Possible Genetic Factors in the Etiology of Rheumatic Fever[1]

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INTRODUCTION

THE tendency for rheumatic fever to run in families has been noted so often that it has become common knowledge. The literature in support of this fact is voluminous. The controversial point lies in the cause of this familial tendency.

It is the belief of some investigators (Faulkner and White, 1924; Griffith et al., 1948) that simultaneous infection is the important cause in the development of rheumatic fever. In a conference of leading workers in the field of rheumatic diseases in England social and economic factors were stressed (Anonymous, 1934).

The strongest advocates of the theory that the susceptibility to rheumatic fever is primarily determined by inheritance are Wilson and Schweitzer. In an intensive study in 1937, these two authors presented evidence supporting the theory that common environmental conditions and communicability are of secondary importance[2].

Analyses of family pedigrees have brought forth evidence in support of three different modes of inheritance. Draper and Seegal's conclusion, that the susceptibility to rheumatic fever is transmitted through sex-linked genes (1923), is based upon a study of 50 families. That a single autosomal recessive gene is responsible is the conclusion reached by Wilson and Schweitzer (1937) after an investigation of 112 families. Single autosomal dominant inheritance is advocated by Beers (1948) on the basis of a single pedigree of four generations. A pedigree of five generations published by Pickles (1943) suggests a similar type of inheritance. So also do pedigrees published by Pribram (1899) and Weitz (1936).

Such in brief is the situation at present in the genetical investigations of rheumatic fever[3]. It seemed important therefore to attempt another investiga-

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[2] This study was further extended by Wilson, Schweitzer and Wheeler and republished in a monograph in 1940 by Wilson. In 1943 Wilson, Schweitzer and Lubschez reported a continuation of the original genetic analysis.

[3] Two other papers on the role of heredity in rheumatic fever have been published since this one was submitted: (1) Gray, F. G., Quinn, R. W., and Quinn, J. P. 1952. A Long-term Survey of Rheumatic and Non-rheumatic Families. Am. J. Med. 13: 400–412. (2) Stevenson, A. C., and Cheeseman, E. A. 1952. Heredity and Rheumatic Fever. Ann. Eugen. 17: 177–210.

tion of the genetics of this disease with fresh data in a different country under what would appear to be different environmental conditions. Such a study is now underway in Toronto. Although the size of the present sample is small this paper is being presented at this time because the results of our investigations do not agree with those of Wilson and Schweitzer whose publications represent the most extensive and important work on the subject. Further data are being gathered to extend our study.

METHOD OF COLLECTING DATA

With the co-operation of the Cardiac Clinic of the Hospital for Sick Children and the Department of Public Health, a list of current cases of rheumatic heart disease, rheumatic fever and chorea among children in Toronto and surrounding districts was obtained. The present study, however, includes only those patients who attended the Hospital for Sick Children and who were definitely diagnosed as rheumatic by one physician who is an accepted authority in this field. In this way the diagnosis of all patients was uniform.

For the purpose of obtaining as complete a family history as possible and of recording environmental and economic conditions, visits were made to the homes of those families who showed a willingness to co-operate. To check the accuracy of the family histories all hospital records of any members of the observed families were examined. Contrary to the findings generally reported in the literature this check revealed that with the exception of two unreported cases of rheumatic heart disease all the inaccuracies were found among those who claimed to have had rheumatic fever but who actually had arthritis or rheumatism.

In order to detect any undiagnosed cases among sibs and parents and to check those individuals who claimed to have had rheumatic fever in the past a thorough heart examination of all members of the families involved was undertaken in the Cardiac Clinic of the Hospital for Sick Children by the cardiologist, Dr. John Keith, and his assistant, Dr. Constance Forsyth. In the few cases in which it was impossible to interview and to examine an individual, army reports and hospital records were accepted upon the approval of the examining physicians. There were five parents for whom no records were available and no examination possible because of death or separation. In all these cases the spouse knew of no definite history of rheumatic fever.

Among the parents examined only those who had evidence of rheumatic heart disease or those for whom written records were available or who could report a definite history of illness in bed with the typical symptoms of rheumatic fever were classified as affected individuals. It may be said that this criterion may exclude a number of individuals who were truly rheumatic. Since a check of hospital histories against personal ones revealed that a larger number of

individuals who claimed to be rheumatic were really non-rheumatic than vice versa, the error involved would be smaller on the side of conservatism.

