THE RELATION OF UPPER RESPIRATORY INFECTIONS TO RHEUMATIC FEVER IN CHILDREN

I. The Significance of Hemolytic Streptococci in the Pharyngeal Flora During Respiratory Infection ¹

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(Received for publication December 1, 1934)

The view that the rheumatic process is initiated or activated by streptococcal respiratory infections has met with wide acceptance. The evidence which has accumulated in support of this conception originated in the long recognized association of tonsillitis and rheumatic fever, as well as the so-called rheumatic sequelae of scarlet fever.

The more recent observations of Glover (1), Schlesinger (2), Coburn (3), Collis (4) and others have stressed a broader view of streptococcal respiratory infections and have included such infections as pharyngitis, common cold, sinusitis, otitis, bronchitis and cervical adenitis. It is important to note that the presence of hemolytic streptococci in the flora of the throat during these infections has been considered by many observers as diagnostic of a streptococcal respiratory infection, the criteria for diagnosis being bacteriologic rather than clinical. Coburn and Pauli (5) from extensive epidemiological, bacteriological and immunological studies postulate that the hemolytic streptococcus initiates the rheumatic process.

The majority of investigators emphasize the *quiescent period* (of apparent health), a period of approximately seven to twenty-one days between the respiratory infection and the subsequent rheumatic recurrence, lending support to the hypothesis that rheumatic fever is allergic in nature. Paul and Salinger (6) from historical family studies have described simultaneous waves of respiratory infections and rheumatic recrudescences in several members of the household. Similar observations have been reported by various investigators, occurring in schools, camps, hospital wards and convalescent homes. In some instances

¹ This study was conducted under a special grant from the Commonwealth Fund.

these episodes have assumed epidemic proportions.

It must be conceded that these various observations appear quite convincing, but their possible specific etiological significance may be questioned in view of the known frequency of respiratory infections in children in the seasons when rheumatic activity is likely to occur. This is illustrated by the following observations conducted for a two year period, 1930 to 1932, in which 222 ambulatory rheumatic subjects five to fifteen years of age were under close observation as part of another investigation. These children were under the medical supervision of the Heart Clinic of the New York Nursery and Child's Hospital and were seen at least monthly. The majority of the subjects were under our care from the onset of the first rheumatic symptom. Every effort was made to record accurately any illness suffered by these children.

The seasonal incidence of respiratory infections and rheumatic recurrences experienced by these subjects is graphically presented in Chart 1.

Here may be noted the three seasons of increased incidence of respiratory infections—fall, winter and spring—common in this section of the country. The trend of the curves representing the seasonal incidence of rheumatic recurrences, while somewhat similar to the respiratory curve, is significantly lower, showing the greatest incidence in the spring season. During this two year period 222 subjects experienced 783 respiratory infections and 401 rheumatic recurrences. It is of some significance that less than 10 per cent of these rheumatic episodes were preceded within a period of three weeks by a respiratory infection. Bacteriological studies of the pharyngeal flora were not made in those years.



CHART 1. SEASONAL INCIDENCE OF RHEUMATIC RECURRENCES AND RESPIRATORY INFECTIONS 1930-1931 This chart illustrates the similar seasonal incidence of respiratory and rheumatic infections for 222 ambulatory rheumatic subjects.

In view of the etiological significance attributed to the presence of hemolytic streptococci in the flora of the throat during respiratory infections, it was considered worth while to include bacteriological and immunological observations in the following investigations.

To evaluate the possible relation of respiratory infections to rheumatic fever, the family was taken as a unit for study. Ninety-two families including 123 rheumatic children, members of the Cardiac Clinic, were selected for this study. These families have been under our observation for a period of two to fourteen years. Since September 1932 all the children attended the New York Hospital. About one-half of the rheumatic subjects are included in the 1930–1931 study.

Information as to the incidence and *time relationship* of respiratory and rheumatic attacks was obtained as accurately as possible. Trained investigators visited the homes weekly and recorded upon a family chart the symptoms of the illness of every member of the household. When necessary, physicians visited the homes. Weekly throat swabs for cultures were taken routinely from all rheumatic children, from a series of controls and from every available member of the household during illness. Children visited the clinic for examination at least monthly. The majority of the members of the household were examined during the year. Observations were continued on children admitted to the pavilions and convalescent cottages of the New York Hospital during the period of study.²

A more detailed discussion of the bacteriological technique and criteria followed in these studies is included in the third paper of this series (7). Throat culture specimens were taken at regular weekly intervals, in some instances more frequently. After inspection of the pharynx, the surface was rubbed with a sterile dry cotton swab. Blood agar plates were inoculated and incubated for twenty-four hours. The relative number of each type of colony was estimated and recorded numerically from 0 to 4. The relative number of colonies of hemolytic streptococci isolated from the pharyngeal flora of each subject

² We wish to acknowledge our indebtedness to the resident staff of the New York Hospital and to Miss Marie L. Troup, Superintendent of the New York Hospital Convalescent Cottages.

was recorded and correlated with the clinical signs and symptoms.

