The Genetics of Rheumatoid Arthritis

Analysis of 224 Families

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THE CAUSES of rheumatoid arthritis are not known. Many theories have been advanced and investigated but none of them adequately explain the clinical phenomena of this disease. It seems desirable, therefore, to investigate thoroughly all factors which seem to play a part in instituting the disease or in influencing its course. Heredity is one of these factors which seem to be of importance. The present study includes the analysis of 224 families of patients with rheumatoid arthritis from the standpoint of heredity.

Rheumatoid arthritis is a chronic systemic disease the most marked manifestation of which involves the joints. Though it may affect all ages, races and sexes, it usually begins insidiously in early adult life, it progresses irregularly with remissions and recurrences, leading eventually to crippling and deformity and sometimes producing complete and irreparable helplessness. Multiple joints are involved usually symmetrically but rarely if ever with the same rapidity or to the same degree. Fusiform swelling of fingers, wrists, knees and ankles are often seen, and there is often deformity, subluxation and ankylosis; subcutaneous nodules, tenovaginitis and muscular atrophy also occur. General health is impaired, and there is loss of weight, loss of strength, decline in vigor and decrease in physical activity. Radiographic examination shows demineralization of bones about affected joints, ulceration and destruction of joint surfaces, decrease in joint space because of loss of cartilage and, ultimately, bony ankylosis. There is rarely fever or leucocytosis, but the erythrocyte sedimentation rate is markedly increased. The patient's blood often shows ability to agglutinate streptococci in high dilution, but there is lack of antistreptolysin titer and antihyaluronidase, the last three characteristics being in marked contrast to the findings in acute rheumatic fever.

LITERATURE

No comprehensive coverage of the literature has been attempted. The data found were largely of the type which tells the number of patients reporting affected relatives without further effort to develop the data or to submit them to statistical analysis. The idea that rheumatoid arthritis runs in families or

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depends upon constitution or that the "virus must fall on fertile soil" emphasized particularly by Pemberton has been current for many years.

Those studies which do present pedigrees and attempt further analysis have assembled rheumatoid arthritis, rheumatic fever and osteoarthritis in the same tabulation and have treated the subject as though all rheumatic disease were related. This view is an old one. It is far from proven, however, and most modern investigators are strong in their feeling that these three diseases had best be handled separately. An extensive literature supports the view that susceptibility to rheumatic fever is inherited as an autosomal recessive trait, but the disease manifests itself only after sensitization following streptococcal infection. Osteoarthritis appears in many forms, each of which seems to have its own sex and age incidence, relation to hard work or trauma or to variation of anatomical development. Heberden's nodes, a form of osteoarthritis of the fingers, has been shown to be an autosomal, sex-influenced character, dominant in women and recessive in men. Osteoarthritis of the spine seems to follow hard work or injury. It is amazing to note how frequently acute rheumatic fever and rheumatoid arthritis appear together in different members of the same pedigree either in horizontal relationships in sibships or a vertical relationship of parent and child. No opinion can be offered as to whether or not there is a positive correlation between these diseases. It seems unlikely that such correlation will be found between rheumatoid arthritis and osteoarthritis.

Barter (1952) has presented a recent study on the familial incidence of rheumatoid arthritis and acute rheumatism, or rheumatic fever as we would call it, in 100 patients with rheumatoid arthritis. Of 538 members of families of patients, limited to brothers, sisters, fathers and mothers, 59 or 11 per cent were said to be affected. The incidence in the different grades of relationship varied considerably, being 5 per cent in fathers, 8 per cent in brothers, 13 per cent in mothers and 15.5 per cent in sisters. Of 543 members of the control families, 35 or 4.6 per cent were affected. The author concludes that an heredofamilial tendency toward the development of acute rheumatism or rheumatoid arthritis occurs in certain families. He discusses this constitutional tendency in relationship to Selye's "General Adaptation Syndrome" and Kendall's view that a hypersensitivity state may underlie rheumatoid arthritis. Regarding the former, certain individuals may have an hereditary weakness in their adaptation mechanism. Regarding the latter, it is suggested that certain individuals may have a constitutional tendency to react to the effects of an antigen-antibody reaction through the medium of the synovial membranes.

Short, et al. (1952), studied a group of 293 persons with rheumatoid arthritis and compared them with 293 controls. They found that 35 patients and 19 controls reported rheumatoid arthritis in the family without mentioning the relationship to the index cases, incidences of 11.9 and 5.1 per cent.

A similar study is reported by Davidson (1952) as an investigation instituted by the Scientific Advisory Committee of the Empire Rheumatism Council. This is based upon an extensive survey, including many factors, of 532 patients with rheumatoid arthritis and 532 controls. It was found that rheumatoid arthritis was reported in the study series in 7 per cent of fathers, 15 per cent of mothers, 3.8 per cent of 2151 brothers and sisters, compared to figures in the control series of 3 per cent of fathers, 9 per cent of mothers, and 1.8 per cent of 2143 brothers and sisters. The figures are statistically significant and lend support to the contention that a familial factor is of etiological importance. This figure suggests that rheumatoid arthritis is about 3 times as common in Great Britain as in the United States.

