Connecticut State Department of Health, Hartford, Connecticut; and
Hadassah Medical Organization, Jerusalem

A Genetic Study of Rheumatic Fever Clustering in Families[1]

Merton S. Honeyman, Eli Davis

SUMMARY

The first-degree relations of 433 rheumatic propositi were examined for evidence of rheumatic fever (RF) or rheumatic heart disease (RHD). The families of 470 control propositi were examined in identical fashion. Of the total propositi, 378 propositi were matched with 378 control propositi for sex, age group, and ethnic community (European or Afro-Asian origin). Of 738 sibs of rheumatic propositi, 19.6% had RF or RHD and of 586 sibs of controls, 3.1% had RF or RHD ($P<0.001$).

In the matched families 2,985 first-degree relations of the propositi were examined: 142 had RF and 141 had RHD, a total of 9.5%. In the members of the families of the rheumatic propositi 232 rheumatics were found in 1,486 first-degree relations (15.6%), while in the control families 51 rheumatics were found among 1,499 (3.4%).

Comparisons and analyses were made of expected and observed numbers according to sibship size using the method of truncated analyses (Lenz-Hogben method). This analysis supported the hypothesis of a simple mendelian recessive inheritance. Unbiased estimates of P, the population frequency of affected individuals, were consistent with the value $P = 0.25$, expected for a mendelian recessive character. The rheumatic fever clustering in families in this study was compatible with a simple recessive mendelian inheritance.

In conditions most favorable to the epidemic spread of hemolytic streptococcal infection, not more than 3% of those infected develop rheumatic fever (RF). Thus, 97% of those exposed to the infection do not develop rheumatic manifestations. Constitutional factors, possibly heredity, may have an important role in the pathogenesis of the disease. A cluster of first-degree relations with RF or rheumatic heart disease (RHD) is not uncommon. Wilson (1940, 1962) and Wilson and Schweitzer (1954) were convinced, after analysis of their RF family experience, that simple recessive inheritance could well explain the frequent familial prevalence that they encountered. This conclusion was challenged by Uchida (1953), who accepted the genetic factor in the etiology of RF, but did not find the evidence for a recessive trait convincing. One of us (E.D.) frequently encountered familial RF both in London and Jerusalem, over a span of thirty years. In the last four years, we have examined and reexamined our Jerusalem RF patients and their families, together with control families, to explore the possibility of hereditary mechanisms.

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Population and Methods

All patients with RF or RHD currently attending the Hadassah RF clinic were asked to enter the project. This RF clinic is open to patients of all ages, and not only to children or adolescents as is usually the case with rheumatic clinics. This advantage is reflected in the wide range of ages of the patients examined. Likewise, all patients who had attended the clinic from 1952 onwards were invited to cooperate. The same request was made to rheumatic and control patients attending our general internal medical clinic at the same time. The physician in charge of the Jerusalem City medical service in cooperation with the school nurses invited all known RF patients from representative schools in each district to cooperate with the project. The patients' physicians gave their consent. Also, after consent had been obtained from the appropriate physicians, the Israel Rheumatic Fever Society recommended to their clients, particularly their larger families, that they cooperate with us.

For all propositi, full examination of themselves and their first-degree relations was offered free of charge, with all the appropriate laboratory tests where relevant. In an appreciable number of persons we were able to examine the whole family, or to get reliable information on the family by using hospital records, physicians' reports and health insurance medical clinic records. The Jerusalem physicians cooperate closely with us and facilitated our work.

A control propositus had to be of the same sex, ethnic community and age group as a rheumatic propositus. The control propositus is one who attended the clinic because of a nonrheumatic disease, and found on examination to be free from RF or RHD.

The rheumatic patients concerned were those who had classical attacks of RF fulfilling the modified Jones' criteria (American Heart Association, 1965) and all had carditis. In addition, persons under the age of 40, but mostly under the age of 30, who on examination had acquired organic heart murmurs grade 2 in intensity or more (on a four-grade scale) and persisting for at least one year and with no evidence of other etiology, were accepted as rheumatic. In many of the latter there was X-ray evidence of cardiac enlargement. There were 433 rheumatic propositi whose families were examined, and 470 control propositi whose families were examined in identical fashion. Of the total propositi, 378 rheumatic propositi were matched with 378 nonrheumatic propositi for sex, age group (less than 15, 15-24, and 25 years or above), and ethnic group (European or Afro-Asiatic origin).

