THE EPIDEMIOLOGY AND PREVENTION OF RHEUMATIC FEVER*

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ALTHOUGH reports concerning the epidemiology of acute rheumatic fever are legion, the conclusions reached by various investigators are frequently contradictory. Various environmental, bacterial and host factors have been studied in relation to the occurrence of this disease. It is well established that the incidence of rheumatic fever may vary from year to year in the same population groups. Occasionally, the epidemic occurrence of the disease is noted. In general, rheumatic fever is most prevalent during the winter and spring months at a time when respiratory infections reach their maximum incidence. Although the disease occurs frequently in the temperate zones, it cannot be said to be rare in all tropical areas. In this country, rheumatic fever is noted for its high incidence along the northern Atlantic sea coast among population groups living under crowded, damp conditions and under poor economic circumstances. In contrast to this environmental status, are the conditions that prevail in another portion of the country, the Rocky Mountain states. Here, at a high altitude, under conditions of low humidity and less concentration of the population units, the incidence of rheumatic disease is about equal to that observed along the northern Atlantic coast.

Many studies concerning the epidemiology of rheumatic fever fail to consider the role of preceding respiratory illnesses. Some observers have felt that the clinical characteristics of this initial infection are important. It has been suggested that scarlet fever and superficial streptococcal infections are especially prone to precipitate an attack of rheumatic fever. Likewise, there are those who believe that certain

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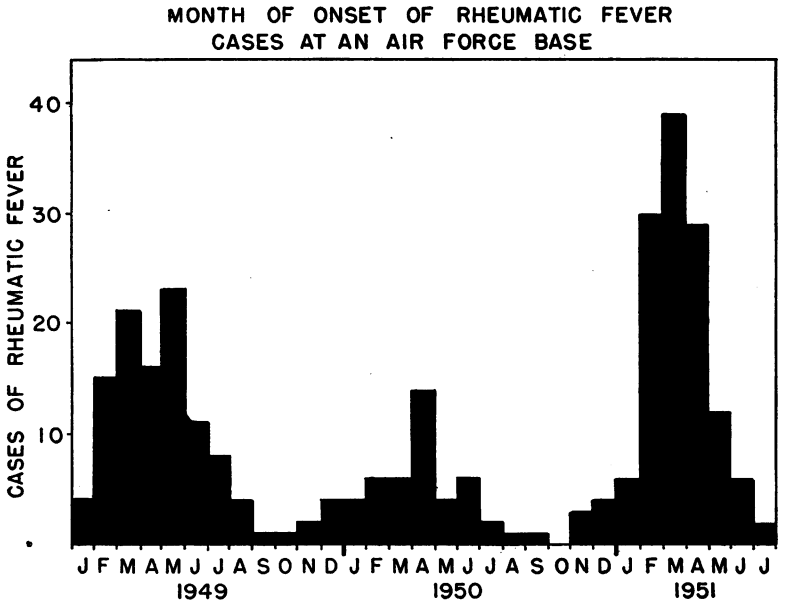

Fig. 1

strains or serological types of streptococci are more rheumatogenic than others.

Rheumatic fever is said to be a disease of children, and yet there have been numerous reports of its occurrence in adults. Because of the high incidence among the younger age groups it has been assumed that age alters the susceptibility to acute rheumatic fever, however, statistical evidence in support of this assumption is lacking.

That some factor in the host may be important in the pathogenesis of rheumatic fever is evident from the high attack rates observed in the offspring of rheumatic parents and also the increased susceptibility conferred by a previous attack of the disease.

The role of these environmental, bacterial and host factors which have been summarized briefly is difficult to assess, primarily because of the inadequacies of methods for diagnosis and lack of agreement among physicians as to the cause of rheumatic fever. Since the evidence now available indicates that infection with group A streptococci is causally related to the disease, the various epidemiological factors will be reviewed in order to define the role of such factors on either the incidence of streptococcal infections or on the incidence of rheumatic fever.

TABLE I.—RHEUMATIC FEVER ATTACK RATES BY YEAR

Year	*Exudative Tonsillitis*	*Rheumatic Fever*	
		Number	*Per cent*
1949	573	14	2.4
1950	439	12	2.7
1951*	194	6	3.1

* Jan. to 15 Feb.

During the past three years the staff* of the Streptococcal Disease Laboratory has been interested in the study of streptococcal infections and acute rheumatic fever. One method employed in these studies has been the determination of the attack rates of rheumatic fever in well defined population units. In the studies to be presented here, the population unit includes airmen admitted to the hospital with exudative tonsillitis or pharyngitis from whom typeable group A streptococci were isolated. None of these patients received therapy with the antibacterial agents. In addition, only those patients who were observed at follow-up examination 21 or more days after the onset of the streptococcal infection are included. For purposes of tabulation rheumatic fever developing within 35 days of the streptococcal respiratory infection was considered a complication of that infection since it has been observed that patients developing rheumatic fever at a later date usually have had an intervening streptococcal infection.[1]

RESULTS

The occurrence of acute rheumatic fever over a three year period at Warren Air Force Base is shown in Figure 1. Only those patients developing rheumatic fever after arrival at Warren are shown. These data emphasize the differences in the epidemic pattern during three different years as well as the seasonal variation in the appearance of acute rheumatic fever. The winter and spring months were associated with the highest incidence of rheumatic fever and this was also the period when most streptococcal and other respiratory infections were observed.

