STUDIES OF RHEUMATIC DISEASE[1]

III. FAMILIAL ASSOCIATION AND AGGREGATION IN RHEUMATIC DISEASE

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AT THE present time the available evidence is insufficient to establish definitely the etiology of rheumatic disease although promising work has been done and is in progress. It has long been recognized that there is a tendency for the disease to occur more frequently in some families than in others. In a previous study (1) based upon the records of the families of patients admitted to the Cardiac Clinic of the Harriet Lane Home, careful statistical analysis suggested that hereditary constitution might be a factor in causing this aggregation. The evidence presented, however, did not exclude the possibility that the familial aggregation might be due solely or principally to common exposure either to a microbic cause and/or to any environmental factor, such as nutritional deficiency, which favored development of the disease.

If the disease were due solely to heredity, it would be expected that it would manifest itself in the various members of the family in such a way that its first acute manifestations (onsets) would be scattered along the time scale of family experience in a random fashion or affected solely by the age of its members. On the other hand, if in addition to hereditary predisposition, an environmental factor or factors were concerned, it would be expected that during certain periods of time in the family experience the risk of attack would vary according to the degree with which the environmental factor was acting. Thus we would expect a certain amount of group-

ing of the onsets of new cases occurring in the family, and after one member had developed acute manifestations of the disease there would be an increased incidence among his familial associates. This expectation would be justified regardless of the environmental factor involved, whether it be an infective agent and/or some other common environmental factor necessary for the development of the disease. In other words, a tendency toward the grouping or aggregation of new cases within the family would appear at certain times, as in the case of infective disease such as diphtheria, scarlet fever, tuberculosis, and in nutritional deficiencies like pellagra.

To elucidate this relationship, the records of the group of families previously used in the study of the hereditary factors have been analyzed to determine the relationship of the first appearance of rheumatic manifestations[3] (onsets) in the various members of these families along a time axis.

MATERIAL AND METHODS

The data upon which this report is based have been extracted from the medical records of ninety-six consecutive admissions of white children to the Cardiac Clinic of the Harriet Lane Home because they were suffering from rheumatic disease, and from the epidemiological record of this disease in their parents and siblings. A manifestation of rheumatic disease was defined as chorea, rheumatic fever, or rheumatic heart disease, and this definition is the same as that used in the two preceding articles (1, 2). Detailed information for each individual in ninety-five[4] of these families is available with respect to the date of birth, date of last observation, and the date of onset, duration, and type of each manifestation of rheumatic disease. The data relative to the rheumatic manifestations have, in most instances, been confirmed by hospital records. The relationship between the acute manifestations of rheumatic disease

[3] This analysis deals only with the time relationship of primary onsets; second and subsequent attacks in any member have been considered as recurrences.

[4] One family in which the records are incomplete has been excluded from the study.
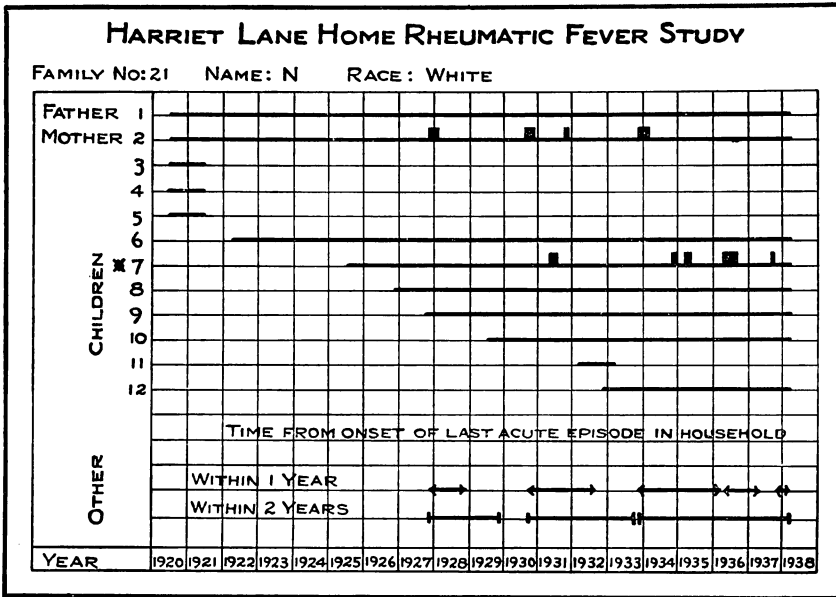
Fig. 1. FAMILY GRAPH. Solid line indicates life-experience in the household. Acute
episodes are indicated by solid blocks on top of line.