It transpired that rheumatic and control groups were comparable for social class. Families were accepted into the investigation if *at least two first-degree relations of a family of four first-degree members were personally examined, or at least three such relations of a family of five or more.* Every effort was made to examine every member, where possible, and in addition records of doctors and hospitals and health insurance medical clinics were sought for all members of the family.

In the families of the 433 rheumatic propositi and 470 control propositi there were 749 persons with RF or RHD, and of these, 428 had had RF and 321 presented with acquired organic heart murmurs (RM). The rheumatic propositi are included in these numbers.

It is realized that our study group is by no means a perfect sample of the Jerusalem population. All sections of Jerusalem's population use Hadassah's clinic services, but there is a relative deficiency of those of high social class. This deficiency was counteracted by propositi, rheumatic and control, drawn from E.D.'s private practice. This last group of patients would not have cooperated with the RF project unless it was their own physician's project. We know of some patients who refused to come to the hospital RF clinics, because

they did not want the hospital personnel of this relatively small city to know that they had RF, knowledge that could conceivably adversely influence their chances of marriage, as some stated. There is reason to believe that many of our clinic rheumatic population who entered the project would not have cooperated in a population survey based on family examination. By concentrating, whenever relevant, on members of the families other than the propositi, we surmounted some of the difficulties of bias in the population studies. In approximately half of the families investigated the examining physician did not know whether a family was a control family or the family of a rheumatic propositus until all the members of the family had been examined.

Findings

It was found that there was a strong familial clustering of rheumatic patients. Tab. I shows the prevalence of RF and RHD in the sibs of propositi, rheumatic and control, in the matched families. Of 738 sibs of rheumatic propositi 19.6% had RF or RHD and of 586 sibs of controls 3.1% had RF or RHD. The difference is significant ($P < 0.001$). In Tab. II information is given on all rheumatic cases found in the matched rheumatic and control families. In the matched families, 2,985 first-degree relations of the propositi were examined: 142 had had RF and 141 RM, making 9.5% with RF or RHD. In the members of the families of the rheumatic propositi 232 rheumatics were found in 1,486 first-degree relations (15.6%), while in the control families 51 rheumatics were found in 1,499 first-degree relations (3.4%).

The sibs of the rheumatic propositi in the age range 15-24 had a prevalence rate of 33.0%, as compared to 5.3% for the sibs of the matched controls (Tab. I). The first-degree relatives of the rheumatic propositi in the age range 15-24 had a prevalence rate of 29.4%, as compared to 5.2% for the first-degree relatives of the matched controls (Tab. II). The ratio of rheumatic disease in the sibs of the rheumatic propositi to control propositi is 6.2, and 5.7 between the first-degree relatives.

Is there evidence for a genetic factor in this familial clustering? In the small families most of the members were personally examined, so that there was complete

Tab. I. Rheumatic disease among sibs of propositi in study and control matched families

Age group	N		Affected with RF or RHD N		Affected with RF or RHD %		Ratio of rates study/control
	Study	Control	Study	Control	Study	Control	
...-15	447	334	66	6	14.8	1.8	8.2
15-24	206	151	68	8	33.0	5.3	6.2
25-...	85	101	11	4	12.9	4.0	3.2
Total	738	586	145	18	19.6	3.1	6.3

NOTES: Rheumatic disease includes a confirmed history of acute rheumatic fever and/or rheumatic heart disease. Each control propositus was selected to match a study propositus for age group, sex, and ethnic origin.

Tab. II. Rheumatic disease among first-degree relatives of propositi in study and control matched families

Age group	N		Affected with RF or RHD N		Affected with RF or RHD %		Ratio of rates study/control
	Study	Control	Study	Control	Study	Control	
...-10	408	354	36	2	8.8	0.6	14.7
11-14	235	224	49	11	20.9	4.9	4.3
15-24	269	232	79	12	29.4	5.2	5.7
25-...	574	689	68	26	11.8	3.8	3.1
Total	1,486	1,499	232	51	15.6	3.4	4.6

NOTE: See notes to Tab. I.

information on many small families. In the larger families there was only limited success in examining every member of the family. However, in many families reliable information on the presence or absence of RF or RHD was available for those members of the family who could not be personally examined, because they were living at a distance or abroad, or had died, or in some cases refused cooperation. If a member of a family, who was regarded as a reliable witness, stated that a first-degree relation (whom we could not personally examine) suffered from RF or RHD, this was checked against records of doctors, hospitals, or insurance medical clinics. Complete information regarding sibship size of our families and the numbers of families in which all the sibs were examined has been given by Davis (1969). The breakdown in sibship size for those families for which the rheumatic state of every first-degree relation was known (had been affected or not) can be seen in Tables III and IV. Tab. III deals with families of all propositi, and Tab. IV with families of matched propositi only.