Edström (1941) reviewed in 1939 all the cases of chronic rheumatism admitted to the Lund Hospital from 1929 to 1933. His study is based on 504 cases of which 242 cases were rheumatic fever followed by chronic arthritis (Febris rheumatica c. arthritis chronica) and 262 cases of rheumatoid arthritis (Polyarthritis rheumatica chronica). The diagnoses of the last group seem to be readily understood. Some at least of the febrile arthritis seems also to fall in this group of rheumatoid arthritis, but a large proportion seem to have had acute rheumatic fever because they developed organic valvular heart disease. Edström includes seven pedigrees with data allowing recognition of rheumatoid arthritis. From these pedigrees 16 sibships were extracted. These included 81 sibs, which after correction for small family size on a 1:1 basis showed 33 affected compared to 45.3 expected affected. Penetrance for the entire group was 73 per cent. Forty-nine per cent of the families had only 1 affected individual, 32 per cent had 2 and 19 per cent had 3 affected. Strangely enough these figures are almost identical with those of the rheumatic fever group. Rheumatoid arthritis affected one or both members of 8 twin pairs. Of 4 sets of identical twins, 2 sets showed concordance for penetrance of 75 per cent; of 4 sets of fraternal twins, one set showed concordance. In the rheumatic fever group one set of identical twins showed both to be affected. Of 5 sets of fraternal twins, all showed only one member affected. One pedigree shows dentical twins with rheumatoid arthritis whose mother had rheumatoid arthritis, a brother and sister had rheumatic fever and one niece, daughter of an unaffected sister, had rheumatic fever. One twin married a man whose mother had rheumatoid arthritis. Seven of their eight children had rheumatic fever, two of them also developing rheumatoid arthritis. Seven children of the second twin were normal. Since rheumatic fever is inherited as a recessive, both twins seem to have been homozygous for the disease. One married a homozygote and had all children affected; the other married a normal and all children escaped.

Hangarter (1939) has published a book on heredity of acute and chronic rheumatism. He has included all rheumatic disease but he presents pedigrees

with sufficient detailed information to identify the chronic cases. Of 32 sibships 23 had one affected with what seems to be rheumatoid arthritis, 7 had 2 and 1 each had 3 and 4 affected. There were a total of 197 children with 43 affected with penetrance of 42.5 per cent.

Hölsti and Huuskonen (1938) reported a woman with rheumatoid arthritis who had 4 of 10 daughters and 1 of 3 sons affected with the disease.

Zellner (1930) reported 6 families with multiple involvement of rheumatic disease. According to the evidence presented, a mother and daughter, 2 sisters and a brother, and 2 sisters had rheumatoid arthritis.

Identical twins with concordant rheumatoid arthritis and cancer of the breast were described by Berglund (1940). Since this study was started, it has been discovered that 2 of our index cases are cousins, and that they had an affected aunt, the sister of their fathers. A proven instance has come to our attention of rheumatoid arthritis affecting a woman and her grandmother, the mother having died without arthritis of cancer at 28.

THE STUDY SERIES

The present study is based upon the family histories of 224 patients with rheumatoid arthritis. These were assembled as a group project by the physician authors from their private practices, the arthritic clinics and the wards of Cleveland City Hospital, St. Vincent's Charity Hospital, Mt. Sinai Hospital and Crile Veterans' Administration Hospital. Careful family histories were planned to reveal all the cases of rheumatoid arthritis which were known to have occurred among the parents, the siblings and the children of the index cases. The occurrence of rheumatoid arthritis among grandparents, uncles, aunts and cousins was recorded but cannot be considered to be complete. No predetermined combination of criteria was established to prove the diagnosis. This depended upon the judgment of the clinician. Many patients were seen by all three. Many patients had been under observation for years and had been subject to searching clinical examination and even autopsy. Other patients were accepted after a single examination. The index cases are considered to have been accurately chosen. It was not possible to examine all the secondary cases. Of 49 secondary cases reported as positive, 23 were dead when the study was made. Five were actually examined. The remaining 21 cases had to be accepted on the basis of history alone. In taking the family history, specific inquiry was made as to the age, state of health and age at death of each parent, sibling and child. Detailed questions were asked as to the presence or absence of arthritis, rheumatism or crippling disease. If any of the above were present, information was sought as to the age and circumstances of onset, duration and progression of disease, number and name of joints involved, the use of canes, crutches or wheel chairs and degree of disability which occurred. An attempt was always made to record the diagnosis given by the doctor.

Despite the fact that only 10 per cent of the secondary cases were examined, the diagnosis of the remaining cases was thought to be reasonably accurate. Very early and very mild cases were undoubtedly overlooked. It is believed, however, that a reasonably accurate account was obtained of all cases of well developed, deforming or disabling rheumatoid arthritis. Since the same technique was applied to the control series, it is believed that the findings of the study series and the control series are comparable.

Of the 224 families of patients with rheumatoid arthritis 47 reported a total of 57 secondary cases in their families. The affected relatives were reported to be 8 fathers, 15 mothers, 5 brothers, 20 sisters, 1 son, 2 paternal aunts, 1 paternal grandfather, 1 paternal grandmother, 2 maternal grandmothers and 2 cousins. Affected relatives were reported in 47 of 224 families or 21 per cent. This rough tabulation simply indicates the familial nature of the disease, but it is of no use for statistical studies because information is not complete, and no evidence is presented as to the number of relatives which were considered.

In 224 index cases of rheumatoid arthritis, 93 patients were men, 131 patients were women. Two hundred twenty-four index cases, 447 parents, 849 siblings and 147 children were included to make a study group of 1667 individuals of whom 273 were affected. In these families, 49 secondary cases of rheumatoid arthritis were found among 1453 parents, siblings and children, an incidence of 3.1 per cent. This varied between the sexes, being 14 out of 704 or 1.9 per cent of the male relatives, and 35 out of 739 or 4.6 per cent among the female relatives. The incidence varied somewhat depending upon the relationship with the index case. Among parents, 23 of 447 or 4.5 per cent were affected. Among fathers this was 8 of 223 or 3.6 per cent; among mothers it was 15 of 224 or 6.7 per cent. It was 5 of 411 brothers or 1.2 per cent and 20 of 438 sisters or 4.6 per cent. Only 1 of 70 sons or 1.5 per cent were affected, but not one of 77 daughters were involved. The incidence among 1453 parents, siblings and children was 49 affected or 3.1 per cent.

These variations in incidence are due not only to difference in sex but also in part to age distribution. If computation is confined to relatives over the age of 50, we find the incidence of fathers to be 8 of 183 or 4.4 per cent, and of mothers to be 13 of 193 or 6.7 per cent; of brothers 4 of 192 or 2 per cent, and of sisters 14 of 203 or 6.9 per cent. There were only 4 children over the age of 50, none of whom were affected. Thus it is seen that rheumatoid arthritis was found in 3.1 per cent of 1453 relatives of rheumatoid arthritis, and 5 per cent of the 775 relatives over 50 years of age. The data are presented in detail in Table 1.

