of Iowa and Iowa State College stand in both Table II and Table III, while Pennsylvania State and Michigan State with an average of about five fields each per year are so far behind their respective state universities that they are excluded from Table III.

Perhaps the most interesting observation from all the tables is that of the entire 14,985 dissertations almost one third were written in the field of chemistry, or well over one third if we include those in biochemistry. Another observation is that well over one third of all the dissertations (5,684 out of 14,985) were accepted by the first eight institutions in Table No. II. Verily we are in an age of chemistry which is dominated by a few great universities.

Any one interested in seeing the titles of these dissertations should consult a file of the nine annuals. These titles reveal the particular lines along which research is being pressed to-day.

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SPECIAL ARTICLES

THE INTEGRATION OF GENETIC AND EPIDEMIOLOGICAL METHODS OF ANALYSIS IN RHEUMATIC FEVER[1,2,3]

IN previous genetic and epidemiological studies of a series of rheumatic families, it was concluded that hereditary factors are primarily responsible for the familial concentration of rheumatic fever. It was postulated that genetic susceptibility for rheumatic fever is transmitted as a single autosomal recessive gene. It was also indicated that age susceptibility must be considered in the study of the familial epidemiology of rheumatic fever.[4,5]

In order to analyze the interaction of the genetic and epidemiological aspects of rheumatic fever, analytical techniques were developed which permit a numerical description of the sequence of events in a group of rheumatic families.

In classical genetic analysis, the final number of cases is estimated by the application of appropriate genetic formulae. In this study, the methods were extended by predicting the final number of cases in the families prior to the time when all the children present who could eventually become cases had an opportunity to be realized. Such a prediction represents an average estimate of the number of genetic susceptibles present in the families at the time of analysis.

This procedure permits the expression in numerical terms of the genetic risk for a group of families, an individual family, or for members within a family group at any time during their life experience. Within a family, the genetic risk or factor may be divided equally among all siblings, or apportioned unequally with respect to any specific variable such as age, sex or exposure.

It is obvious that in rheumatic fever, where the peak age of onset in children occurs at about 6 years of age, the current age risk for a two-year-old child or a twelve-year-old child is less than that for his six-year-old sibling. In order to apportion the genetic risk with respect to this age risk, a numerical measure of the age expression of rheumatic fever was obtained.

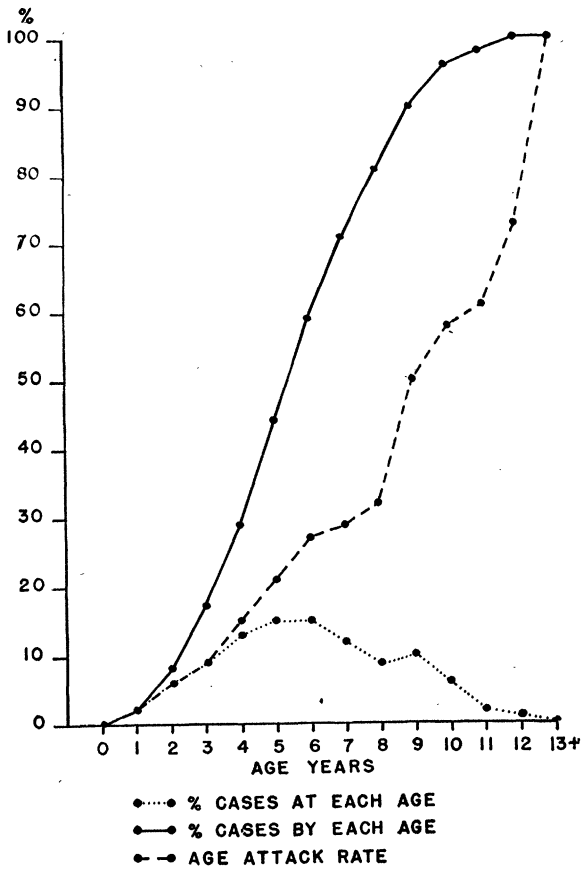

FIG. 1. Age factors derived from a rheumatic series of 688 case onsets.

[1] From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

[2] This work was aided by a special grant from the Commonwealth Fund.

[3] We gratefully acknowledge our indebtedness to Dr. Lowell J. Reed for his continued interest and constructive criticism during the progress of these studies.

[4] M. G. Wilson and M. D. Schweitzer, *Jour. Clin. Invest.*, 16: 555, 1937.