In Tables III and IV comparisons and analyses are given of expected and observed numbers of rheumatic cases in the families according to sibship size. The expected numbers were based on the hypothesis of a recessive inheritance. A truncated analysis (Lenz-Hogben method) was used and the propositi were included. Chi square was calculated for the deviation of each sibship and for the pooled contributions. The numbers available permitted the analyses of only those families in which neither, or only one parent was affected with RF or RHD. There were not sufficient numbers available to obtain a reliable chi square value for the category of both parents affected.

The hypothesis tested was that rheumatic fever is inherited as a simple mendelian recessive character. The analysis of the 187 sibships of rheumatic matched propositi with neither parent affected among the matched families gave a chi square which is not statistically significant, supporting the hypothesis (Tab. III). On analysis of all 42 sibships with one parent affected among the matched families, the chi square was significant (Tab. IV). However, if sibships of size 7 and 8 are excluded, then

Tab. III. Rheumatic sibs in sibships. Neither parent affected

Sibship size	No. of families	Affected Exp.	Affected Obs.	Not affected Exp.	Not affected Obs.	Total sibs
2	52	59.4	65	44.6	39	104
3	37	48.0	55	63.0	56	111
4	29	42.4	42	73.6	74	116
5	19	31.1	29	63.9	66	95
6	21	38.3	37	87.7	89	126
7	3	6.1	4	14.9	17	21
8	14	31.1	28	80.9	84	112
9	8	19.5	14	52.5	58	72
10	4	10.6	10	29.4	30	40
Total	187	286.5	284	510.5	513	797

$\chi^2 = 0.033$, $\chi^2_{(0.05,1)} = 3.841$, $P = 0.75$-0.90; $\chi^2 = 7.39$, $\chi^2_{(0.05,8)} = 15.51$, $P = 0.25$-0.50.

NOTES: All rheumatic subjects (propositi included). All sibs and parents known.

Tab. IV. Rheumatic sibs in sibships. One parent affected

Sibship size	No. of families	Affected Exp.	Affected Obs.	Not affected Exp.	Not affected Obs.	Total sibs
2	21	28.0	28	14.0	14	42
3	10	17.2	14	12.8	16	30
4	5	10.7	6	9.3	14	20
5	2	5.2	4	4.8	6	10
6	1	3.0	3	3.0	3	6
7	1	3.5	1	3.5	6	7
8	2	8.0	2	8.0	14	16
Total	42	75.6	58	55.4	73	131
		$\chi^2 = 9.69$, $\chi^2_{(0.05,1)} = 3.841$				
Eliminate sibships size 7 & 8:	39	64.1	55	43.9	53	108
		$\chi^2 = 3.18$, $\chi^2_{(0.05,1)} = 3.841$				

NOTES: All rheumatic subjects (propositi included). All sibs and parents known.

the chi square value is not significant and the expected ratio was observed. As sibships of size 7 and 8 only contribute three sibships to the total analysis, there is ground for their elimination.

The analyses of the data support the hypothesis of inheritance of susceptibility to RF as a simple mendelian recessive character. It is emphasized that the diagnostic

criteria for RF were strict and, had we included in the study patients fulfilling Jones' criteria for RF in the absence of carditis, the number of family cases would have increased appreciably.

A possible criticism is that our data are biased. In order to check for bias, two independent estimates of P were made: P represents the frequency of affected individuals in the population at risk. First, the data in Tab. III were corrected to estimate the total number of children represented by the families observed as described by Li (1961). The correction shown in Tab. V represents the ratio of affected to non-affected children and includes those families in which no affected children occurred. The corrected total number of children is 1,146.2, with 284 observed affected, which gives a value of $P = 0.248$. Gart (1967) presented a method of estimating P which is more efficient than the simple sib method. Tab. VI shows this analysis resulting in an estimate of $P = 0.246$. These two estimates of P which are unbiased do not differ from the theoretical value of $P = 0.25$ for a mendelian recessive.

Bad social class has been stated to be a contributory factor in the etiology of RF. We can use the hypothesis of a simple mendelian recessive heredity to examine the contribution of social class to etiology. The sibships of neither-parent-affected and one-parent-affected families were examined as to whether they belonged to either Social Class 1 and 2 (higher and average) together, or 3 (lower). If social class is contributory and there is an increased frequency of RF and RHD in one of these classes due to it, then the truncated analysis should not support the recessive hypothesis. Chi square was not significant in any of the comparisons made, showing that in this population the effect of social class as a contributing factor was not sufficiently large to be statistically demonstrated.

