendorp-Boerma, de Blécourt, and Valkenburg, 1968; Lawrence and others, 1970). It would seem that the rheumatoid factor in sero-positive arthritic patients is produced mainly as a result of the disease process and depends little, if at all, on genetic predisposition to produce rheumatoid factor. In the ARC twin study, dizygous co-twins of dual positive probands had five times the expected dual positivity, where as monozygous co-twins had eighteen times the expected amount (Table XXIII, opposite). Though this may indicate that a predisposition to produce wide-spectrum rheumatoid factors is inherited, we must accept the concept with caution, since the dual positive co-twins all had arthritis, and the twin data may simply reflect the genetic predisposition to develop arthritis.

(5) ERRORS OF METABOLISM

A number of apparent errors of metabolism have been found in patients with rheumatoid arthritis. They have been concerned mainly with the heterocyclic amino acids, tryptophan and histidine.

Excessive amounts of such urinary metabolites of tryptophan as kynurenine and 3-hydroxykynurenine are excreted in rheumatoid arthritis and also in systemic lupus erythematosus (Beetham, Fischer, and Schrohenloher, 1964; Bett, 1964). The abnormality is found in a small proportion of relatives and can be corrected by administering pyridoxine but without improvement in the clinical condition. The mean serum kynurenine is raised and, following a tryptophan load, the urinary output of both kynurenine and 3-hydroxykynurenine is much higher than normal (Haupt and Ogryzlo, 1968). The abnormality is present in other diseases, but is said to be unrelated to tissue destruction or to drugs used in treatment. It is, however, found in pneumonia, myocardial infarction, and cancer (Pinals, 1964). A shunt of tryptophan into the kynurenine pathway due to increased hepatic tryptophan pyrrolase activity has been suggested by Spiera (1966), and

Table XXIII SCAT and LFT in twins

Index twins		Co-twins					
		Total tested	SCAT + LFT+		LFT+ only		SCAT+ only
			Observed	K	Observed	K	
Monozygous	SCAT+ LFT+	14	4***	18	1	2	0
	LFT+ only	6	0		1	4	0
	SCAT+ only	3	0		0		0
Dizygous	SCAT+LFT+	38	3	5	2	1.3	0
	LFT+ only	26	0		4	4	1
	SCAT+ only	3	0		0		0

Note: The figures in this table are provisional since the data from the Netherland twins are incomplete.

it has been pointed out that a high excretion of tryptophan metabolites correlates with a high turnover of fibrinogen which is rich in tryptophan.

Increased urinary excretion of substances binding copper ions, such as histidine and 3-methyl histidine, has also been found in patients with rheumatoid arthritis (Gerber, 1966a), but the serum level is low. Histidine is present in the B1 and NVIr peptide chains in the collagen molecule, but only in very small amounts (Hannig and Nordwig, 1964). Gerber (1966b) has postulated that disulphide interaction proceeds more readily when the level of histidine in the serum is low. A number of amino acids have been found to be increased in the serum in arthritis (Biesiadecki, Tourtelotte, Digeorge, and Auerbach, 1968). Apart from ornithine, these are all part of the collagen molecule, and their excess in the serum could be due to destruction of collagen. The metabolism of tyrosine, however, appears to be abnormal in arthritis (McCormick, Robinson, Smith, and Day, 1962). The tyrosine metabolite, *p*-hydroxyphenyl-lactic acid, is found in the urine in some 40 per cent.

of cases, but in only 2 to 9 per cent. of controls.

The green serum of rheumatoid arthritis may indicate a metabolic error, though it is present in only some 13 per cent. of cases. It is not related to the extent of the arthritis or to treatment, but is found more often in sero-positive cases of long duration. Shah and Wright (1968) consider that it is due to a deficiency of yellow pigment, possibly carotene. There is no clear indication whether any of these metabolic abnormalities runs in families.

Psoriasis

This condition was found with roughly four times the expected frequency in both sero-positive and sero-negative arthritic families in Manchester, even when probands with psoriasis were excluded (Table XXIV). The numbers in the sero-negative group did not attain significance, but Baker (1966) also found psoriasis in 5 per cent. of sibs in his sero-negative families. Though he found it in only 1.6 per cent. of sibs of sero-positive arthritic patients, there can be little doubt that the psoriatic trait, though seldom

Table XXIV Percentage with psoriasis in first-degree relatives of psoriatic and arthritic probands

Probands	Relatives					
	All first-degree			Sibs only		
	Total examined	Psoriasis		Total examined	Psoriasis	
		Grade 2-4	K		Grade 2-4	K
Psoriasis without arthritis	105	16	14***	46	26	24***
Psoriatic arthritis	81	7	7***	61	8	7***
Arthritis without psoriasis						
Sero-positive	281	5	5***	187	4	4***
Sero-negative	129	3	3 ^{NS}	65	5	4 ^{NS}
Gout	138	1.5	1.4 ^{NS}	70	1.4	1.3 ^{NS}
Total population samples examined in Leigh, Wensleydale, Watford, and the Rhondda						1.1 per cent.