CONTROL SERIES

A control series was assembled from the family histories of 488 patients who did not have rheumatoid arthritis. These consisted of 260 families of pa-

tients seen in the office in consultation who were found to be free of rheumatoid arthritis. These included a large variety of diagnoses as well as no disease. To this group were added the data from 122 patients with Heberden's nodes, 59 patients with ankylosing spondylitis and 47 patients with gout. Data on the second group had been gathered for specific studies of these diseases. In most instances, the siblings were actually seen. Family histories were taken with the same care in the control group as had been used in the study group, and the results are comparable. The control series included 488 index cases and 2759 of their relatives, parents, siblings and children, of whom 16 were affected.

TABLE 1. INCIDENCE OF RHEUMATOID ARTHRITIS—FAMILY DATA

	TOTAL			MALE			FEMALE		
	No.	Affected	%	No.	Affected	%	No.	Affected	%
Study Series—224 Families									
Index Cases	224	224	100	93	93	100	131	131	100
Parents	447	23	4.5	223	8	3.6	224	15	6.7
Over 50	*376*	*21*	*5.6*	*183*	*8*	*4.4*	*193*	*13*	*6.7*
Siblings	849	25	2.8	411	5	1.2	438	20	4.6
Over 50	*395*	*18*	*4.5*	*192*	*4*	*2.0*	*203*	*14*	*6.9*
Children	147	1	0.7	70	1	1.5	77	0	0
Over 50	*4*	*0*	*0*	*4*	*0*	*0*	*0*	*0*	*0*
Total Relatives	1453	49	3.1	704	14	1.9	739	35	4.6
Over 50	*775*	*39*	*5.0*	*379*	*12*	*3.2*	*396*	*27*	*6.8*
Total Group	1667	273	15.8	797	107	13.4	870	166	18.3
Control Group—488 Families									
Total Relatives	2759	16	0.58	1348	7	0.52	1411	9	0.64
Over 50	*1530*	*14*	*0.9*	*721*	*5*	*0.69*	*809*	*9*	*1.1*

In analysing the 488 control families, the index cases are omitted because by definition they were all free of rheumatoid arthritis. Since each member of the family can be considered as an independent selection, the relationship to each other is of no significance; so the parents, siblings and children are assembled in one large group as a segment of the population selected at random. This population included 2759 individuals of whom 16 or 0.58 per cent were affected with rheumatoid arthritis. These included 7 of 1348 men, an incidence of 0.52 per cent affected, and 9 of 1411 women, an incidence of 0.64 per cent affected. If computation is limited to individuals over the age of 50, we find 5 of 721 or 0.69 per cent of men affected and 9 of 809 or 1.1 per cent of women affected, or a total of both sexes of 14 out of 1530, an incidence of 0.9 per cent.

Thus it is seen that rheumatoid arthritis affected all relatives of patients

with rheumatoid arthritis 5 times as frequently (3.1 per cent to 0.58 per cent) as it did the population in general, and in people over 50 years of age relatives were affected 6 times as frequently (5.8 per cent to 0.9 per cent) as the population in general. The study is made on 224 families of arthritis with 1667 relatives and 448 controls with 2759 relatives, a total of 4914 individuals of whom 289 had rheumatoid arthritis.

HEREDITY IN RHEUMATOID ARTHRITIS

If one assumes that rheumatoid arthritis is caused by a constellation of conditions to which the whole population is uniformly exposed and to which everyone is equally susceptible, then the multiple occurrence in sibships should follow the law of small independent probabilities, and thus conform to the Poisson distribution.

In the present study there are 203 sibships with 1 person affected, 17 sibships with 2 affected, 3 with 3 and 1 with 4 affected. For applying the Poisson

TABLE 2. TESTS OF POISSON DISTRIBUTION RHEUMATOID ARTHRITIS

NO. OF CASES PER FAMILY	NO. OF SIBSHIPS FOUND	EXPECTED NUMBER
0	12180	11937
1	203	240
1	17	2.4
3	3	0.016
4	1	0.00008

distribution, it is necessary to have an estimate of the number of sibships with none affected from the equivalent population. For this estimate it seems permissible to use the 488 sibships of the control series. The control series contained 16 individuals with rheumatoid arthritis. Eight of these were found as sibs of the index cases; 8 others were found among the parents. Since only sibs are admissible in the following computations, there are 8 affected sibs in 488 families or one affected in 60 families. Then a sample from the population which gives at random 203 sibships with one affected would give 60×203, or 12,180 sibships with none affected.

The comparison between these figures and the expected number of sibships calculated on the basis of the Poisson distribution may be seen in Table 2. Since the 1 per cent level of significance for 3 degrees of freedom gives chi square = 11.34, it can be seen from the table without further calculation that the series of multiple occurrences of rheumatoid arthritis observed in the present study does not by the longest chance conform to the law of small independent probabilities. The conclusion is unavoidable that the basic causal factor in rheumatoid arthritis is very probably genetic.

THE SEX RATIO

It is usually said that two times as many women as men get rheumatoid arthritis. This is borne out by certain aspects of the present data. Of the entire series there are 166 women and 123 men. As pointed out the large number of men is a result of the non-random sampling from hospital clinics and the admission of index cases from the Veterans' Hospital. There were 23 parents of the index cases affected of which 15 are mothers and 8 fathers, effectively a 2 to 1 ratio. Furthermore, excluding the index cases, there are 41 women and 16 men affected in the entire series, very close again to the usual ratio, 2.5 women to 1 man, and statistically significant since the deviation from a 1:1 ratio is over 3 times the standard error.