Discussion

Diamond (1957, 1962) gave evidence in favor of a " rheumatic constitution ". Wilson (1940, 1962) and Wilson and Schweitzer (1954) have studied the problem of hereditary susceptibility to RF. They reported that genetic analysis of their RF family experience gave good agreement with simple recessive inheritance while excluding other mechanisms. They concluded that they have good evidence that RF susceptibility is inherited as a simple recessive trait. This conclusion was not confirmed by Uchida (1953), who accepted a genetic factor in the etiology of RF but did not find the evidence for a recessive trait convincing. Stevenson and Cheeseman (1953, 1956) gave evidence in favor of hereditary susceptibility but their data did not support any specific mode of inheritance. Davies and Lazarov (1960), working in a kibbutz where the members shared the same environment, found that the prevalence of RHD in children of affected parents was two-and-a-half times greater than that in children of unaffected parents. Harvald and Hauge (1965), in the Institute of Human Genetics, Copenhagen, undertook comprehensive studies on Danish twins. Among other diseases, they also considered RF. They found a higher concordance rate for RF in MZ than DZ twins, but were cautious regarding the conclusion that

Tab. V. A priori correction method applied to Tab. III

Size of sibship s	No. of sibships n_s	No. of children $sn_s = t_s$	Observed no. of affected r_s	Theoretical total children $c_s = t_s/[1-(3/4)^s]$	Corrected proportion of affected $b_s = r_s/c_s$
2	52	104	65	237.7	0.273
3	37	111	55	192.0	0.286
4	29	116	42	169.7	0.247
5	19	95	29	124.6	0.234
6	21	126	37	153.3	0.241
7	3	21	4	24.2	0.165
8	14	112	28	124.5	0.225
9	8	72	14	77.8	0.180
10	4	40	10	42.4	0.236
Total	187	797	284	1,146.2	0.248

Tab. VI. Estimate of *P* by Gart method

Sibship size	No. of families	Affected sibs	No. of sibships with only one affected	Total sibs
2	52	65	39	104
3	37	55	23	111
4	29	42	19	116
5	19	29	12	95
6	21	37	9	126
7	3	4	2	21
8	14	28	7	112
9	8	14	5	72
10	4	10	1	40
Total	187	284	117	797

$$P = (284-117)/(797-117) = 0.246$$

the reason was genetic. Reed (1964) tabulated 284 twin pairs with RF reported by thirteen different groups. In 127 MZ twins, 28% had RF; in 157 DZ twins, 7% had RF. O'Brien (1968) reviewed the twin studies in rheumatic disease.

Taranta et al (1959, 1961) reported on RF in MZ and DZ twins. The data presented were consistent with, but did not prove, the hypothesis that genetic factors have a part in the etiology of RF. However, less than one-fifth of MZ twin pairs were definitely concordant.

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Reed (1964) also reviewed twin studies in RF. He analyzed 284 twin pairs reported by thirteen different groups and concluded that, although the precise genetic mechanism is unknown, the most probable mechanism is a homozygous recessive gene with other less important modifying genes: " Presumably there must be an infection, although it is not known how massive this must be ". For counseling purposes, he stated that there would be about a 10% chance of an affected sibling if neither parent has had the disease, and about a 15% chance of an affected sibling if one parent was affected. A patient can expect a 15-20% chance of having at least one affected child.

Our own twin experience is meagre. But of our 10 twin pairs with prolonged follow-up, there was concordance for RF in 6 pairs and in the remaining 4 pairs only one of the twins was affected. However, it is important to point out that each member of the pair may show the disease at markedly different ages, so that twins should be followed up until at least the age of 35 before conclusions are drawn.

There is no question that the best way of examining the problem of heredity in RF would be the follow-up of a large series of twins for a long period, say up to the age of 35. The population available to us did not provide sufficient patients for us to undertake a significant twin study. Consequently, we worked with the population available, a nonrandom one, but a population we knew well and could follow up for a long period.

