Pattern of Hereditary Susceptibility in Rheumatic Fever

By May G. Wilson, M.D., and Morton Schweitzer, Ph.D.

This study is concerned with the pattern of inheritance of susceptibility to rheumatic fever. To investigate the genetic mechanism of inheritance in rheumatic fever the families of a selected parent were brought under observation without regard for the presence or absence of rheumatic fever in the unselected mate or collateral relatives. These data are preferable for genetic analysis since they are not biased by selection of affected children and can therefore be analyzed directly by the application of simple Mendelian ratios. Two hundred ninety-one families including 646 siblings were under continuous medical supervision at The New York Hospital for an average period of 10 years. Rheumatic fever occurred in 40 children among a total of 121 offspring in 52 genetically susceptible families. By contrast in 239 nonsusceptible families with a total of 525 children, there were only three children who developed rheumatic fever. Genetic analysis of the data gave good agreement with simple recessive inheritance while excluding other mechanisms. The previous conclusion that susceptibility to rheumatic fever is inherited as a simple recessive trait was corroborated.

GENERAL and epidemiologic studies in 1937 and 1943 revealed that the distribution of cases among 471 children in 113 rheumatic families was consistent with a genetic mechanism of simple recessive inheritance. These families were selected because of the presence of at least one rheumatic child. It was concluded that hereditary susceptibility is the primary factor responsible for the concentration of rheumatic fever in certain families.

An hereditary factor in rheumatic fever has been reported by other investigators. In 1952 Gray, Quinn and Quinn reported agreement with a simple recessive gene hypothesis in 40 New Haven families similarly selected. There was a paucity of cases in three positive by positive matings. In a Toronto study by Uchida in 1953, it was concluded from a genetic analysis of 58 affected families that no definite mode of inheritance could be established from the limited data. In 1953 Stevenson and Cheeseman studied 462 families in Belfast which were ascertained by an affected child and 51 families ascertained by an affected mother. It was concluded that inheritance played a major role in determining familial aggregation of cases but that a Mendelian mechanism could not be established.

To investigate further the pattern of inheritance in rheumatic fever, the families of a selected parent were brought under observation without regard for the presence or absence of rheumatic fever in the unselected mate or in collateral relatives. These families are preferable for genetic analysis because they can be analyzed directly by the application of simple Mendelian ratios in contrast to families selected by an affected child. The latter require statistical treatment. This report is concerned with the genetic analysis of data for 646 children from 291 families who were under continuous medical supervision for an average period of 10 years.

Material

The parents selected included 224 members of the Pediatric Cardiac Follow-Up Clinic of The New York Hospital, consisting of 192 rheumatic and 32 congenital cardiac patients, 24 consecutive patients with rheumatic heart disease admitted to the Lying-In Hospital, and 43 brothers or sisters of rheumatic members of the Cardiac Clinic. The 291 families, including 646 children, were representative of a mixed population in greater New York City. The living conditions and economic status of two-thirds of the families were considered favorable.

History of the presence or absence of rheumatic fever among unselected mates and their collateral relatives was obtained on initial contact and periodically reviewed during the period of observation.
unselected mate and the majority of collateral relatives were given a complete physical examination at the clinic, including fluoroscopic examination of the heart. The progeny were under continuous close medical supervision in a special pediatric clinic. Periodic physical, fluoroscopic and electrocardiographic examinations were made. In addition, clinical, immunologic and biochemical investigations were conducted among these families during the period of observation. Routine clinic visits were made at least four times a year. Home and clinic visits were made during any intercurrent illness. The majority of children were observed from infancy. The diagnosis of rheumatic fever in parents, collateral relatives and children was based on the occurrence of manifestations of rheumatic fever confirmed by evidence of rheumatic heart disease on physical, fluoroscopic and electrocardiographic examination.

**Method of Genetic Analysis**

The data were arranged in parental mating types and appropriate Mendelian ratios applied. Standard tests for dominant, sex-linked, and recessive inheritance were made. The principal criteria for establishing Mendelian inheritance are as follows:

A. Dominant inheritance passes by direct descent from a parent to half of his children. Individuals who are negative do not transmit the condition to their offspring. Sex-linked inheritance passes usually from a male to his grandson through a daughter who is unaffected. Mates who are negative do not transmit the condition. Daughters of affected males are all carriers although themselves usually unaffected, and transmit to half of their sons.