in the various members of each family, and the age of each indi-
vidual when exposed to these attacks, can be ascertained from these
reports. As an aid in this analysis, family graphs were drawn for
each family showing the intrafamilial relationship of all attacks of
rheumatic disease. A sample graph is shown in Figure 1.

In order to hold the factor of heredity constant, as far as possible,
the families were divided according to whether or not their parents
had a history of rheumatic disease. There were forty-three families
in the group in which one or both parents were rheumatic, and fifty-
two families in which neither parent had a rheumatic history. The
children of these families have been studied to determine if an in-
creased risk of developing the disease was associated with the occur-
rence of an acute episode of the disease in any other member of the
household (adult or child).

It should be noted that the ninety-five families under study were
selected because at least one member (a child) was admitted to the

clinic suffering from rheumatic disease. The children who are responsible for the inclusion of their families in the study are known as "index cases" to distinguish them from their siblings who enter the study because of their familial relationship. The index case is not necessarily the first case to occur in the family, but it is the first to come to the clinic suffering from the disease. Because index cases are the means through which the families are selected and, by definition, must have had an attack of rheumatic disease, they have been excluded from the tabulations in order to avoid bias and attention has been confined to the occurrence of the disease in their siblings who are unselected, except with regard to their familial relationship.

The final composition of the group studied was:

	Number of Families	Number of Siblings of Index Cases
Rheumatic Disease in Parents	43	156
No Rheumatic Disease in Parents	52	191

The life-experience of these siblings, in each of the above groups, has been divided into that which preceded familial association[5] with another member of the household (adult or child, including index cases) suffering from an acute manifestation (primary or recurrence) and that which followed such association. By this procedure it is possible to compare the incidence of new cases in the children during these two periods.

The occurrence of rheumatic disease in the children of these families could be expressed as the percentage who had the onset of their first attack before, as compared to after, association with an acute episode, but such a statement is not fully satisfactory because it fails to take into consideration the time during which each was at risk during these periods and the possible differences in age sus-

[5] The word association is preferred because the terms "exposure" or "contact" would imply that the effective environmental factor is opportunity for transmission of an infective agent. For present purposes it is desirable to avoid this assumption.

ceptibility. For this reason, the experience of these children has been recorded in the terms commonly applied in the general population to express incidence of any disease, namely, the age-specific annual rates of morbidity.

In order to state the observations on this group in these terms it is necessary to reduce the prior and subsequent experience to a comparable base. This can be done by expressing the experience of these children in person-years of life before and after the date of the first intrafamilial association with an acute episode of the disease. By this method consideration can be given not only to the number of children in the family group, but also the length of time and the various ages during which each child was under observation.

If the purpose is to calculate morbidity prior to familial association with an acute attack, the age at which observation begins is at birth, because all of these children entered their respective families at birth. The age at which observation ends is dependent upon the occurrence of the first of four possible events: (*1*) death, (*2*) familial association with an acute attack in another member of the family, (*3*) onset of rheumatic disease, and (*4*) termination of observation without association. If the purpose is to show morbidity subsequent to association the observation begins with the age attained when first associated with an acute attack and ends with either (*1*) death, (*2*) onset of rheumatic disease, or (*3*) termination of observation. The actual procedure necessary to convert the observations into person-years of experience is that described by Frost (3) and Stewart, Gass, Gauld, and Puffer (4) in their studies on tuberculosis.