The leading heredity studies in RF reported in the literature have been examined by us. Among these studies are those of Gray et al (1952), Wilson and Schweitzer (1954), Stevenson and Cheeseman (1956), Taranta et al (1959, 1961), Harvald and Hauge (1965), and the Connecticut twin study (Honeyman, 1968). Using the method of truncated analysis on the family studies it was found that none of these reports supported a mendelian recessive hypothesis for RF. But the same technique applied to the findings of the present study showed that, in families where neither parent was affected, the results were in conformity with a hypothesis of a recessive inheritance. Two independent unbiased estimates of P confirmed a population frequency of 0.25, which is expected for a mendelian recessive character. The fact that the Jerusalem study population was drawn from many parts of the world, favors the conclusion that the possible recessive inheritance in RF is not specific to Jerusalem but could be expected elsewhere. These findings give evidence for the view of Wilson and Schweitzer that hereditary susceptibility in RF exists and can best be explained on the basis of simple mendelian recessive inheritance.

It is realized that evidence of compatibility with heredity is not proof that heredity is of certainty a factor in the pathogenesis of RF. However, some evidence is given above, and more evidence has been given by Davis (1969), that hemolytic streptococcal infection and poverty in themselves are not sufficient to explain the development of RF. Fresh evidence has therefore emerged that heredity should be regarded as important in the development of RF.

References

American Heart Association (1965). Ad Hoc Committee to Revise the Jones' Criteria (modified) of the Council on Rheumatic Fever and Congenital Heart Disease. Jones criteria (revised) for guidance in the diagnosis of rheumatic fever. Circulation, **32**: 664.

Davies A. M., Lazarov E. (1960). Heredity, infection and chemoprophylaxis in rheumatic carditis: an epidemiological study of a communal settlement. J. Hyg. (Camb.), **58**: 263.

Davis E. (1969). Rheumatic Fever. Clinical, Ecological and Familial Aspects. Charles C. Thomas, Springfield.

Diamond E. F. (1957). Hereditary and environmental factors in the pathogenesis of rheumatic fever. Pediatrics, **19**: 908.

Diamond E. F. (1962). Is there a rheumatic constitution? J. Pediat., **54**: 341.

Gart J. J. (1967). A simple nearly efficient alternative to the simple sib method in the complete ascertainment case. Ann. Hum. Genet., **31**: 283.

Gray F. G., Quinn W., Quinn J. P. (1952). A long term survey of rheumatic and non-rheumatic families with particular reference to environment and heredity. Amer. J. Med., **13**: 400.

Harvald B., Hauge M. (1965). Hereditary factors elucidated by twin studies. In: J. V. Neel, M. W. Shaw, W. J. Schull: Genetics and the Epidemiology of Chronic Diseases. Public Health Service Publication No. 1163.

Honeyman M. S. (1968). Unpublished data. Lecture Hebrew University, Hadassah Medical School.

Li C. C. (1961). Human Genetics. McGraw-Hill Book Co., New York.

O'Brien W. M. (1968). Twin studies in rheumatic diseases. Arthritis Rheum., **11**: 81.

Reed S. (1964). Parenthood and Heredity. John Wiley & Sons, Inc., New York.

Stevenson A. C., Cheeseman E. A. (1953). Heredity and rheumatic fever. A study of 462 families ascertained by an affected child and 51 families ascertained by an affected mother. Ann. Eugen., **17**: 177.

Stevenson A. C., Cheeseman E. A. (1956). Heredity and rheumatic fever. Some later information about data collected in 1950-55. Ann. Hum. Genet., **21**: 139.

Taranta A., Torosdag S., Metrakos J. D., Jegier W., Uchida I. A. (1959). Rheumatic fever in monozygotic and dizygotic twins. Circulation, **20**: 778.

Taranta A., Torosdag S,, Metrakos J. D., Jegier W., Uchida I. A. (1961). Rheumatic fever in monozygotic and dizygotic twins. Proc. Int. Congr. Rheumatic Diseases, Rome. Minerva Med., **2**: 1-4.

Uchida I. A. (1953). Possible genetic factors in etiology of rheumatic fever. Amer. J. Hum. Genet., **5**: 61.

Wilson M. G. (1940). Rheumatic Fever. The Commonwealth Fund, New York.

Wilson M. G., Schweitzer M. (1954). Pattern of hereditary susceptibility in rheumatic fever. Circulation, **10**: 699.

Wilson M. G. (1962). Advances in Rheumatic Fever 1940-1961. Hoeber Med. Div., Harper & Row, New York.