B. Recessive inheritance, unlike the other types, is transmitted through both parents. A negative individual who has no close relatives with the condition will not transmit it, and all of his children will be free from the condition regardless of the genetic circumstances of his mate. The children of two affected individuals are all expected to be affected. When an affected individual marries a carrier, one-half of the progeny are affected. Among the children of two carriers, one-fourth will be affected.

In order to compute the ratios, the carriers must first be identified. Children of affected individuals are carriers. Among the siblings of cases, two-thirds will be carriers. When the kinship of an individual is less close, the risk of being a carrier is reduced. Due to the small size of human families, carriers can not always be identified by knowledge of the kinship. When this occurs, statistical estimates are used.

D. More complex patterns of inheritance are known in animals, and to some extent in man, but the results of these will approximate the preceding, differing only in the numerical quantities. For present purposes they need not be considered.

E. In studying diseases which exhibit a range in age of onset, adjustments are necessary for children who have not reached the susceptible age. The method for making this adjustment in rheumatic fever has been previously presented.

**Observations**

In table 1 are summarized the source and classification of selected and unselected parents. It will be noted that 222 selected parents were rheumatic, 37 were carriers of rheumatic patients and 32 were nonrheumatic. Twelve of the unselected parents were rheumatic, 41 had rheumatic collateral relatives and 237 were negative.

The age distribution of children of different parental types at last observation is presented in table 2. Among 121 offspring from 52 genetically susceptible families, 89 per cent had passed the peak age of onset of rheumatic fever; 11 per cent were under 6 years of age, 44 per cent were between 6 and 13 years of age, and 45 per cent were past 13 years of age. Among the 525 children of 239 nonsusceptible families, 80 per cent had passed the peak age of onset; 20 per cent were under 6, 56 per cent were between 6 and 13 years of age, and 24 per cent had passed 13 years of age.

The ages at onset of the 43 children who developed rheumatic fever was 2 to 5 years in 25 patients, and 6 to 10 in 18 patients. All experienced one or more episodes of active carditis associated with constitutional symptoms.

**Table 1.—Source and Classification of Families by Parental Diagnosis**

<table>
<thead>
<tr>
<th>Selected Parent*</th>
<th>Unselected Mate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected Parent</td>
<td>Unselected Mate</td>
</tr>
<tr>
<td>I 216 0 0</td>
<td>8 30 178</td>
</tr>
<tr>
<td>II 6 37 0</td>
<td>3 11 29</td>
</tr>
<tr>
<td>III 0 0 32</td>
<td>1 0 31</td>
</tr>
<tr>
<td></td>
<td>222 37 32</td>
</tr>
<tr>
<td></td>
<td>12 41 238</td>
</tr>
</tbody>
</table>

* (I) Rheumatic parent from Cardiac Clinic or Lying-In Hospital. (II) Brothers or sisters of (I). (III) Patients with congenital heart disease from Cardiac Clinic.

In this and succeeding tables: + = rheumatic; C = nonrheumatic member of a rheumatic family (carrier); = nonrheumatic, no rheumatic collateral relatives.
In 20 patients, carditis was subacute, and in two it was the only manifestation. Subcutaneous nodules occurred in four patients, 10 patients experienced one or more attacks of chorea, 25 had polyarthritis and 32 arthralgia. Epistaxis and erythema multiforme occurred in 18 patients. At last observation residual cardiac involvement was present in all of the patients. Enlargement of the left ventricle and left auricle was moderate in 34, and marked in 9 patients. Mitral insufficiency was present in 40, mitral stenosis in 3. No auscultatory murmurs were heard in three patients. There were two deaths, one due to bacterial endocarditis and one to cardiac failure.

**GENETIC ANALYSIS**

Genetic analysis supported the simple recessive hypothesis and excluded sex-linkage, dominant and multiple-gene hypotheses. In table 3 is presented a comparison of the number of cases so far observed and the number expected for different parental family types. The number expected at the present age was obtained by application of an age correction factor. There were 52 families which were considered genetically susceptible and in this group (table 3, a–e) there were 40 cases observed among 121 siblings. The familial incidence was negligible in the genetically nonsusceptible families (lines f–h). Only three cases were observed among 525 children in 239 families.

It will be noted that of 49 cases finally expected.