INCIDENCE OF RHEUMATIC DISEASE IN THE CHILDREN OF THE FAMILIES
OF RHEUMATIC INDEX CASES, PRIOR AND SUBSEQUENT TO EXPOSURE
TO ACUTE RHEUMATIC MANIFESTATIONS IN ANY MEMBER
OF THE HOUSEHOLD

The experience of the children in the study group expressed in person-years, along with the cases of rheumatic disease, and the

Age	Prior to Association with an Acute Episode			Subsequent to Association with an Acute Episode		
	Person-Years	Cases	Rate per 100	Person-Years	Cases	Rate per 100
	NO PARENTAL HISTORY OF RHEUMATIC DISEASE					
Under 2	338.5			20.50		
2-4	425.5			62.50	2	3.20
5-14	706.5	10	1.41	336.00	9	2.68
15+	89.5	2	2.23	121.75	2	1.64
Total Over 2 Years	1,221.5	12	0.98	520.25	13	2.50
	PARENTAL HISTORY OF RHEUMATIC DISEASE					
Under 2	243.0			48.50		
2-4	257.0	4	1.55	128.25	3	2.34
5-14	305.0	6	1.96	397.50	18	4.53
15+	17.0			99.00	4	4.04
Total Over 2 Years	579.0	10	1.73	624.75	25	4.00

Table 1. Life-experience, cases of rheumatic disease, and annual attack rates among the siblings of ninety-five rheumatic index cases, prior and subsequent to first association with an acute manifestation of the disease, and according to the history of rheumatic disease in the parents.

annual morbidity rates are shown in Table 1. In this table the children are grouped according to the history of rheumatic disease in their parents, and the experience divided into that which preceded and that which followed first association with an acute episode.

In calculating the total incidence of rheumatic disease for these two periods, only the experience of the children after their second birthday has been used. This has been done because the occurrence of rheumatic manifestations under two years of age is rare, and no cases occurred during this age period in these families.[6]

When the annual rates for all ages over two years are compared, before and after association, it is found that the incidence in both groups of children is more than doubled in the period following

[6] The effect of this deduction from the total life-experience has been to minimize the differences found between the incidence in the two periods.

association with an acute episode in the household. In those children whose parents gave no history of rheumatic disease, the rate increased from 0.98 to 2.50 per 100 per year, while in those whose parents had a history of rheumatic disease the increase was from 1.73 to 4.00. Although based upon a comparatively small experience, these differences are sufficiently large to have statistical significance; the probability of a difference of this size occurring by chance in this group is only two in one hundred trials.

It should be further noted that, although the experience in each age group is not large enough to give statistical significance to the differences, with one exception the age-specific rates are consistently higher after familial association with the acute disease.

From the data in Table 1 it is also possible to compare the incidence in children of rheumatic and nonrheumatic parents. This comparison may be expressed in a ratio as follows:

Ratio of Incidence

$$\frac{\textit{Children of Rheumatic Parents}}{\textit{Children of Nonrheumatic Parents}} \times 100$$

Prior to Association with an Acute Episode $\dfrac{176}{100}$

Subsequent to Association with an Acute Episode $\dfrac{160}{100}$

It is interesting to note that the incidence is 60 to 80 per cent higher in the children of rheumatic parents than in the children of nonrheumatic parents, and that this ratio is not materially altered by association with an acute manifestation of the disease.