Data such as shown in Figure 1 have been presented many times,

* These data could not have been obtained without the interest and support of Doctors William R. Brink, George C. Eckhardt, Edward O. Hahn, and Harold B. Houser who were members of the professional staff some time during the period of this study.

TABLE II.—RHEUMATIC FEVER ATTACK RATES BY SEASON

Year	Months	Exudative Tonsillitis	Rheumatic Fever	
			Number	Per cent
1949	Jan.-June	451	12	2.7
	July-Dec.	122	2	1.6
1950	Jan.-June	333	8	2.4
	July-Dec.	106	4	3.8

TABLE III.—RHEUMATIC FEVER ATTACK RATES BY SEASON (1949-1950)

Months	Exudative Tonsillitis	Rheumatic Fever	
		Number	Per cent
Jan.-June	784	20	2.6
July-Dec.	228	6	2.6

but they fail to define the factors responsible for these variations. The data presented in Table I show that the attack rate for rheumatic fever as based on population units known to have had a streptococcal infection was relatively constant throughout the period of study. In Table II the data are presented according to season. During the winter months of 1949 and 1950 the attack rates varied little, but during the summer and fall the attack rate in 1949 was 1.6 and in 1950 was 3.8 per 100 streptococcal infections. These latter variations are probably due to the small number of infections included in the summer and fall months. If the experience during the two years is combined (Table III), the attack rate is constant and is independent of the season. These data indicate that the effect of season and year on the incidence of rheumatic fever is related to the effect of such factors on the incidence of the preceding streptococcal illness.

It is commonly believed that rheumatic fever occurs less frequently in certain geographical areas than in others.[2] That this variation may be due to factors which influence the incidence of streptococcal infection is indicated by the data presented in Table IV. Unfortunately, few follow-up studies have been made after defined infections, but it is believed that the populations included in Table IV are relatively comparable in that most of the infections were probably streptococcal

TABLE IV.—RHEUMATIC FEVER ATTACK RATES BY GEOGRAPHICAL AREAS

Location	*Year*	*Type*	*Streptococcal Infections*	*Rheumatic Fever*	
				Number	*Per cent*
North Carolina (3)	1943	5	100	3	3.0
Wyoming	1949-51	5	234	7	3.0
Denmark (4)	1926	—	840	30	3.6
Boston (5)	1950	—	102	4	3.9

in origin, and it was stated by the author that all patients were followed for complications.

The incidence of rheumatic fever following streptococcal infections appears to be constant in North Carolina[3] and Wyoming. Both of these studies were conducted in a similar manner and included only young adult males infected with type 5 streptococci. One was at a high altitude (over 6,100 ft.), the other at a low altitude (under 200 ft.). The study in Denmark[4] was done on 840 patients reported to have septic sore throat. The authors believe that the attack rate of rheumatic fever may be somewhat high since there was a tendency to report a case of sore throat if a complication developed. The figures from Boston[5] were obtained in a group of scarlet fever patients observed for at least three weeks. The methods of observation and diagnosis in the latter investigation would tend to give higher rates than in the Wyoming and North Carolina studies.

These figures (Table IV) indicate relatively little direct effect of altitude, climate, or humidity on the attack rate of rheumatic fever. Further studies would be desirable, especially following proved streptococcal infections in tropical areas.

As stated previously, acute rheumatic fever is commonly believed to be a disease of the young. In Wilson's[2] series the average age of onset of rheumatic fever was about six to seven years, although it is recognized that the disease frequently occurs after the age of twenty-five.[6] The data concerning attack rates following known streptococcal infections according to the age of the individual are meager, but they fail to show that the young child is more susceptible to rheumatic fever than the adult (Table V). The data of Collins[7] have shown that the age of highest incidence of scarlet fever is six, suggesting that the

TABLE V.—RHEUMATIC FEVER ATTACK RATES BY AGE AND TYPE OF DISEASE

Description	*Sterptococcal Infections* *Type*	*Number*	*Rheumatic Fever* *Number*	*Per cent*
Male adults, average age 20 (Wyoming)	Air-borne Tonsillitis	1206	32	2.6
Children, average age 11 (Boston (5)	Air-borne Scarlet Fever	102	4	3.9
One-third under 15 (Denmark*)	Milk-borne Tonsillitis	92	3	3.3

* Henningsen, E. J. and Ernst, J. Milk epidemic of angina, originating from a cow with mastitis and due to Streptococcus pyogenes (Lancefield group A), *J. Hyg. 38*:384-91, 1938.