The following rheumatic manifestations were recognized as evidence of activity: active carditis, chorea, arthritis, growing pains, pains in the joints, eruptions of the skin and rheumatic nodules.

Respiratory infections included the common cold, nasopharyngitis, tonsillitis, otitis, cervical

throat and the high incidence of respiratory infections in contrast to the insignificant rise of rheumatic recurrences during the months of March, April and May.

During the year, 98 per cent of the subjects experienced a total of 649 respiratory infections. About one-third of the respiratory infections were associated with either marked local or constitutional symptoms, the remaining were common



CHART 2. MONTHLY INCIDENCE OF RHEUMATIC RECURRENCES AND RESPIRATORY INFECTIONS EXPERIENCED BY 123 RHEUMATIC SUBJECTS 1933-1934

adenitis and bronchitis. When such infections were associated with the presence of hemolytic streptococci in the pharyngeal flora, they were designated as "streptococcal" respiratory infections for brevity. This, we believe, is in accord with the criteria apparently accepted in comparable investigations, although contrary to our own conception.

A comparison of the monthly incidence of respiratory infections and rheumatic recurrences experienced by the 123 rheumatic subjects over a period of twelve months, from September 1933 to September 1934, is graphically presented in Chart 2. Of particular interest is the increased incidence of hemolytic streptococci in the flora of the colds. Many children suffered from persistent ethmoiditis and sinusitis during the period of observation. Three hundred and fifty-three (54 per cent) of the total respiratory infections were associated with hemolytic streptococci in the pharyngeal flora. In about one-third hemolytic streptococci predominated in the pharyngeal flora.

The designation, streptococcal respiratory infection, judging from the recent literature, is solely a bacteriological distinction and does not appear to be based on any diagnostic local signs or symptoms in the majority of instances. That such a bacteriological differentiation of respiratory infections would not appear to be a valid one, is indicated by the following. During the months



CHART 3. RELATIVE INCIDENCE OF RESPIRATORY INFECTIONS AND RHEUMATIC RECURRENCES 1933-1934 (123 RHEUMATIC SUBJECTS)

of March, April and May, hemolytic streptococci appeared in the pharyngeal flora in the majority of the subjects. It is significant that during this period hemolytic streptococci predominated in the pharyngeal flora of 50 per cent of the subjects who were well, 40 per cent during respiratory infections and 10 per cent during rheumatic activity. It is of interest that the majority of these respiratory infections were the common cold.

In marked contrast to the prevalence of respiratory infections during the year was the relatively low incidence of rheumatic recrudescences. Of the total 649 respiratory attacks only 16 per cent were associated with rheumatic activity. There did not seem to be any direct relation between the pharyngeal flora, or the type or severity of the respiratory infection and the rheumatic activity that happened to follow such infection. It is perhaps of some significance that during these observations the majority (84 per cent) of the respiratory infections experienced by these rheumatic subjects were not associated with rheumatic activity.

Sixty-one subjects (49 per cent) experienced

Rheumatic activity	Total number of cases	Preceded by		During respiratory infection		Not associated with respiratory infection		
		"Strepto- coccal" respiratory infection	Non- streptococcal respiratory infection	"Strepto- coccal" respiratory infection	Non- streptococcal respiratory infection	Preceded by streptococci in throat	Negative	Classification doubtful
Carditis, arthritis, nodules Arthritis Chorea Skin (purpura, urticaria) Joint pains	cases 8 9 16 6 100	cases 0 2 1 2 1 1	<i>cases</i> 0 1 2 0 19	cases 4 3 5 2 27	cases 2 1 3 0 19	cases 1 0 2 1 13	cases 1 2 3 0 11	1
Total cases Per cent	139	16 11.5	22 16	41 29	25 18	17 12	17 12	1

 TABLE I

 Relation of rheumatic activity to respiratory infection

139 rheumatic symptoms; about three-fourths, 100, were recurring joint pains, 6 purpura, 16 chorea, 9 arthritis and 8 carditis, arthritis and nodules. Analysis of the time relationship between these rheumatic recurrences and respiratory infections, summarized in Table I, is of interest. month before the onset of rheumatic activity. The intervening period of apparent health was designated as the *quiescent interval*. Sixteen per cent of the rheumatic episodes were preceded by a respiratory infection (unassociated with hemolytic streptococci in the flora of the throat) and only 11.5 per cent of the 139 rheumatic recur-

1933-1934



CHART 4. MONTHLY INCIDENCE OF RHEUMATIC RECURRENCES AND RES-PIRATORY INFECTIONS EXPERIENCED BY 62 RHEUMATIC SUBJECTS AT THE NEW YORK HOSPITAL CONVALESCENT COTTAGES.