*** P < 0.01 NS = not significant.

expressed in sero-positive cases, produces a general predisposition to arthritis. The fact that psoriatic arthritis is usually sero-negative suggests that antigen IgG-antibody complexes are not involved in this predisposition. Flesch and Jackson Esoda (1957) have postulated the lack of a dipeptidase activator which results in abnormal cellular decomposition and abnormal utilization of amino acids for keratin synthesis.

As would be expected, the families of patients with psoriatic arthritis show a higher prevalence of psoriasis than the families of those with simple arthritis. An even greater prevalence was noted in Manchester in the families of psoriatics without arthritis, but these were patients attending a dermatology clinic and had more severe skin involvement. The greater prevalence in sibs in these last families suggests an intermediate inheritance with more extensive skin involvement in the homozygotes than in the heterozygotes.

Still's disease

This condition differs from rheumatoid arthritis not only in the age at onset but also in the sex distribution, the frequent occurrence of iritis, and the pattern of joint involvement. The sacroiliac joints and hips are more often affected and ankylosis is a feature of Still's disease but not of rheumatoid arthritis (Ruderman, Marchesano, Abruzzo, and Calabro, 1966). Genetically it also differs from the adult form of rheumatoid arthritis. As the genetic aspects of this disease have been dealt with fully by a previous and more distinguished Heberden Orator (Bywaters, 1967), I need not consider them now.

Environmental influences

Burch (1963a, b), from an analysis of the age-specific prevalence of inflammatory polyarthritis in the Leigh and Wensleydale population samples, concluded that the data were consistent with the view that the condition arose from a series of random events occurring in genetically predisposed individuals. Following Burnett (1959), he suggested that these events were somatic mutations occurring in the X-chromosome of immunologically competent cells such as lymphocytes and that they gave rise to forbidden clones producing cell-bound antibody to a normal component of synovial tissue. Though in females the Leigh and Wensleydale data provide a reasonable fit for Burch's theoretical curves, in males the relationship is less satisfactory. This may be due to small numbers in some age groups, but the addition of data from other surveys has not so far produced a perfect fit.

If somatic mutations were responsible, moreover, it would be expected that populations exposed to

undue amounts of ionizing radiation would show a higher incidence of arthritis, but this has not been found to be so (Wood, Kato, Johnson, Uda, Russell, and Duff, 1967). Persons exposed to radiation from the atomic bomb in Hiroshima and Nagasaki did not show an increased prevalence of definite rheumatoid arthritis. In those who did develop arthritis, the age at onset of symptoms was about the same for those who were near the hypocentre as for those who were farther away. This, though it does not exclude the somatic mutation hypothesis, makes it less likely.

We must therefore look for another type of random event and infection at once springs to mind. There is evidence from work with experimental animals that a series of infections is required to produce arthritis. A single inoculation of *Bedsonia* into monkeys is without effect, but a second inoculation 30 days later is rapidly followed by arthritis (Jones, Schachter, and Meyer, 1966). The production of chronic progressive arthritis in pigs or rabbits with *Erysipelothrix insidiosa* requires repeated intravenous inoculations (Lightfoot, Neher, Aho, and Christian, 1966; Astorga, 1968). On the other hand, prior vaccination with dead *Erysipelothrix* protects (Shuman, Wood, Monlux, and Cheville, 1965). Glynn (1970) has suggested that bacteria and viruses act as haptens which combine with tissue proteins, rendering them antigenic and capable of inducing an autoimmune response after repeated exposure. The production of experimental arthritis by lysosomes or by release of lysosomal enzymes also requires a series of insults to produce the rheumatoid type of arthritis (Weissmann, Spilberg, and Krakauer, 1969; Pras and Weissmann, 1966).