Twice as many women as men with rheumatoid arthritis is suggestive of a sex-linked dominant factor. But in a sex-linked dominant, a father transmits to all his daughters and to none of his sons. In this series with 8 fathers affected there were 5 with an affected son, which rules out the hypothesis of a sex-linked dominant factor.

The data on sibships may be used to test the homogeneity of the sexes independently of the selection of the material. It is found that sister-sister combinations occurred 20 times, brother-sister combinations were found 8 times and brother-brother pairs 3 times. Since the number of brother-sister (B) pairs is approximately twice the geometric mean of the number of sister-sister (A) and the brother-brother (C) pairs, it follows that these three numbers, giving the various sib-pair combinations, approximate a good fit to the binomial $(p + q)^2N$, where p and q are the observed proportions of females and males in all sib pairs.

$$p = \frac{2A + B}{2N} = \frac{40 + 8}{62} = 77 \text{ per cent}$$

$$q = \frac{B + 2C}{2N} = \frac{8 + 6}{62} = 23 \text{ per cent}$$

$$\chi^2 = 2.12 \qquad P \textit{ ca } 0.16$$

The chi-square test shows that it is reasonably probable that the sib pairs are homogeneous with respect to sex and confirms the conclusion from the analysis by inspection of the pedigrees that a sex-linked factor is not involved, although sex has an influence on the manifestation of the autosomal factor. This test shows a sex ratio of 3.35 women to 1 man.

IRREGULARITIES OF THE DATA

Variations in expressivity lead to irregularity in the data. Rheumatoid arthritis may begin as a violent, acute illness with prompt involvement of

many joints including swelling, pain and stiffness, leading in a few months to complete and irreparable helplessness. On the other hand, onset may be so mild and progress so slow as to make diagnosis difficult or impossible. No completely satisfactory specific tests of rheumatoid arthritis are available, and those which have limited value have never been widely used. Probably many affected people escape recognition.

One of the chief factors in causing the irregularity in the data on rheumatoid arthritis is the variable age of onset, which ranged from 13 to 71 years (Fig-

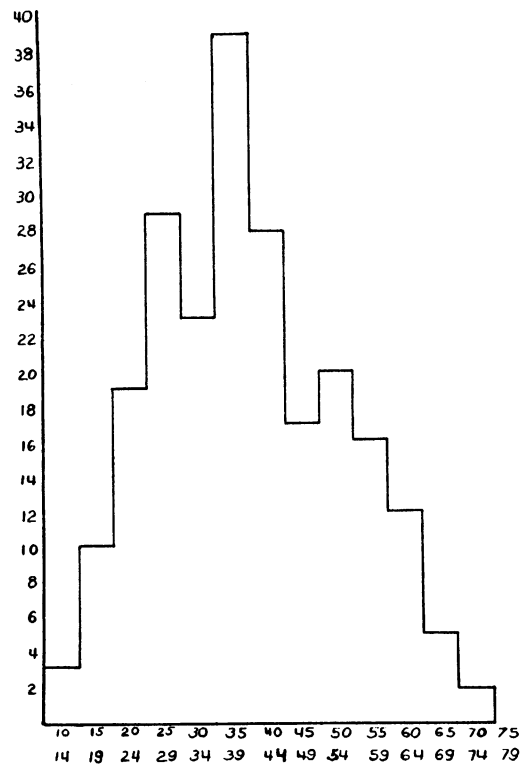

FIG. 1

ure 1). The average age of onset for 127 women was 38.7 ± 1.2 years with a standard deviation of 13.4 ± 0.84 years. For 96 men the corresponding figures are 40.3 ± 1.4 years and the standard deviation 13.5 ± 0.96 years. The difference in the average is 1.6 ± 1.8 years, clearly not a significant difference, although the view prevails that on the average women get rheumatoid arthritis somewhat earlier in life than men. For the two series combined, the average is 39.2 ± 0.9 years with a standard deviation of 13.5 ± 0.64 years.

Non hereditary influences which affect the fetus in utero have been recognized in the production of developmental anomalies, such as hare lip, cleft

palate and mongolian idiocy. These factors are not recognizable from the data at hand. There is no information about the maternal age at time of birth or of the comparative ages of onset of the affected sib pairs. Data is presented in Table 3 as to the birth order of the patient compared to family size. The birth order seemed to be of no significance. In the calculation the last class has been omitted because of the small numbers. The result shows X^2 (for 8 degrees of freedom) equals 5.557 which is P ca 0.70. There is no relationship between birth order and susceptibility to rheumatoid arthritis.

TABLE 3. RHEUMATOID ARTHRITIS

BIRTH ORDER OF PATIENT VERSUS FAMILY SIZE

FAMILY SIZE	BIRTH ORDER										TOTAL	EXPECTED
	1	2	3	4	5	6	7	8	9	12		
1	18										18	
2	13	15									28	14
3	12	13	7								32	10.66
4	12	7	3	8							30	7.50
5	8	6	11	6	7						38	7.60
6	3	5	2	4	6	9					29	4.83
7	2	3	5	6	1	3	7				27	3.85
8	5	2	4	2	2	3	1	3			22	2.75
9	0	2	1	2	1	0	1	2	2		11	1.22
10	0	0	0	0	0	1	0	0	2		3	0.33
11	0	0	0	0	0	0	0	0	0		0	0.00
12	0	0	0	0	0	0	0	0	0	1	1	0.08
13	0	0	0	0	0	1	0	0	0	1	2	0.15
Total observed.....	73	53	33	28	17	17	9	5	4	2	241	
Expected.....	71	53	39	28.3	20.8	13.2	8.4	4.5	1.8	1.5		

ANALYSIS AS A DOMINANT

In genetic analysis of pooled human material it is usually necessary to correct for small family size. This has been done in Table 4 according to the method of Hogben (1933) for both simple autosomal dominant on a 1:1 basis and as a simple autosomal recessive on a 3:1 basis. As will be seen, penetrance is 44 per cent. When correction is made for age, it is seen that after the age of 50, 278.3 are expected to be affected instead of 250 as found. This correction shows penetrance as a dominant of 49.5 per cent.