**TABLE 2.—Age Distribution of Siblings in Genetically Susceptible and Nonsusceptible Families**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Families</th>
<th>No. of Siblings</th>
<th>Total</th>
<th>Under 6 yrs.</th>
<th>6-13 yrs.</th>
<th>Over 13 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ X +</td>
<td>8</td>
<td>15</td>
<td>8</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ X C</td>
<td>35</td>
<td>83</td>
<td>8</td>
<td>33</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>C X C</td>
<td>9</td>
<td>23</td>
<td>4</td>
<td>12</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>121</td>
<td>14</td>
<td>53</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 3.—Comparison of the Number of Rheumatics Observed and Expected Based on Test for Recessive Inheritance.**

<table>
<thead>
<tr>
<th>Mating Type</th>
<th>Families</th>
<th>Siblings</th>
<th>No. of Children Under 6 Years</th>
<th>Cases Observed</th>
<th>Cases Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) + X +</td>
<td>8</td>
<td>15</td>
<td>2</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>(b) + X C</td>
<td>7</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>(c) + X C*</td>
<td>28</td>
<td>63</td>
<td>8</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>(d) C X C</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(e) C* X C*</td>
<td>7</td>
<td>19</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>(f) + X -</td>
<td>183</td>
<td>399</td>
<td>80</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>(g) C X -</td>
<td>30</td>
<td>65</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(h) - X -</td>
<td>26</td>
<td>61</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>239</td>
<td>525</td>
<td>105</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>291</td>
<td>646</td>
<td>119</td>
<td>43</td>
<td>49</td>
</tr>
</tbody>
</table>

(a) Positive mated with positive; in this mating all children are expected to be positive.
(b) Positive mated with negative who is the child of a rheumatic; half of the children are expected to be rheumatic.
(c) Positive mated with negative who is the sibling of a rheumatic; one-third of the children are expected to be rheumatic.
(d) Two negative individuals who are both children of rheumatics; one-quarter of the children are expected to be rheumatic.
(e) Two negative individuals, both of whom have some close kin who are rheumatic; fewer than one-quarter of the children are expected to be rheumatic.
(f) Positive mated with negative who has no rheumatic parentage or close kin (siblings, aunts, uncles, nieces and nephews); no rheumatic children are expected.
(g) Negative who has a rheumatic parent or sibling mated with a negative with no rheumatic parentage or close kin; no rheumatic children are expected.
(h) Both parents negative, with no rheumatic parentage or close kin; no rheumatic children are expected.

C*—nonrheumatic parent who had a rheumatic close relative other than parent. C is a nonrheumatic parent who had one rheumatic parent.
pected, 40 have so far been observed. Since all of the siblings had not passed the peak age of onset of the disease, the data were corrected for present age. On this basis, 45 cases are expected at the attained age and 43 are observed. Good agreement is noted at the attained age of the children. A few additional cases are expected in the susceptible families as the younger children reach the ages of maximum incidence. It is unlikely that any considerable number of new cases will occur at older ages. In the previously reported study, 130 individuals who were non-rheumatic at the ages of 13 to 25 years have remained non-rheumatic during 11 additional years.

**Comment**

Genetic analysis of human data is limited by the relatively small family size as compared with experimental material. This may preclude complete expression of an hereditary trait. In addition, diagnostic difficulties may prevent adequate ascertainment of cases. This is particularly true in the diagnosis of rheumatic fever in adults since physical signs of rheumatic heart disease often regress and childhood illness is not accurately recalled. In the absence of a specific diagnostic test, complete reliance is frequently placed on historical information or a limited physical examination. In this study, evidence of rheumatic heart disease determined by physical, fluoroscopic and electrocardiographic examinations was required for confirmation of a diagnosis of rheumatic fever. In spite of the rigid diagnostic criteria utilized, there were probably a few errors in parental classification in families where information was limited concerning collateral relatives. The continuous medical supervision of the families, the majority from infancy to past the peak age of onset, minimized possible diagnostic errors in the children.

The conclusion that the pattern of inherited susceptibility is a recessive character rests on the agreement between observation and expectation. Equally important for the interpretation of recessiveness are the observations in the lower half of table 3, (f-h). The insignificant number of cases in 239 families where one parent is non-rheumatic and not known to have close kin who are rheumatic is strong evidence that recessive inheritance is involved.