An infective theory is consistent with a greater incidence of arthritis in females. In experimental animals a greater host response has been found in females in connection with graft rejection and with inoculation with bacteria, foreign proteins, and tumour cells, the sex difference being greater in animals vaccinated prior to infection (Brent and Medawar, 1966; Wheeler and Hurst, 1961; Gorer and Kaliss, 1959). This has been confirmed in human females, who have higher levels of immunoglobulins than males. In our population sample in Leigh, *Salmonella* antibodies were found in higher titre in females and there is a very significant sex difference in antibody response to challenge with, for example, *Brucella*, indicating a greater immunological competence in females (Rhodes, Markham, Maxwell, and Monk-Jones, 1969a). It is of interest in this connection that the amount of IgM in the serum is related to the number of X chromosomes in XY XX XXX XXY and XXXY individuals (Rhodes, Scott, Markham, and Monk-Jones, 1969b).

Evidence of infectious trigger

That the onset of arthritis is triggered by an infective agent can most readily be adduced in the benign self-limiting form, in which the onset is more acute and the disease runs a relatively short course (Lawrence and Bennett, 1960). In such cases the onset usually occurs in the winter months and seldom in July or August. An association with respiratory infection would thus seem likely, and Šitaj, Svec, and Urbanek (1964) have reported preceding upper respiratory infection in 38 per cent. of cases of episodic benign arthritis. Adenoviruses are common in spring and winter and cause upper respiratory infection in all age groups (Watson, 1969), and antibodies to them are sometimes found in patients with benign polyarthritis. Some cases which have developed after respiratory infection have been associated with a high titre of complement-fixing antibodies to *M. pneumoniae* (Lambert, 1968), but benign polyarthritis has been reported after a large number of acute virus infections and also infections with *Salmonella* (Geiger, 1918; Berglōf, 1963; Smith and Sandford, 1967). These transient forms of arthritis are usually sero-negative, and it is from sero-negative forms of polyarthritis such as Reiter's disease that *Bedsonia* and *Mycoplasma* have mainly been isolated (Siboulet and Galistin, 1962; Engleman, Barnes, Jones, Schachter, and Meyer, 1966; Brown, Bailey, Felts, and Clark, 1966), but the diphtheroids isolated from synovial membrane and fluid by Stewart, Alexander, and Duthie (1969) and by McCormick (1969) were mainly from sero-positive arthritics, and the development of both sero-negative and sero-positive polyarthritis after respiratory or gastrointestinal virus infections has been reported by Hollander, Brown, Jessar, Hummeler, and Heule (1962). These were not all benign, since in a third of the cases the arthritis persisted for at least 4 years and exacerbation of known rheumatoid disease was also reported. Moreover, chronic sero-positive arthritis has been reported after rubella,

associated with a persistence of antibodies to the virus (Martenis, Bland, and Phillips, 1968). Though infections can be described as random events they are not so strictly random as somatic mutations, and this may explain the lack of strict adherence to the curves which Burch constructed for age and sex incidence. It cannot be said, however, that the case for an infectious trigger is proved. Indeed, the lack of any urban/rural difference in the prevalence of clinical arthritis is in favour rather of somatic mutations.

Geography

If the initiation of arthritis depends on a series of specific infections, geographical differences in prevalence would be expected. Rheumatoid arthritis has been described as a disease of temperate climates and this is to some extent true, but only because the age distribution of populations in such climates includes a larger number of old persons, particularly of the female sex. When allowance is made for this, the excess in temperate regions disappears and indeed, of eight fully-documented population samples completed in 1965, the population in Jamaica with the highest prevalence of rheumatoid arthritis was subtropical (Lawrence, Behrend, Bennett, Bremner, Burch, Gofton, O'Brien, and Robinson, 1966). When these were arranged in order of latitude, it became obvious that there was no relationship to distance from the equator. Moreover, the geographical differences applied only to probable arthritis. A blind reading of all the x rays from these eight population samples showed that the Jamaicans had more erosive arthritis than any of the other populations but only of the milder forms (Grade 2). In striking contrast to the family and twin studies, no geographical difference was found between populations in the prevalence of Grade 3-4 erosive arthritis. Such differences as were present when Grade 2 was included were seen in the sero-negative cases (Table XXV).

Table XXV Sero-positive and sero-negative erosive arthritis in eight populations aged 35-64 (unweighted mean)

Area	Latitude	Total x-rayed and tested	Percentage erosive arthritis hands or feet (Grade 2-4)	
			Sero-positive	Sero-negative
Wensleydale	54°	464	1.1	2.4
Queen Charlotte Island	54°	172	1.3	NS 6.4**
Leigh	53°	698	0.7	NS 1.9
Watford	51°	178	0	1.1
Oberhörten	50°	210	0	6.2
Montana	48°	722	1.1	3.0
New Haven	41°	256	0.4	2.8
Arizona	33°	632	2.0	6.3
Jamaica	18°	505	NS 0.4	12.3**

New Haven data from Prof. Roy M. Acheson ** 0.05 > P > 0.01 NS = not significant.