One-fourth (24 per cent) of the 139 rheumatic episodes were unrelated to respiratory infections. About one-half (47 per cent) of the rheumatic recurrences occurred either simultaneously with a respiratory infection or more frequently during a chronic respiratory infection, such as persistent ethmoiditis so commonly present in children. In some instances the respiratory infection occurred during the course of the rheumatic activity.

Of particular interest is a consideration of the incidence of rheumatic recurrences which were preceded (within a month) by a respiratory infection. Respiratory infections were considered to precede rheumatic activity if the termination of the respiratory infection was within a period of a rences were preceded by a "streptococcal" respiratory infection. The quiescent interval subsequent to respiratory infections was infrequently observed to precede rheumatic activity. This is not in accord with the observations of other investigators.

In children it is particularly difficult to determine the onset of rheumatic disease when res-, piratory symptoms are present. Fever is frequently the only early objective symptom of rheumatic activity. It is suggested that in such cases rheumatic fever may be present at the onset of what appears to be a respiratory infection, although not easily detected clinically, and that the quiescent period may then represent the apparent symptomless period, so commonly observed during the course of rheumatic activity (see Protocol J. V., Paper II of this series).

The occurrence of a crop of nodules, a sharp rise of temperature or a pericardial rub, following an apparently symptomless period of a week or ten days, is a characteristic train of symptoms during the course of rheumatic activity in children, unassociated with respiratory infections. Such episodes frequently lead one to attribute erroneously etiological significance to events, or to therapeutic or diagnostic measures, just preceding the appearance of these objective symptoms.

A consideration of the relation between respiratory infections in the household and the occurrence of rheumatic fever is of interest. Complete data for analysis were obtained for 79 rheumatic families comprising 117 rheumatic individuals under sixteen years of age, 164 nonrheumatic children and 183 adults. The monthly incidence of household infections for ten months (September to July) was as follows: two or more members per month experienced respiratory infections 193 times, respiratory infections with streptococci in the pharyngeal flora 102 times, and carried hemolytic streptococci in the throat 106 times (in apparent good health). During this period 50 children experienced 106 rheumatic recurrences. These rheumatic episodes did not appear directly related to the presence of household infections, occurring as frequently in the absence of such respiratory infections. It is perhaps of some significance that rheumatic subjects experienced an average of five respiratory attacks compared with three in the control group for the ten month (September to July) period.

During this investigation a series of 62 rheumatic children who were under daily observation at the New York Hospital Convalescent Cottages for a period of from two months to one year gave an opportunity for a more accurate study of the relation of respiratory infections to rheumatic fever in children living in close contact. The majority of the subjects were convalescing from severe rheumatic recrudescenses, many were completely at rest in bed, others were ambulatory. Non-rheumatic convalescent children were also under the same supervision, and no attempt was made to isolate the rheumatic child. During the period of observations 105 respiratory infections, of which 53 were accompanied by hemolytic streptococci in the pharyngeal flora, were experienced by the rheumatic children. Six subjects suffered nine rheumatic recurrences; three of the rheumatic episodes were preceded by "streptococcal" respiratory infections. Although three severe epidemics of respiratory infections associated with a predominance of hemolytic streptococci in the pharyngeal flora (October, March, May) were observed among these susceptible rheumatic subjects, there was no appreciable increase in the incidence of rheumatic activity during this period such as might have been expected from the reported epidemics in institutions under similar circumstances.

It is significant that during these various observations, although the majority (98 per cent) of the rheumatic children experienced one or more respiratory infections, only 16 per cent of these infections were associated with rheumatic activity. About one-half (49 per cent) of the children suffered one or more rheumatic recurrences, but only 11.5 per cent of the rheumatic episodes were preceded by "streptococcal" respiratory infection.

COMMENT

This investigation was conducted over a period of several years, comprising studies of a large group of rheumatic children observed in the homes, hospital wards and convalescent cottages. These studies are comparable to those reported by the majority of investigators with the exception that our investigations were limited to children.