Complete agreement, with a specific hereditary mechanism may not always be obtained even in conditions of proven heredity. It is well known in experimental material that certain modifying factors, endogenous or exogenous, may influence the expression of hereditary traits. This may also occur in human disease. The differences in type and severity of manifestations of rheumatic fever among members of a family suggest different degrees of susceptibility which perhaps reflect endogenous modifying influences. There are probably also exogenous factors which may influence the expression of the disease in a susceptible child.

The adequacy of recessive inheritance to describe the distribution of cases among these families does not exclude a more complicated mechanism. It is, however, the simplest hypothesis, requiring no additional assumptions.

The results of this investigation confirm the conclusion of simple recessive inheritance previously reported. It may be noted that the analytic procedures in the two studies were different. The procedures in the present study are more satisfactory because they do not require the statistical adjustments that must be made when the affected child is the index case. When data are collected based only on parental selection, the standard Mendelian methods of analysis are fully adequate. Where information on the antecedents of the parents is meager, statistical analysis based on estimates of population frequency is used to determine the pattern of inheritance. This method of analysis requires a series of families collected as a random sample. This important condition is not fulfilled in clinic families, and the use of this method is therefore not warranted.

The primary role of heredity in the familial concentration of rheumatic fever has been confirmed in this and other published investigations. These observations emphasize the importance of identifying the genetically susceptible family to facilitate early diagnosis and treatment. The medical supervision of these families affords an opportunity for investigation of the nature of the inherent factor responsible for susceptibility. They are also useful for
the study of exogenous factors which may be responsible for the development of rheumatic fever in a susceptible child. Current etiologic concepts may be explored within this framework. Clinical, immunologic and biochemical pilot investigations have so far revealed no significant differences among susceptible and nonsusceptible children in these families. It is of interest that the incidence and frequency of illness, particularly respiratory infections, was comparable in the two groups.

The demonstration of hereditary susceptibility does not exclude the operation of environmental factors. Like most published family studies the present investigation concerns a clinic population which excludes families of higher economic level. The economic status and living conditions which prevailed among the susceptible and nonsusceptible families was comparable and far superior to those in the earlier investigation.

It is frequently stated that the incidence of rheumatic fever may be declining. The data collected during the past 25 years have been examined in order to see whether the familial incidence has changed. There is no evidence of reduced penetrance in recent years. This is apparent in the positive by positive families where the observed incidence in families completed 10 or more years ago is the same as in the current series. It is of interest that the age of onset and pattern of rheumatic fever were comparable in both series of families. These observations would seem to indicate that the prevalence and pattern of rheumatic fever in greater New York City has not changed significantly in the past two decades.

**Summary**

The families of 291 selected parents including 646 children were under continuous medical supervision for an average period of 10 years.

The parents selected included 224 members of the Pediatric Cardiac Follow-Up Clinic of The New York Hospital, 24 consecutive patients with rheumatic heart disease admitted to the Lying-In Hospital, and 43 brothers or sisters of rheumatic members of the Cardiac Clinic.

Forty of 121 children from genetically susceptible families developed rheumatic fever compared with 3 of 525 children from nonsusceptible families.

Genetic analysis of the various mating types gave good agreement with simple recessive inheritance while excluding other mechanisms. Corroboration of the previous conclusion that rheumatic fever susceptibility is inherited as a simple recessive trait was obtained.

**Sumario Español**

Las familias de 291 padres seleccionados incluyendo 646 hijos estuvieron bajo continua supervisión médica por un tiempo promedio de 10 años.

Los padres seleccionados incluyeron 224 miembros de la Clínica Cardíaca de Progreso “Follow-up” de Pediatría del Hospital de Nueva York, 24 pacientes consecutivos con enfermedad reumática del corazón admitidos al Lying-In Hospital y 43 hermanos o hermanas de miembros reumáticos de la Clínica Cardíaca.

Cuarenta de los 121 pacientes de familias geneticamente susceptibles desarrollaron fiebre reumática comparados con 3 de 525 niños de familias no susceptibles.

Análisis genético de los varios tipos de apareamiento produjo buena concordancia con herencia recesiva sencilla a la vez que excluyó otros mecanismos. Corroboration de la conclusión previa que la susceptibilidad a la fiebre reumática se heredó como un rasgo sencillo reesivo se obtuvo.

**Acknowledgment**

We wish to acknowledge our indebtedness for helpful suggestions in the genetic analysis of the data to Dr. Bruce Wallace, Biological Laboratory, Cold Spring Harbor, Long Island, N. Y.

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