In view of what has been said about the relationship of sero-negative polyarthritis to infection, it would seem reasonable to suppose that the somewhat haphazard geographical distribution of this form of arthritis depends on local infections. A possible clue is to be found in the *distribution* of the lesions, which, in Jamaica, occurred mainly in the feet (Table XXVIA). Since most Jamaicans walk barefoot, frequent small cuts must occur and no doubt many become infected. This is confirmed by surveys in Nigeria and Liberia undertaken by Valkenburg and his team. In Nigeria 13 per cent. of males and 11 per cent. of females had erosive arthritis in the feet. Direct trauma to a joint, however, can also cause erosions, and may be responsible for the frequency of such lesions in individuals who walk barefoot. The erosions are indistinguishable from the healed erosions seen in patients with rheumatoid arthritis (Fig. 1).

Table XXVIA *Percentage erosive arthritis in the feet in six regions, by sex*

Region	Footwear	Erosive arthritis in feet	
		Male	Female
Queen Charlotte Island	Boots	5.6	5.4
Montana	Moccasins	2.6	1.5
Oberhörln	Boots	6.5 ^{NS}	1.8 ^{NS}
Arizona	Moccasins	3.4	6.4
Jamaica	None	12.6	7.9
Nigeria	None	13.1	10.8

NS = not significant.

If injury to a joint or local inflammation can induce autoantibody formation of such intensity that other joints become affected, it would be expected that erosive arthritis in, for example, the hands would also be found with increased frequency in Jamaicans and Nigerians, particularly in males. This, however, was not found to be the case (Table XXVIB). In both these populations the women had, if anything, more erosive arthritis in the hands.

Table XXVIB *Percentage of erosive arthritis in the hands in six regions, by sex*

Region	Chief occupation	Sex	
		Male	Female
Queen Charlotte Island	Fishermen	5.1	1.2
Montana	Ranchers	4.4	1.4
Oberhörln	Builders	5.6 ^{NS}	0.8 ^{NS}
Arizona	Cotton growers	4.4	4.4
Jamaica	Cultivators	4.2	5.6
Nigeria	Farmers	2.9	5.2

NS = not significant.

It is of interest that, where the predominant occupation in males involves the possibility of local trauma and infections, as for example in Oberhörln where the predominant male occupation is building, and in Queen Charlotte Island where it is fishing, the men had four to seven times as much erosive arthritis in the hands as the women. The numbers are small and not significant, but they confirm similar indications in surveys in northern Europe (de Graaf, Laine, and Lawrence, 1963). The greater frequency of erosions in the dominant hand and the sparing of paralysed limbs confirms the baleful influence of quite minor trauma in rheumatoid subjects (Glick, 1967), but most of those in the population samples with erosions had no clinical evidence of rheumatoid arthritis.

In the US National Health Survey (1966), this question was approached in a different way by comparing erosive arthritis in groups with different standards of education. In males with less than 5 years of education, erosive arthritis of the hands or feet was present at 1.4 times the expected rate, whereas in those with 13 or more years the rate was only 0.4 times that expected. There was, however, in this survey a relationship to symmetrical joint swelling, severe morning stiffness, and high titres of rheumatoid factor (Bentonite flocculation test 512 +), indicating that the less skilled workers had a greater prevalence of generalized arthritis. However, no relationship between inflammatory polyarthritis or erosions and social class had been found in populations in the United Kingdom.

Longitude

Although there is no relationship between rheumatoid arthritis and latitude, evidence has recently been accumulating that a relationship to longitude may exist. Šitaj and others (1964) reported a very low prevalence of arthritis in Czechoslovakia. Comparison with published data from Western Europe indicates that significant differences may exist (Table XXVII, opposite). These are the more interesting since they include definite as well as probable arthritis and sero-positive as well as sero-negative.

At about this time Dr. Wilhelm Zinn of Bad Ragaz in Switzerland was planning a survey of rheumatic diseases in the village of Azmoos. With the sample in Oberhörln in West Germany examined by Dr. Behrend and those in Leigh and Wensleydale, we thus had five European population samples in which routine clinical, radiological, and serological tests had been performed. They covered longitudes 2°W to 18°E. The x rays from these five surveys were mixed and read blind. A study of the ARA criteria in these five populations showed the marked and haphazard variation in probable arthritis which

Table XXVII *Percentage rheumatoid arthritis in English and Czechoslovak population samples (aged 35 +)*

Population	No. examined	3+ criteria		5+ criteria
		Sero-positive	Sero-negative	
Czechoslovakia	951	0.5***	0.8***	0.6**
England	1,528	1.6***	5.0***	1.7**

*** $P < 0.01$ ** $0.05 > P > 0.01$

Per cent. = unweighted mean of four age groups

we have come to expect, but a lower prevalence of definite disease in Czechoslovakia than in any of the other surveys.