The rigid standards adhered to in this investigation provide strict control of the material used. For this reason as well as for the purely voluntary nature of the study, efforts to gather a larger sample have necessarily been restricted.

DESCRIPTION OF DATA

This study is based upon a group of 58 families with a total of 256 offspring. Children under the age of 2 years have not been included. A breakdown of the material used is given in Table 1.

TABLE 1. SUMMARY OF DATA USED IN THE TORONTO STUDY

	SEX	AFFECTED			UNAFFECTED	TOTAL
		RHD	RF	Total		
Offspring	♂	21	14	35	101	136
	♀	17	15	32	88	120
	Total	38	29	67	189	256
Parents	♂	1	0	1	57	58
	♀	2	5	7	51	58
	Total	3	5	8	108	116

RHD, rheumatic heart disease; RF, rheumatic fever. Those who had evidence of rheumatic carditis at the time of the study were classified as rheumatic heart disease, while those who had never suffered from or who have completely recovered from heart disease are classified under rheumatic fever.

The range for the age of onset of the disease was from 3 to 13 years, with a median age of 7.1 years (males 6.4 years, females 7.4 years). Three females were omitted from this analysis because an accurate age of onset could not be established. For Wilson and Schweitzer's sample the age range is from 1 to 17 years with a median of 4.9 years.

Because of varying environmental influences our sample has been restricted to one economic class, the lower income group. All the families were drawing incomes of approximately $2400 or less per year per family of five. This is the amount necessary to maintain a minimum level of health and self-respect as estimated from the data issued by the Welfare Council of Greater Toronto for 1949.

In order to keep the racial factor as constant as possible the present sample is restricted to "white" families only, of which 7% are of Jewish origin. No definite statistical data are available regarding the incidence of rheumatic fever among the Jewish people except for Hedley's analysis of mortality statistics (1940) in which no difference was noted between Jewish and Gentile populations.

RESULTS

Sex Distribution Among Offspring

Of a total of 120 girls and 136 boys, 26.7% of the girls were affected and 25.7% of the boys (Table 1). There is no significant difference between the sexes. This fact is in keeping with the findings of the 1948–49 Cardiac Registry, a survey of Toronto school children (Gardiner and Keith, 1951).

Sex Distribution Among Parents

In the present sample of 58 families 8 parents were affected. Of these 7 mothers and 1 father were rheumatic. This unusual distribution among the parents may be of etiological importance.

Evidence of Inheritance

a. *Familial Incidence.* Of the 58 families studied there were 8 in which one parent had a positive history of rheumatic fever or rheumatic heart disease. There were no families in which both parents were affected. From Table 2 it is obvious that the type of parental mating, rheumatic or non-rheumatic, made no difference in the incidence of rheumatic fever in the children.

Because ascertainment of affected individuals in the present sample is almost complete Haldane's maximum likelihood method (1932, 1938) is used in this analysis. With the aid of tables supplied by Finney (1949) for the solution of maximum likelihood equations the incidence of rheumatic fever in these families can easily be obtained. For families with one affected parent the incidence is .11 $\pm$ .07 while the incidence in families with both parents unaffected is .08 $\pm$ .03. Since there is no significant difference between these values the data were combined giving a total incidence of .08 $\pm$ .07 (see Table 3).

The frequency of rheumatic fever in the general population of Toronto can be estimated from the results of the 1948–49 Cardiac Registry (Gardiner and Keith, 1951). For the age group 0–15 years the frequency was determined at 2.3 per 1,000. Since it has been shown in surveys of all age groups that the median of the frequency of the age at onset ranges from 12–14 years (Hedley, 1940), it seems safe to assume an incidence of not more than twice the above frequency, i.e. 4.6 per 1,000 or .0046, for the population of Toronto. The frequency in the present sample is obviously much higher than in the total population.

b. *Genetic Analyses.* A strong argument for the importance of genetic factors in the development of a trait is found in the demonstration of a definite mode of inheritance. Accordingly the data were examined in an attempt to determine a definite method for the transmission of the susceptibility to rheumatic fever.

There is no evidence in the Toronto data to suggest a sex-linked mode of inheritance.