If rheumatoid arthritis is an autosomal dominant, and if there were nothing irregular in its inheritance, then at least one parent should be affected. Of the 224 index cases there were 23 with 1 parent affected. When these 23 sibships are pooled and correction is made for small family size, on the basis of 1:1 ratio, it is found that 28 are affected and 55 expected affected for penetrance

of nearly 51 per cent. Of the remaining 201 index cases neither parent is affected, but, on the assumption of a dominant, one parent at least should be heterozygous for the dominant factor, and so again a 1:1 ratio is expected. This showed 222 affected compared to 506 expected for 44 per cent penetrance. Since 23 parents out of 224 expected have rheumatoid arthritis, there is among the parents of the index cases a penetrance of about 10 per cent. This low penetrance seems clearly to be the result of low expressivity, resulting in some of the parents having had a mild or an unrecognized case of the disease or having died before the disease developed.

TABLE 4. CORRECTION FOR SMALL FAMILY SIZE

Comparison of Affected Compared to Expected Affected Siblings

SIZE OF FAMILY	NO. OF FAMILIES	NO. OF SIBS	AFFECTED SIBS	SIMPLE AUTOSOMAL DOMINANT (1:1) RATIO		RECESSIVE (3:1) RATIO	
				Factor	Expected affected	Factor	Expected affected
1	16	16	16	1.	16.	1.	16.
2	29	58	31	1.333	38.657	1.1428	33.1412
3	30	90	30	1.714	51.420	1.2970	38.910
4	38	152	40	2.134	81.092	1.4628	55.5864
5	32	160	34	2.581	82.592	1.6389	52.4448
6	28	168	33	3.048	85.344	1.8248	51.0944
7	21	147	28	3.532	74.172	2.0196	42.4116
8	19	152	26	4.016	76.304	2.2225	42.2275
9	4	36	5	4.508	18.032	2.4321	9.7284
10	5	50	5	5.	25.	2.649	13.245
12	1	12	1	6.	6.	3.098	3.098
13	1	13	1	6.5	6.5	3.329	3.329
Total.....	224	1054	250		561.113		361.2163
Correction for age. Number expected affected after 50 years: 278.3				Penetrance—44.6% Penetrance—49.5%		Penetrance—69.2% Penetrance—77%	

Because of the known difference in sex incidence in rheumatoid arthritis, penetrance was computed for each sex separately. This was done by considering all the sibs of the same sex as the index case and disregarding those sibs of the other sex. This method eliminates many unaffected sibs. The tables are not given, but the final summary shows that 99 of 243 males were affected compared to 158 expected, for a penetrance of 63 per cent. There were 155 of 393 females affected compared to 232.5 expected, for a penetrance of 66 per cent. In the two series there was consequently a total of 628 individuals compared to the 1054 of the original table. Increased penetrance in this instance was due to elimination of 426 unaffected sibs from the computation. These are surprising results on penetrance in view of the greater incidence of rheumatoid arthritis in the female sex which are not readily explained.

ANALYSIS AS A RECESSIVE

If we entertain the assumption that rheumatoid arthritis is an autosomal recessive, Table 4 shows 361 expected affected on a 3:1 basis compared to 250 found affected, a penetrance of 69.2 per cent. When correction is made for age, there are 278 finally affected compared to 356 expected for penetrance of 77 per cent. In 23 families one parent is affected or homozygous; the other parent is assumed to be heterozygous. Inheritance will be on a 1:1 basis, and after correcting for small family size, 51 per cent penetrance is found. Neither of the parents in 201 remaining families are affected, so 3:1 inheritance is expected. Thus it is found that 380 are expected affected compared to 250 found for penetrance of 66 per cent.

GENE FREQUENCY

The data are irregular in the sense that they do not conform to any simple Mendelian mechanism. In the early days of applying Mendelian ratios to human data, the irregularities in the data not infrequently led to the postulation of complex genotypes which failed to be convincing. In the present series there are 23 cases with one parent affected, in the other 201 neither parent shows the trait. This is the equivalent of skipping a generation in the more extensive pedigrees. This is suggestive of a simple recessive, but it is also recognized that a dominant with diminished penetrance resembles a recessive in many pedigrees, depending upon the degree of penetrance. Perhaps most genes for defective traits are recessive to the normal, but in many cases, owing to the system of outbreeding in human society, they are for the most part kept in a heterozygous state. Consequently, the results of cousin marriages are especially important in deciding between a dominant, with diminished penetrance, and a recessive. In the present series no cousin marriages were found, but Wittinghill and Hendricks (1951) in a brief report of an extensive pedigree which included ten cousin marriages ruled out recessive inheritance. This strengthens the probability that rheumatoid arthritis is an autosomal dominant.

From the analyses above there is no way to be sure directly from the numerical tests of the data whether rheumatoid arthritis is an autosomal dominant with about 50 per cent penetrance or an autosomal recessive with a higher penetrance in the neighborhood of about 70 per cent. The conclusion from such tests, however, needs to be reasonably consistent with the gene frequency in the population which supplied the sibships. Since the attempt to estimate the penetrance in males and females separately revealed no essential difference, it seems best to take an overall figure of 50 per cent for the case of a dominant and a round figure of 70 per cent if rheumatoid arthritis is a recessive. Another figure which is needed for the calculation of the gene

frequency is an estimate of the incidence of rheumatoid arthritis in the population of Northern Ohio, which supplied the data for the study series. The control series included a total of 2759 individuals of whom 16 or 0.58 per cent were affected with rheumatoid arthritis. For the United States with 156,000,000 people, of whom 60 per cent are above 20 years, it turns out that there should be 543,000 persons with rheumatoid arthritis. Since these include only obvious, undoubted and advanced cases, it is seen that this is quite compatible with