It is evident from the data that our observations do not give support to the conception of a specific etiological relationship between respiratory infections and rheumatic fever. Their association would seem almost inevitable because of the observed frequency of respiratory infection in children. It is also possible that the rheumatic child is constitutionally vulnerable to both infections. This possibility is indicated by the frequency of a simultaneous onset of rheumatic activity and respiratory infection (following a common exciting factor). It is also suggested by the greater susceptibility of the rheumatic child to respiratory infection compared with that of a non-rheumatic brother or sister. Although it is generally well recognized that the organisms isolated from throat cultures do not represent an accurate picture of the pharyngeal flora, merely indicating the fluctuation in the relative numbers of the various organisms rather than their presence or absence, recent investigations tend to ascribe etiological significance to the isolation of hemolytic streptococci from the flora during respiratory infections. Emphasis seems to be placed on the relative numbers of colonies of hemolytic streptococci present rather than on the local signs or symptoms.

Our observations would tend to minimize the diagnostic significance of the presence or absence of hemolytic streptococci in the pharyngeal flora. It was found that the relative numbers of these organisms in repeated consecutive cultures varied from predominance to few or none. The specificity of "streptococcal" respiratory infections based solely upon bacteriological criteria does not appear convincing in view of the observed comparable carrier rate of hemolytic streptococci in the pharyngeal flora of sick and well children. The immunological studies reported in the second paper of this series, showing a rise in the titre of antistreptolysin following respiratory infections unassociated with hemolytic streptococci in the pharyngeal flora is pertinent.

It is of interest to note in passing that since tonsillectomy has become an early routine procedure in children, tonsillitis is observed infrequently in the course of rheumatic disease. Recent investigators tend to substitute in its place nasopharyngitis.

The etiology of the rheumatic sequelae following scarlet fever is still controversial. Of interest is the evidence of Paul and Salinger (8) in their studies of the relation of rheumatic sequelae to scarlet fever that "like respiratory infections, scarlet fever activates the rheumatic process in the rheumatic child."

Wilson, Lingg and Croxford (9) suggested that the common age and seasonal incidence of rheumatic fever and scarlet fever may be factors influencing their association. In their observations, scarlet fever was more frequently followed by rheumatic recrudescences within the age period of five to nine years. Seventy-five per cent of the rheumatic subjects developing scarlet fever at other age periods did not have rheumatic sequelae. During these observations (as can be seen in Protocol 4 (10)) the occurrence of scarlet fever during a severe carditis did not appear to influence the course of the latter.

While it is appreciated that the occurrence of respiratory infections in a rheumatic child may not be a fortuitous event, it would seem from our observations to bear no more specific etiological relationship to rheumatic disease than would be attributed to similar episodes occurring in the tuberculous child.

SUM MARY

1. There are presented investigations conducted over a period of several years comprising epidemiological, bacteriological and clinical studies of a large group of rheumatic children, observed in the homes, hospital wards and convalescent cottages.

2. Two hundred and twenty-two ambulatory rheumatic subjects five to fifteen years of age experienced 783 respiratory infections and 401 rheumatic recurrences (for a two-year period of observation 1930 to 1932). Less than 10 per cent of the rheumatic attacks were preceded within three weeks by a respiratory infection.

3. Of a total of 123 rheumatic subjects under close observation for twelve months, September 1933 to September 1934, 98 per cent suffered 649 respiratory attacks; of which 353 were associated with the presence of hemolytic streptococci in the throat flora. Eighty-four per cent of the respiratory infections were not associated with rheumatic activity.

4. Forty-nine per cent of the subjects experienced 139 rheumatic episodes; a *quiescent interval*, subsequent to "streptococcal" respiratory infection, preceded 11.5 per cent of the rheumatic episodes.

5. Sixty-two rheumatic subjects were under daily observation at the Convalescent Cottages for a two to twelve month period. During three epidemics of respiratory infection associated with a predominance of hemolytic streptococci in the pharyngeal flora, there was no appreciable increase of rheumatic activity.

6. Rheumatic subjects experienced an average of five respiratory attacks compared with an average of three for the non-rheumatic children of their respective households. 7. During the spring of 1934 hemolytic streptococci appeared in the pharyngeal flora of the majority of the rheumatic and non-rheumatic subjects.

8. During this season of its highest incidence, hemolytic streptococci predominated in the pharyngeal flora of 50 per cent of the rheumatic subjects during health, 40 per cent during respiratory infections, and 10 per cent during rheumatic activity.

CONCLUSIONS

The evidence presented does not support the conception of a specific etiological relationship between respiratory infections and rheumatic fever in children.

Our observations would tend to minimize the diagnostic significance of the presence or absence of hemolytic streptococci in the pharyngeal flora during respiratory infections. The designation *streptococcal respiratory infection*, based solely on bacteriological findings, would not appear to be justified.

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