Riassunto

Sono stati esaminati i parenti di primo grado di 433 pazienti di reumatismo articolare acuto (RF) o cardiopatia reumatica (RHD). Allo stesso modo sono state esaminate le famiglie di 470 soggetti di controllo. Del totale dei pazienti, 378 corrispondevano ad altrettanti controlli per età, sesso e comunità etnica (origine europea o afroasiatica). Dei 738 fratelli e sorelle dei pazienti reumatici, il 19.6% risultava affetto da RF o RHD; mentre dei 586 fratelli e sorelle dei controlli, lo era soltanto il 3.1% ($P<0.001$).

Nelle famiglie che si corrispondevano, sono stati esaminati 2985 parenti di primo grado, 142 dei quali sono risultati affetti da RF e 141 da RHD, per un totale del 9.5%. Dei 1486 parenti di primo grado dei pazienti reumatici, erano affetti 232 (15.6%); mentre dei 1499 parenti dei controlli, lo erano solo 51 (3.4%).

I valori osservati sono stati raffrontati a quelli attesi in base alle dimensioni delle fratrie, mediante il metodo di Lenz-Hogben. L'analisi conferma l'ipotesi di un modello mendeliano semplice di tipo recessivo. Le stime (esenti da fonti di errore) della frequenza popolazionistica degli individui affetti concordavano con il valore teorico, $P = 0.25$, atteso per un carattere mendeliano recessivo. Le frequenze familiari di RF sono risultate compatibili con un modello recessivo semplice.

RÉSUMÉ

Les parents de premier degré de 433 sujets atteints de rhumatisme articulaire aigu (RF) ou de cardiopathie rhumatique (RHD) ont été examinés, ainsi que les familles de 470 sujets de contrôle. Age, sexe et communauté ethnique (origine européenne ou afroasiatique) se correspondaient chez 378 sujets et 378 contrôles. Des 738 frères et sœurs des sujets rhumatiques, 19.6% ont été trouvés atteints par RF ou RHD; tandis que des 586 frères et sœurs des contrôles, seulement 3.1% l'étaient ($P<0.001$).

Dans les familles qui se correspondaient, 2985 parents de premier degré ont été examinés: 142 ont été trouvés atteints par RF et 141 par RHD, avec un total de 9.5%. Au sein des 1486 parents des patients rhumatiques, 232 (15.6%) étaient atteints; tandis que au sein des 1499 parents des contrôles, seulement 51 (3.4%) l'étaient.

Les valeurs observées ont été comparées aux valeurs attendues sur la base des dimensions de la souche, moyennant la méthode de Lenz-Hogben. L'analyse appuye l'hypothèse d'un mécanisme mendélien simple récessif. Les estimes non biasées de la fréquence d'individus atteints dans la population sont en accord avec la valeur théorique, $P = 0.25$, attendue pour un caractère mendélien simple. Les fréquences familiales de l'RF ne sont pas résultées en désaccord avec l'hypothèse.

ZUSAMMENFASSUNG

Von 433 Patienten mit rheumatischem Fieber (RF) oder rheumatischen Kardiopathien (RHD) sowie von 470 Kontrollpersonen wurden die Blutsverwandten ersten Grades untersucht. Aus den Patienten übereinstammen 378 mit einer gleichen Anzahl Kontrollpersonen in bezug auf Alter, Geschlecht und Volksursprung (europäische oder afroasiatische Volkszugehörigkeit). Von den 738 Geschwistern der Rheumapatienten litten 19.6% an RF oder RHD, von den 586 Geschwistern der Kontrollpersonen hingegen nur 3.1% ($P<0.001$).

Von den insgesamt 2985 untersuchten Angehörigen ersten Grades litten 283 (9.5%) an rheumatischen Erkrankungen (142 an RF und 141 an RHD). Von diesen fielen 232 (15.6%) auf die 1486 Angehörigen der Rheumapatienten und nur 51 (3.4%) auf die 1499 Angehörigen der Kontrollpersonen.

Die Ergebnisse wurden mit denjenigen verglichen, die auf Grund der Sippendimensionen gemäss der Methode nach Lenz-Hogben zu erwarten waren. Die Hypothese eines einfachen rezessiven Modell wurde bestätigt. Die Abschätzung (ohne Fehlerquelle) der Frequenz der rheumaleidenden Personen in der Bevölkerung stimmten mit dem theoretischen Wert $P = 0.25$ überein, der für ein rezessives mendelsches Merkmal zu erwarten ist. Das Vorkommen des Rheumafiebers in den Familien schien mit dem eines einfachen rezessiven Modells übereinzustimmen.

Dr. M. S. HONEYMAN, Director, Connecticut Twin Registry, State Department of Health, 79 Elm Street, Hartford, Connecticut 06115, USA.