In dominant inheritance under ideal conditions of 100% penetrance a trait should be expressed in every generation. Since 86% of the families of the present sample had unaffected parents a low penetrance of 14% is indicated in the parental generation. Among the offspring there is an incidence of .08 (see above) or a penetrance of 16%.

TABLE 2. PERCENTAGE FREQUENCY OF RHEUMATIC CHILDREN OF AFFECTED AND UNAFFECTED PARENTS

TYPE OF MATING	NO. OF MATINGS	TOTAL NO. CHILDREN	% AFFECTED CHILDREN
Both parents unaffected	50	216	26.4
One parent affected	8	40	25.0

TABLE 3. ANALYSIS OF FAMILIES ACCORDING TO NUMBER OF AFFECTED OFFSPRING IN SIBSHIPS OF FIXED SIZE

	NO. OF FAMILIES				
	Both parents unaffected			One parent affected	
No. Affected Offspring / Size of Family	1	2	3	1	2
1	2				
2	4	1		1	1
3	12				
4	11	1		1	
5	5	1		3	
6	6		1		
7	1	1		1	
8	3				
9					
10		1			1
Total	44	5	1	6	2
Incidence	p = .08 ± .03			p = .11 ± .07	
	Combined p value = .08 ± .07				

It has already been pointed out that about equal proportions of offspring were affected regardless of the type of parental mating. This is to be expected under a hypothesis of dominant inheritance with reduced penetrance.

To test for recessive inheritance, the data can be treated in two different ways: (a) by analysis of the offspring and (b) by analysis of the parents.

Among the offspring of matings between two unaffected individuals (both

heterozygous: $H \times H$) there is an incidence of .08 ± .03 (see Table 3), a value which is obviously different from the expected 25% under a hypothesis of recessive inheritance. Similarly an incidence of .11 ± .07 among the offspring of affected by unaffected matings (recessive × heterozygous: $R \times H$) is much lower than the expected 50%.

Analysis of the parents can be made by comparing the proportion of $H \times H$ and $R \times H$ matings. If mating takes place at random (and there is no reason to believe otherwise in the present case) and if the gene frequencies in the population are known, then the expected proportion of matings of $H \times H$ to that of $R \times H$ can be estimated. Because of the nature of the ascertainment of the

TABLE 4. TEST FOR RECESSIVE INHERITANCE OF TORONTO SAMPLE BY RANDOM MATING

SIZE OF FAMILY s	BOTH PARENTS UNAFFECTED ($H \times H$)		ONE PARENT AFFECTED ($R \times H$)		PROP'N OF $H \times H$ MATINGS
	n_s	$N_s = \frac{n_s}{1 - q^s}$	n_s	$N_s = \frac{n_s}{1 - q^s}$	$\hat{p} = \frac{N_{H\times H}}{N_{H\times H} + N_{R\times H}}$
1	2	8.0	—	—	1.00
2	5	11.4	2	2.7	0.81
3	12	20.8	—	—	1.00
4	12	17.5	1	1.1	0.94
5	6	7.9	3	3.1	0.72
6	7	8.5	—	—	1.00
7	2	2.3	1	1.0	0.72
8	3	3.3	—	—	1.00
9	—	—	—	—	—
10	1	1.1	1	1.0	0.52
	50	80.8 (90.08%)	8	8.9 (9.92%)	$\bar{p} = 0.85 \pm .06$
Expected prop'ns (incidence .0046)		.0160 (93.02%)		.0012 (6.98%)	

material used, i.e., the presence of the proband in all the observed families, certain adjustments must be made in the analysis of the data*.

An estimate, N, the total number of matings of a particular genotype, can be determined from the observed data by the following:

$$\sum N_s = \sum \frac{n_s}{1 - q^s}$$

where n_s is the observed number of families of sibship size s, and $q = \frac{3}{4}$ or $\frac{1}{2}$, the expected proportions of normal offspring from $H \times H$ and $R \times H$ matings respectively. The proportions of matings of $H \times H$ to $R \times H$ can then be compared with the expected proportions based upon the frequency of the trait

* The method used in this analysis was suggested by Professor D. B. W. Reid.

in the general population. The results of this analysis are given in Table 4, the expected proportions being based upon an incidence of the order of .0046 as determined from the Cardiac Registry (see above).