TABLE 5. RHEUMATOID ARTHRITIS
GENE FREQUENCY AS DOMINANT

	d 0.006	r 0.994
d 0.006	dd 0.000036	dr 0.00596
r 0.994	dr 0.00596	rr 0.9884

50% Penetrance
dd and dr are affected. rr are normal.
d = 0.006 r = 0.994

TABLE 6. RHEUMATOID ARTHRITIS
MATING AS DOMINANT

		Constitution of the Father		
		dd 0.000036	dr 0.0119	rr 0.9884
Constitution of the Mother	dd 0.000036	dd × dd 13 × 10^{-10}	dd × dr 43 × 10^{-8}	dd × rr 36 × 10^{-6}
	dr 0.0119	dd × dr 43 × 10^{-8}	dr × dr 0.00014	dr × rr 0.0118
	rr 0.9884	dd × rr 36 × 10^{-6}	dr × rr 0.0118	rr × rr 0.9769

dr × rr should contribute 99.88 per cent of the affected families or 223.7 out of 224 of this series.
rr × rr are matings with normal offspring only.

the estimate of the Arthritis and Rheumatism Foundation of 700,000 cases of rheumatoid arthritis in the United States.

Since the estimate of the penetrance is 50 per cent, the gene frequency of individuals with a genetic constitution for rheumatoid arthritis is twice this or 0.0116. With random mating of a population in genetic equilibrium the homozygous dominants, the heterozygotes and homozygous recessives are present in the relative frequencies $d^2 + 2dr + r^2 = 1$ where d is the frequency of the factor for rheumatoid arthritis, r is the frequency of the normal recessive allele, and $d + r = 1$. Consequently the frequency of d is 0.006 and the value

for r is 0.994. The frequency of those homozygous for the dominant factor for rheumatoid arthritis is 36 in a million and the heterozygotes are nearly 12 per thousand (Table 5). It may be seen in Table 6, that practically all matings expected are rr × rr or dr × rr, and that those including a person dd in constitution are exceedingly rare.

TABLE 7. RHEUMATOID ARTHRITIS
GENE FREQUENCY AS RECESSIVE

	d 0.909	r 0.091
d 0.909	dd 0.8263	dr 0.0827
r 0.091	dr 0.0827	rr 0.0083

70% Penetrance
rr are affected. dr and dd are phenotypically normal.
d = 0.909 r = 0.091

TABLE 8. RHEUMATOID ARTHRITIS
Mating as Recessive

		Constitution of the Father		
		dd 0.8263	dr 0.1654	rr 0.0083
Constitution of the Mother	dd 0.8263	dd × dd 0.6828	dd × dr 0.1367	dd × rr 0.0069
	dr 0.1654	dd × dr 0.1367	dr × dr 0.0274 177	dr × rr 0.0014 22
	rr 0.0083	dd × rr 0.0069	dr × rr 0.0014 22	rr × rr 0.00007 3

rr constitution is the only one genotypically susceptible. They are possible only in the matings of the lower right hand corner.

The second number gives the distribution expected of 224 families although individual families cannot be identified.

On the other hand, if rheumatoid arthritis is a recessive with 70 per cent penetrance, then the frequency of genotypes for the disease in the population is 0.0083. Again, assuming random mating and genetic equilibrium, the value of r is 0.091 and for d the frequency is 0.909 (Table 7). The frequency of heterozygote is therefore 2dr or 0.1654. About 1 in every 6 of the population is carrying the recessive factor for rheumatoid arthritis. The expected frequencies of the various types of matings are given in Table 8.

Another minor point, which may be worth mentioning, is that the best known recessives in human genetics, such as albinism, blue eyes, phenylkatonuria, and alkaptonuria, are remarkably uniform in their manifestation, in contrast to the great variability of many of the undoubted dominants. From this analysis and from the previous considerations, it seems more plausible that rheumatoid arthritis is an autosomal dominant with about 50 per cent penetrance.

DISCUSSION

It seems desirable to give some consideration to the nature of rheumatoid arthritis. Many theories of etiology have been advanced and have successively held ascendancy for varying periods of time, only to be supplanted later as the mode or as scientific discovery seemed to dictate. This is not the place for a full discussion on the subject aside from presenting some of the facts revealed in a recent comprehensive, cooperative survey conducted by the Scientific Advisory Committee of the Empire Rheumatism Council and presented in 1950 (Lewis-Faning) as a supplement to the "Annals of Rheumatic Disease." This study depends upon data assembled from numerous arthritis clinics and research centers in Great Britain. Five hundred thirty-two patients with rheumatoid arthritis of less than 5 years duration were matched with the same number of people of the same age, sex, marital experience and no arthritis. Detailed histories revealed a strikingly similar experience in both groups. The sex ratio of the patients was 100 men to 132 women. The mean age of onset was 42 for men and 41 years for women. These figures compare with 40 and 39 years in the present series. Forty-three specific diseases were listed in the questionnaire, but no statistical difference was found between the two groups. The same result was found concerning psychological precipitating factors which were found in 39 per cent of both groups.

Infection noted within 3 months of onset were found in 19 per cent of patients compared to 11 per cent of controls. While this is a statistically significant difference, it was pointed out that patients are more likely to reveal these facts than are the controls. Besides this, infections were not noted before onset in 80 per cent of patients. Allergic diseases, endocrine diseases, focal sepsis, pregnancy and menstrual disorders and occupations did not seem to be significantly different.

Certain clinical features of rheumatoid arthritis were confirmed by this study. These included abnormalities of the peripheral circulation, sweaty hands, sweaty feet and cold fingers, found in 43, 36 and 15 per cent of patients compared to 6, 3 and 5 per cent of controls. Prodromal symptoms such as fatigue and loss of weight were noted, and it was confirmed that small joints are usually affected first, that involvement tends to be symmetrical and that exposure to cold and wet adversely affect arthritis. The most significant find-

ing of the study was that the incidence of involvement in relatives was about twice as great in patients as in the controls.