[5] M. G. Wilson, "Rheumatic Fever." New York: The Commonwealth Fund, 1940. Chapter III, pp. 21–65.

From an independent series of 688 rheumatic children whose onsets occurred between the ages of 2 and 13 years, several standard expressions of case incidence were derived which were found valid by analysis for defining the age risk under various circumstances (Fig. 1).

Using age and genetic factors in combination, it was possible to estimate the number of case onsets expected at various times during the life experience

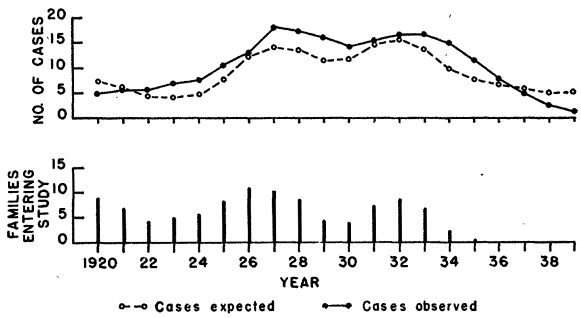

FIG. 2. Annual incidence of cases expected and observed during a twenty-year period, 1920–1939, in 102 rheumatic families.

of a group of 109 rheumatic families, including 456 rheumatic and non-rheumatic siblings.

The annual incidence of case onsets over a period of twenty years from 1920 to 1939 was estimated. Good agreement was obtained between expectation and observation (Fig. 2). It is apparent that in each year the total number of individuals defined by this procedure as genetic susceptibles of a susceptible age were realized as cases.

The general procedure was to assign to each sibling an equal fraction of the total final genetic expectancy for his family, correcting this for age in each calendar year using the cumulated age factor. Siblings were entered from the calendar year in which the families first came under observation. Siblings born subsequent to this year were entered at birth. In order to obtain the number of cases expected in any year, the total cumulated expectancy for the year preceding was subtracted from that of the current year, giving the annual expectancy. Case onsets were treated similarly.

In a communicable disease the occurrence and distribution of primary and secondary cases in a family is of epidemiological significance. The primary case in the family is frequently a source of exposure for other members of the household. Some observers have suggested that in rheumatic fever an active case constitutes a risk for the other siblings in the family.[6, 7]

[6] R. L. Gauld and F. E. M. Read, *Jour. Clin. Invest.*, 19: 393, 1940.

[7] A. Rosenblum and R. L. Rosenblum, *Am. Heart Jour.*, 23: 71, 1942.

When age and genetic factors were used to estimate the number of primary and secondary cases expected in this series of families, adequate agreement was obtained between cases expected and actually observed. In 59 families where both parents were negative, 57.92 primary and 43.61 secondary cases were expected when 60 and 41 cases, respectively, were observed. Similar agreement was found in the group of families where one parent was rheumatic. It is apparent that the risk for susceptible children to develop rheumatic fever is no greater before or after the onset of a case.

The primary and secondary cases expected were estimated as follows:

At the time of onset of the primary case, there is a specific sampling problem, since regardless of which siblings are genetically susceptible in the families, no cases have occurred up to the time of analysis. The total genetic expectancy for the family was apportioned unequally according to the age chance for each sibling to be the first case, using the age incidence factor. The actual number of primary cases expected was obtained by the application of the age attack rate factor.

The prediction of secondary cases was obtained by the direct use of simple genetic ratios corrected for current age risk using the cumulated age incidence factor.

In these analyses by the simultaneous application of age and genetic factors, the intrafamilial pattern of spread of rheumatic fever in 109 families was described in numerical terms. It is of epidemiological significance that during a period of twenty years, the annual incidence of cases and the occurrence of primary and secondary cases were satisfactorily estimated in these families on an age and genetic basis. It is apparent that whatever the nature of the agents responsible for the onset of the disease in genetic susceptible children at a susceptible age, they were uniformly operative at all times during the life experience of these families.

Interpretation of the fundamental basis for these findings must be speculative. It is reasonable to consider that the genetic risk is primary. It is possible that the age risk is inherent in the genetic risk. However, it is more likely that the age risk is secondary, reflecting the interval of time necessary for the expression or development of manifest disease.

The integration of genetic and epidemiological methods of analysis is an approach hitherto not formulated for rheumatic fever. The methods described may be utilized to evaluate etiologic concepts as well as prophylactic measures. Their usefulness in these studies suggests that their extension to other comparable problems of investigation may be profitable.

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