To give some indication of the significance of the difference between observed and expected frequencies estimates of the proportion of $H \times H$ matings for each family size and the simple unweighted average along with its standard error are also given in Table 4. These analyses do not suggest a real discrepancy between observed and expected frequencies.

DISCUSSION

For the inheritance of a predisposition to rheumatic fever two theories have been suggested: single autosomal dominant and single autosomal recessive.

TABLE 5. TEST FOR RECESSIVE INHERITANCE OF NEW YORK SAMPLE BY RANDOM MATING

SIZE OF FAMILY s	BOTH PARENTS UNAFFECTED $(H \times H)$		ONE PARENT AFFECTED $(R \times H)$		PROP'N OF $H \times H$ MATINGS
	n_s	$N_s = \frac{n_s}{1 - q^s}$	n_s	$N_s = \frac{n_s}{1 - q^s}$	$\hat{p} = \frac{N_{H \times H}}{N_{H \times H} + N_{R \times H}}$
1	1	4.0	6	12.0	0.25
2	9	20.6	7	9.3	0.69
3	14	24.2	11	12.6	0.66
4	12	17.5	9	9.6	0.65
5	10	13.1	3	3.1	0.81
6	5	6.1	6	6.1	0.50
7	3	3.5	2	2.0	0.63
8	4	4.4	3	3.0	0.59
9	1	1.1	3	3.0	0.27
	59	94.4 (60.9%)	50	60.7 (39.1%)	$\bar{p} = 0.56 \pm .06$
Expected prop'ns (incidence .03)		.0820 (82.7%)		.0172 (17.3%)	

Beers' theory of dominant inheritance is based upon a single pedigree. Wilson and Schweitzer's theory of recessive inheritance is the result of a series of studies with a group of about 112 families. In Beers' pedigree dominant inheritance cannot be denied because the path of the gene can be traced through four successive generations. The work of Wilson and Schweitzer, however, is open to criticism.

In their analysis of offspring of $H \times H$ matings Wilson and Schweitzer found the observed to exceed the expected frequency by a difference of borderline significance (1940, 1943). In attempting to evaluate this difference the authors conclude that 3 of the parents may have been inaccurately diagnosed as unaffected individuals. A penetrance of 100% is assumed for the offspring of $H \times$

H and $R \times H$ matings while examination of the offspring of two affected parents gives a penetrance of 86%. These two percentages are incompatible and throw doubt upon the theory of recessive inheritance. Furthermore when the New York data are subjected to the above test for random mating, the proportion of $R \times H$ matings far exceeds the expected (see Table 5).

In the present sample the theory of recessive inheritance fits the data as far as the parents are concerned but differs significantly from the observed incidence among the offspring unless a greatly reduced penetrance is taken into consideration. On the other hand dominant inheritance, also with very low penetrance, cannot be ruled out either. For Wilson and Schweitzer's data, however, neither recessive nor dominant inheritance is acceptable.

The conflict between Wilson and Schweitzer's data and the present sample may be caused by differing standards of diagnosis or forceful environmental influences making a comparison of the two groups impossible. The difficulty encountered in the attempt to establish a simple method of inheritance may be the result of these environmental influences or perhaps a more complex method of inheritance is the answer. It is hoped that with a larger sample more definite conclusions can be reached.

CONCLUSIONS

An attempt has been made to evaluate the genetic factors in the development of rheumatic fever. If there is a genetic basis for rheumatic fever, it appears from the existing data that no simple genetic theory can adequately explain the transmission of the susceptibility to the condition. With the publication of Wilson and Schweitzer's studies it was thought that the genetic problems had been solved. However, it is now felt that only a beginning has been made and the work must be continued with much more extensive data.

SUMMARY

The present study is based upon a group of 58 families with a total of 256 offspring. The median age of onset is 7.1 years with a range of 3 to 13 years. The sample is limited to the lower income group and to the white race.

There is no difference in the sex distribution of rheumatic children in Toronto. However, there is a significant difference among the parents, the mothers being more often affected than the fathers.

There is a higher concentration of rheumatics in the present sample than among the general population of Toronto.

Analysis of the present sample indicates that if a greatly reduced penetrance is considered both simple recessive and simple dominant inheritance fit the data but neither of these theories is compatible with the New York data. It is concluded therefore that no definite mode of inheritance can yet be established.

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