This extensive study revealed no hint as to the extrinsic factors which play a part in the causation of rheumatoid arthritis, but suggest the importance of constitutional factors as they are determined by heredity.

An explanation for some of the phenomena of rheumatoid arthritis can be sought in the fields of experimental biology and heredity. The data clearly indicate that the main factor is genetic and autosomal. To proceed with the analysis, it is necessary to make the assumption that the genetic factor is the same in all sibships. To completely justify this assumption the data would have to include extensive linkage studies, which are still hopelessly inadequate in human genetic analysis. The assumption implies that the irregularity in the data is not the result of several different major factors for rheumatoid arthritis. In the present state of knowledge nothing can be said of multiple alleles at the main locus.

There is a bare possibility that rheumatoid arthritis may be dominant in some families, recessive in others. If a person were heterozygous for the dominant gene and the modifying factors suppressed its effect, the gene would have a chance to spread through the population, particularly if the reproductive fitness of such people were greater than their sibs with dominant rheumatoid arthritis. Depending on the number and strength of the genetic modifiers, it could come about that the patient would need to be homozygous for the main gene for rheumatoid arthritis to manifest itself. This is merely conjectural in the case of rheumatoid arthritis, although the mechanism is known, from experimental genetics, in which a gene is dominant with one set of modifying factors and recessive in the presence of other modifying factors. This situation is known to prevail in baldness in women (Osborn, 1916), Heberden's nodes in men (Stecher, et al., 1944), coat color in cattle and horns in sheep (Snyder, 1946). In certain lines of inbred guinea pigs, Wright (1934) found that 2 times as many females as males are otocephalic monsters.

THE CAUSES OF RHEUMATOID ARTHRITIS

The primary cause of rheumatoid arthritis is not known. So many different and contradictory theories have been advanced that the fact itself requires an explanation. From experimental zoology, phenomena are known in which a wide variety of physical and chemical agents can trip an intrinsic mechanism, which is the sine qua non for some vital process to occur. The outstanding examples of this are the many physical and chemical agents which have been successfully employed in studies on artificial parthenogenesis and the many factors which are known to successfully produce the organizer effect in studies on Amphibian embryonic development. It seems that a somewhat similar situation exists in regard to rheumatoid arthritis. Although some data show

that an infectious agent has been found in about 30 per cent of the cases, no one has ever demonstrated a specific pathogenic agent for the disease. In a similar way, although about 30 per cent of the patients show an abnormal basal metabolic rate, the other patients are normal in this respect. Emotional stress, altered Ca and P metabolism, hypochlorhydria and other factors have been suggested as the etiological factor in rheumatoid arthritis, but without any convincing demonstration. It is hardly an exaggeration to say that whenever an internal physiological or an external condition of stress has been found between the rheumatoid arthritis patient and the normal, someone has suggested the condition as the cause of rheumatoid arthritis. This is an instance of the common fallacy that gives up the search for the factor that is common to all cases of rheumatoid arthritis and to find over what physiological pathway the common factor acts to produce its effects.

These factors which have been mentioned as well as others not listed as among the suggested causes of rheumatoid arthritis may be regarded as contributory factors which tip the balance or bring about a proper physiological state for the onset of rheumatoid arthritis. And some, no doubt, act to affect the progress of the disease, to make it more devastating in some cases or to ameliorate the effect of the disease in others.

The pooled data are analyzed above both from the standpoint of an autosomal dominant and an autosomal recessive. But first it is important to discuss the irregularities in the data. In almost all, if not actually in all, cases of extensive data on human hereditary traits, irregularities appear. As pointed out, the irregularities in the early days, on the tacit assumption that penetrance was complete, often led to the postulation of complex genotypes which were unconvincing. When the irregularity in the data was slight, the few exceptional cases were usually explained away on the basis that the legal parentage did not coincide with the biological parentage, owing either to illegitimacy, to concealed adoption or the unrecognized switching of infants.

Irregularity in the data due to variable age of onset has been presented above. The age of onset refers to the effective or critical time in the life cycle when the phenotypic trait becomes manifest. Obviously the great variability in the age of onset is not the result of any lack of precision in biological processes, but instead is an indication of considerable complexity in the internal and external subsidiary causal factors. When the genetic factors and the external factors are constant from individual to individual, then the critical period for the population may be greatly restricted. For example, in certain highly inbred lines of mice which presumably have an extreme degree of homozygosis, Dunn (1940) and his collaborators have been able to show that a lethal effect in a certain tailless mouse stock is produced at 10¾ days in all mice with the genetic constitution for the lethal action. In other words, the time for the effective action of the genes, or the age of onset, is greatly restricted and is essentially the same for all the mice of the stock with the

appropriate genetic constitution, and consequently the critical period is very short, and there is 100 per cent penetrance.

But in several closely inbred lines of guinea pigs with polydactyly and presumably also each with the same high degree of homozygosis, since they were inbred by brother-sister mating since 1906, Wright (1934) found that the penetrance differed and varied in each line predominantly with the age of the mother, but also there was a seasonal variation. It is of especial interest and importance for human genetics that Wright's analysis showed that the several inbred lines which differed in the degree of penetrance with age of the mother differed in several genetic modifiers which also affected the degree of penetrance.

It seems in this case that the critical period for the determination of polydactyly was also greatly restricted in duration, and the inbred lines differed in the degree of penetrance at different ages of the mother because of the subsidiary genetic modifiers in which the several lines differed.

In these different strains of guinea pigs, the degree of penetrance decreased with increasing age of the mother, which is in contrast to the classic human case of Mongolism in which the penetrance increases with the age of the mother toward the end of the reproductive period (Penrose, 1938).