The New York Criteria for rheumatoid arthritis showed a similar haphazard variation in the prevalence of clinical disease (Criteria 1 and 2) (Table XXVIII). Except that the Czechoslovak population had significantly less than any of the others, there was no relationship to longitude or latitude, but sero-positive arthritis (Criterion 4) and arthritis confirmed radiologically (Criterion 3) revealed an East-West gradient, the Czechoslovak population having significantly less than the English. What does this East-West difference mean? Hewitt (1965), investigating possible reasons for an East-West difference in the prevalence of spina bifida in white Americans, concluded that the lower prevalence in the West depended on greater outbreeding in the newer and more recently settled states. It is unlikely that this would apply in Europe, but migration trends could offer an explanation, since the more fit tend to emigrate and the less fit to stay behind. Thus the East-West difference may depend on varying facilities for emigration. A still lower prevalence, only 0.3 per cent. with definite rheumatoid arthritis, has been found in a mainly immigrant population in Jerusalem (Adler, Abramson, Elkan, Hador, and Goldberg, 1967). Still further East in Japan, low prevalences similar to those in Czechoslovakia have been encountered (Wood and others, 1967; Shichikawa, Mayeda, Komatsubara, Yanicimoto, Akabori, Hongo, Kosugi, Miyanchi, Orihasa, and Taniguchi, 1966). Until it is possible to confirm this finding in samples submitted to routine x rays and serological

studies, it would be unwise to draw any finite conclusions.

Conclusions

From the data which have been presented it is clear that heredity plays little part in the aetiology of sero-negative polyarthritis but that in the more severe sero-positive disease genetic predisposition is important. The subject is, however, of great complexity and the genes responsible will take time to unravel. Meanwhile much can be done to elucidate environmental influences.

Probably the most satisfactory way to investigate environmental factors in a disease such as sero-positive rheumatoid arthritis, which is influenced so substantially by heredity, is to look at discordant monozygous twins. This was done by Meyerowitz, Jacox, and Hess (1968) and produced some interesting results which seem to confirm the role of psychological stress in initiating arthritis as postulated by

Table XXIX *Emotional stability in 45 persons who later developed rheumatoid arthritis*

Stability	Observed	Expected
Total	45	45
Stable	36	41
Doubtful	6	
Neurotic	2	3.1
Psychotic	1	1.0

Table XXVIII *Rheumatoid arthritis by the New York criteria in four European population samples (aged 35 +)*

Country	Longitude	Total examined	Positive criteria (per cent.)				
			1+2	1+2+3	1+2+3+4	1+2+4	
England	2°W	1,420	4·6****	1·7**	0·9	**	0·4
West Germany	8°E	261	2·1***	1·7	0·4		0·4
Switzerland	9°E	402	6·5***	1·0	0·4		0·4
Czechoslovakia	18°E	951	0·8****	0·7**	0·5	**	0

Note: English data based on original Leigh and new Wensleydale survey.

** $0.05 > P > 0.01$ *** $P < 0.01$ **** $P < 0.001$

Kasl and Cobb (1969). Retrospective studies, however, have certain disadvantages and a prospective approach is to be preferred. Such an approach has been used in follow-up studies of population samples in Leigh and Wensleydale, but with negative results (Table XXIX). The proportion of individuals thought to be neurotic or psychotic when seen before the onset of arthritis was no more than would be expected in a sample of the population. Clearly such a study can be more profitably pursued in discordant monozygous twins, all of whom have a genetic predisposition, than in a random sample in which only 4 per cent. are pre-disposed. A twin population is also the most suitable in which to examine other environmental causes of arthritis.

I should like to thank all those physicians who have contributed to the success of these family and twin surveys by contributing probands and allowing access to their case notes.

I owe a deep debt of gratitude to Prof. J. H. Kellgren, who has not only contributed most of the index cases but has also taken an active part in the planning of the Manchester Family Survey.

The results which I have described owe much of their reliability and significance to the accuracy of the serological tests and in this I have been fortunate in having the generous cooperation of Dr. J. Ball and his technical staff.

I am also grateful to Dr. H. Colenbrander whose data on the Dutch twins are included in Tables XIX, XX, and XXIII; he has asked me to say that these data are provisional.

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