THE TIME RELATIONSHIP BETWEEN ASSOCIATION AND THE ONSET OF NEW CASES OCCURRING SUBSEQUENTLY

The analysis up to this point has dealt with the total incidence of new cases of rheumatic disease among siblings of index cases which preceded and followed the *first* familial association with an acute

episode. This fails to take into consideration the fact that a child might be associated with more than one acute episode in other members of the family before showing clinical evidence of having contracted it. If the oc- currence of an acute epi- sode in one member of the family is an indica- tion that an environ- mental factor or factors, which have etiological significance, are operat- ing at this particular time, then it would be expected that during the time interval closely fol- lowing this event the risk of attack would be increased for other members in the same family. This in turn would be reflected in an increased case rate during a proximal subsequent period as com- pared with later periods.

Table 2. Time interval between last prior association with an acute episode in another member of the family and the onset of rheu- matic disease in thirty-eight cases.

Interval	Number of Cases
Less Than 1 Year	15
1-2 Years	8
2-3 Years	5
3-4 Years	1
4-5 Years	5
5-9 Years	2
Over 10 Years	2
TOTAL	38

In Table 2 is shown the distribution of thirty-eight cases which occurred among the siblings of index cases according to interval elapsing between the time of association with the last prior acute episode and the time of onset.

It will be noted that fifteen of the thirty-eight cases had their onset within one year, and twenty-three (15 + 8) within two years of their last prior association with an acute episode in another member of the family. At first glance the distribution suggests that the risk is greatest among these children within a year or two fol- lowing association with an acute attack. This tabulation, however, does not show the number of cases in proportion to the number of persons still under observation in the stated intervals and, accord- ingly, does not indicate the relative risk in these periods.

Using the onset of each separate acute episode as a focal point,

TIME FROM LAST ASSOCIATION WITH AN ACUTE EPISODE	PERSON-YEARS EXPERIENCE	CASES ONSET DURING PERIOD	RATE PER 100 PERSON-YEAR
	PARENTS—NO HISTORY OF RHEUMATIC DISEASE		
Less Than 1 Year	257.50	7	2.7
1 to 2 Years	120.75	4	3.3
More Than 2 Years	142.00	2	1.4
	PARENTS—HISTORY OF RHEUMATIC DISEASE		
Less Than 1 Year	312.25	8	2.5
1 to 2 Years	130.50	4	3.1
More Than 2 Years	182.00	13	7.1

Table 3. Showing the incidence of rheumatic disease subsequent to first association with an acute manifestation according to its proximity in time to acute attacks in other members of the family.

it has been possible to divide the total experience of each child, subsequent to first association, according to its proximity to the onset of the last acute attack in another member of the family. This division was made in three time bands: (1) the experience which fell within one year following association with an acute episode, (2) that which was more than one year and less than two years following association, and (3) that which was more than two years following association.[7]

After the total experience following first association of each child was divided in this way, that of the group as a whole was obtained by adding the individual experiences together. Rates can be calculated for each interval by dividing the cases having their onset within it by the corresponding total person-years experience. These rates express the annual incidence of the disease in those at risk according to the proximity to *all* acute episodes with which the children were associated.

Although the experience is small, it shows no tendency for new cases appearing in other members of the family to be grouped or

[7] In making this division, the procedure was to calculate for each individual the amount of experience following first association which was within one year and that which was

aggregated closely about the time at which one member comes down with acute manifestations. Indeed, if any inference at all is within two years of association with an acute episode in the household. The detail for calculations on Individual 6, Family 21 (shown graphically in Figure 1), was:

BEGINNING OF ASSOCIATION		END OF PERIOD		EPISODES WITH WHICH ASSOCIATED		NUMBER OF MONTHS IN PERIOD
Date	Age	Date	Age	Date of Onset	Individual Attacked	
A. EXPERIENCE WITHIN ONE YEAR OF BEGINNING OF ASSOCIATION WITH AN ACUTE EPISODE						
December, 1927	5	December, 1928	6	December, 1927	No. 2	12
September, 1930	8	November, 1932	10	September, 1930	No. 2	
				June, 1931	No. 7	
				November, 1931	No. 2	26
December, 1933	11	April, 1936	14	December, 1933	No. 2	
				December, 1934	No. 7	
				April, 1935	No. 7	29
May, 1936	14	May, 1937	15	May, 1936	No. 7	12
October, 1937	15	February, 1938	15	October, 1937	No. 7	5
						84
B. EXPERIENCE WITHIN TWO YEARS OF BEGINNING OF ASSOCIATION WITH AN ACUTE EPISODE						
December, 1927	5	December, 1929	7	December, 1927	No. 2	24
September, 1930	8	November, 1933	11	September, 1930	No. 2	
				June, 1931	No. 7	
				November, 1931	No. 2	38
December, 1933	11	February, 1938	15	December, 1933	No. 2	
				December, 1934	No. 7	
				April, 1935	No. 7	
				May, 1936	No. 7	
				October, 1937	No. 7	51
						113
C. TOTAL EXPERIENCE SUBSEQUENT TO FIRST ASSOCIATION WITH AN ACUTE EPISODE						
December, 1927	5	February, 1938	15		No. 2 and No. 7	123

Final allocation of experience:

Experience within one year of association (A) $\frac{84}{12}$ = 7 person-years.

Experience more than one and less than two years following association (B-A)

$\frac{113-84}{12}$ = 2-5/12 person-years.

Experience more than two years following association (C-B) $\frac{123-113}{12} = \frac{10}{12}$ person-years.

permissible, it is the contrary one, *i.e.,* that after the disease has oc-
curred in one member of the family it may be a matter of years
rather than of months before another member is attacked.

SUMMARY AND DISCUSSION

The children of ninety-five families, in each of which one child
entered the clinic because of some rheumatic manifestation, were
studied with respect to the relationship of the occurrence of the
disease among them to familial association with an acute episode
of the disease in another member of the family. As far as possible
hereditary factors were held constant throughout the analysis, and
the index cases were excluded from the tabulations because of the
bias which they introduced.

The analysis showed that the risk of contracting the disease
among the siblings of the index cases was increased, following asso-
ciation with an acute episode in another member of the family, to
more than twice that which prevailed prior to this association. This
suggests that there is an environmental factor which plays a rôle in
the causation of this disease.

The children of rheumatic parents had higher attack rates than
the children of nonrheumatic parents, both before and after their
first familial association with an acute episode. The interpretation
of this finding should be made with caution because the children
who have parents with a rheumatic history are, in most instances,
also associated with what might be called the chronic quiescent
phase of the disease in these parents. The higher incidence in these
children could, therefore, be due either to an increased hereditary
susceptibility or to long continued association with the disease in
chronic form. Considered along with the findings of the previous
article (1), the first would seem to be the more probable explana-
tion, *i.e.,* that heredity plays a definite rôle in the etiology of the
disease.

The time relation between episodes in the family and the occur-

rence of subsequent cases in other members did not show a definite tendency for the incidence of subsequent attacks to be highest within short time intervals of an association with acute episodes. This finding would suggest that either long continued exposure to the cause (whether it be parasitic or nonparasitic) is necessary, or that the disease is slow in developing to the point where it becomes clinically manifest. In this respect, if it be due to an infection, it therefore resembles tuberculosis rather than an acute infection such as scarlet fever or diphtheria, and the results of exposure in any household should not be measured in weeks or months but in years.

These findings are consistent with the hypothesis that in the etiology of rheumatic disease there are both hereditary and environmental factors involved, and that the environmental factor to produce the disease must act over a long period of time, and/or the disease has a long period of subclinical development before becoming manifest. They are consistent with such an hypothesis, but do not prove it, because other explanations could fit the observed facts.

CONCLUSIONS

Careful observations over varying periods of time on 347 siblings of ninety-five children who were admitted to the clinic because of some rheumatic manifestations showed that the attack rate:

1. Increased after association with an acute episode.

2. Was higher among the children of rheumatic parents both before and after such association.

3. Showed no tendency, following association with an acute episode, to be higher within a short proximal period as compared with a more remote later period.

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