The instances mentioned concern traits which come to expression during the gestation period, and so are present at the time of birth. For hereditary characters which become manifest after birth or during adult life there is, at least so far as human data go, a great length to the critical period in the life cycle when the trait may manifest itself in that fraction of the population which has a genetic constitution for the trait. For example, in the case of Heberden's nodes (Stecher, et al , 1944), the conclusion drawn from the data was that the population had passed the effective period at an advanced age, about the ninth decade, and penetrance was complete. A similar phenomena is observed in the case of Huntington's chorea, and in Leber's optic atrophy (Bell, 1935). In the case of rheumatoid arthritis it was demonstrated that at an advanced age, the penetrance is little more than 50 per cent even though the population by and large has passed through the effective period.

The traits mentioned above from the field of experimental genetics which showed an effect of the age of the mother are characters which come to expression during the period of gestation. Although it is not impossible, yet it seems improbable that a difference in the age of the mother at the time of gestation would cause a difference in the development of a trait which comes to expression much later in adult life. The data at present are not available to test whether there is any causal relation between age of mother at gestation and the time of onset for rheumatoid arthritis in the progeny, and this perhaps holds for any other adult human hereditary trait. The same conclusion applies to the seasonal effect, which Wright found in the polydactylous guinea pigs mentioned above. But it is clear that the only way in which the matter can

be adequately tested would be for such data to be included in pedigrees collected in the future.

The conclusion that many individuals in early and later old age have a genetic constitution for rheumatoid arthritis but are not recorded as arthritics requires some special comment. The curve for the age of onset mentioned above is made up of two components. The one is for the individual and embraces the time from the very first recognizable beginnings of rheumatoid arthritis until the full development of the disease. This is obviously much longer than the restricted time for characters which develop during the embryonic or fetal period as in the tailless lethal mice mentioned above. Since this time for the development of rheumatoid arthritis in the life cycle varies from individual to individual, the second component is made up of the critical period for the population which extends almost throughout the entire adult life and according to the data from the present series begins at age 13. The dissection of such a curve was made for the temperature effective period for the reduction of certain bristles in Drosophila melanogaster by Child (1935), who clearly pointed out the compound nature of such curves. In the case of D. melanogaster, since the data were collected from adults, the embryonic curve could be inferred only indirectly. But in the case of hereditary human traits which become manifest in the adult, such curves can be dissected on the basis of direct observations, but the data on rheumatoid arthritis are not adequate for the task. One thing, however, is clear: in many individuals rheumatoid arthritis has an insidious onset and may not come to the attention of the clinician sometimes for years. This, of course, extends the age of onset at the upper limits of the curve.

An illuminating example in some respects is supplied by Gordon's (1951) work on the experimental genetics of platyfish and swordtails. For example, in crossing geographical races of platyfish, he found in F_1 a diminished penetrance in the development of melanomas, which was dependent upon genetic modifiers in which the two geographical races differed, similar to the case of polydactylous guinea pigs of Wright mentioned above. But it is also clear in the results from Gordon's fish crosses that the major gene for macromelanophores was the sine qua non for the development of the melanoma. Gordon emphasizes that the diminished penetrance and lowered expressivity was dependent upon the subsidiary genetic modifiers in which the races differed. In at least one cross Gordon found a diminished penetrance accompanied by a heightened expressivity. This may also be the case sometimes with rheumatoid arthritis in those families where a son or daughter develops a worse case of arthritis than a parent. In his discussion Gordon emphasized what Little (1947) pointed out in a discussion of the incidence of tumors in hybrid mice that the experimental study of the genetics of hybrids is of special importance in the study of irregular human traits. And since in America the "melting pot" is an extraordinary mixture of biological types from diverse geographical

areas, the degree of heterozygosis is an important factor in the production of irregularities in human genetic data. Moreover, Heston (1951) in a recent discussion of the genetics of neoplasia in mice says, ". . . the development of mammary tumors in mice is influenced by many extrinsic and intrinsic (genetic and non-genetic) factors whose effects are cumulative in increasing the probability that the tumors will occur."

The mild and quiet cases which may never come to the attention of the physician, the cases with sub-clinical manifestations or in genetic terms, with low expressivity, affect the estimate of the expressivity and consequently the degree of penetrance. The differences in age of onset, in the time for definitive development in the individual, the low expressivity and the diminished penetrance in rheumatoid arthritis and the presence or absence of external conditions of stress, are all perhaps an expression of subsidiary genetic modifiers.

The analytic results from the field of experimental vertebrate genetics allow the conclusion that irregularities in human data may be caused by diverse internal and external factors. Age of mother, seasonal effects, secondary genetic modifiers and factors still unknown may all act to produce variability in age of onset, diminished penetrance and altered expressivity. The irregularities in the data on rheumatoid arthritis apparently involve some or all of these factors which have been demonstrated in experimental genetics.

SUMMARY

This study is based on pedigrees of 224 patients with rheumatoid arthritis, including 1677 persons, which are compared with pedigrees of 488 controls, including 2759 persons. Of relatives of rheumatoid arthritis patients, 3.1 per cent of all relatives and 5 per cent of relatives over 50 years of age had rheumatoid arthritis, compared to 0.58 per cent of all relatives and 0.9 per cent of relatives over 50 years of age in the control group. That heredity affects rheumatoid arthritis is indicated by the lack of agreement with the Poisson distribution of multiple cases.

The data are extremely irregular due in part to irregular penetrance and a number of exogenous influences which affect expressivity. When correction is made for small family size, penetrance is found to be about 50 per cent as a dominant and 70 per cent as a recessive. Gene frequency analysis as a dominant shows 6 genes per thousand for the trait, and matings at random will provide 36 in a million as homozygous for the trait, 12 per thousand as heterozygous susceptible and the rest homozygous normals. If rheumatoid arthritis is assumed to be a recessive with 70 per cent penetrance, 9 per cent of genes are recessive for the trait, and mating at random provides 8 per thousand homozygous susceptible.

Intrinsic factors are proving to be of increased importance in the etiology of rheumatoid arthritis. Explanations of the phenomena of rheumatoid arthritis are sought in the fields of experimental biology and heredity. Variations in

penetrance and irregularities of expressivity can be explained by diverse internal and external factors acting as secondary gene modifiers.

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