explanation for the high incidence of rheumatic fever in the young age group is due to the high incidence of streptococcal infections. It is of some interest to note that the attack rate for many respiratory infections is highest at about the age when the child first attends school, and is lowest in the adult.[7, 8]

It would seem reasonable to assume that the effect of crowding on the incidence of rheumatic fever is related to an increased incidence of streptococcal infections under such circumstances. Data supporting such an assumption are not conclusive, but it has been shown that the attack rate of other respiratory infections tends to increase as the size of the family unit increases.[9] In a study of Navy personnel Breese[10] has shown that the amount of respiratory disease is related to the number of individuals housed in a single unit. Certainly epidemics of rheumatic fever in the military organizations are usually associated with streptococcal infections among personnel living under crowded conditions.[11]

There is little evidence that the type of disease produced by the group A streptococcus alters the attack rate for acute rheumatic fever. The three groups of infections shown in Table V include an air-borne outbreak of tonsillitis and scarlet fever, and a milk-borne epidemic of septic sore throat. The attack rate in each instance was relatively comparable.

In contrast to these data are the reports of Watson, Rothbard and Swift[12] and Coburn and Young.[11] The former authors record that in a group of 110 patients with scarlet fever, eight patients subsequently developed clinical attacks of acute rheumatic fever, an attack rate of 7.3.

TABLE VI.—RHEUMATIC FEVER ATTACK RATES BY THE SEROLOGICAL TYPE OF STREPTOCOCCUS

Type	*Exudative Tonsillitis*	*Rheumatic Fever*	
		Number	*Per cent*
1	42	2	.....
5	234	7	3.0
6	35	0	.....
12	42	0	.....
14	630	17	2.7
24	198	5	2.5

One of these cases of rheumatic fever would have been excluded in the studies at Wyoming because of the long latent period of forty days. Furthermore, two additional patients had such mild and transient symptoms that they would not have been discovered without very careful observation. In a group of 500 patients with scarlet fever in a Navy installation, Coburn and Young[11] state that there were 106 cases of rheumatic fever, however, no details are recorded. These authors note that there was a correlation between the attack rates of scarlet fever and rheumatic fever in various Navy installations, but it does not necessarily follow that strains of streptococci which produce scarlet fever are always associated with a high rheumatic fever incidence.

It is possible that the rheumatogenic capacity of various strains of streptococci vary. Thus, Coburn and Young[11] state that two outbreaks caused by types 1 and 12 streptococci failed to precipitate rheumatic fever, whereas in the 500 scarlet fever patients presumably infected with type 17 streptococci, 21 per cent developed this complication. To date the studies at the Streptococcal Disease Laboratory fail to show significant variations in the attack rate according to the type of streptococcus isolated from the preceding streptococcal illness (Table VI). Furthermore, there did not appear to be a difference in the attack rate early and late during the course of an epidemic due to a single type.[13]

There are several factors that appear to be related to an increased attack rate for rheumatic fever following streptococcal infections. These include a positive familial history, a previous attack of rheumatic fever, and an altered antibody response exhibited to the preceding streptococcal infection.

TABLE VII.—RHEUMATIC FEVER ATTACK RATES IN SUBJECTS WHO HAVE HAD RHEUMATIC FEVER

Author	Sterptococcal Infections		Rheumatic Fever	
	Type	Number	Number	Per cent
Kuttner[18]	C 51	12	6	50
	4	32	0	0
	97 T	6	0	0
	27	39	8	20.5
Schlesinger[17]	.....	62	22	35.6
Coburn[19]	single type	16	14	87.5
Collis*	.....	32	24	75
Coburn[20]	.....	38	19	50

* Collis, W. R. F. Discussion on some problems concerning the prevention and treatment of acute rheumatic infection, *Proc. roy. Soc. Med.* 25:1631-35, 1932.

Attack rates for rheumatic fever following known streptococcal infections in individuals with a positive family history are not available for analysis. The observation of St. Lawrence[14] that 14.8 per cent of persons exposed to a patient with rheumatic heart disease within a family unit showed evidence of rheumatic fever or rheumatic heart disease suggests an increased susceptibility in such families or increased exposure to a rheumatogenic agent. Paul[15] in a study of 15 rheumatic families observed the simultaneous appearance of both primary and recurrent bouts of rheumatic fever. The studies of Wilson[2] and Gauld[16] have shown that the risk of rheumatic fever is greater in children of parents with a history of rheumatic fever than in children of parents who have not had the disease. These data indicate that heredity may be a factor in the determination of the attack rate of rheumatic fever.

There is little doubt that a previous attack of rheumatic fever usually increases the risk of recurrent attacks following a streptococcal infection.[17] Examples of rheumatic fever occurring after such infections are shown in Table VII. These data also show a remarkable variation in the attack rates, suggesting that certain strains or types of streptococci vary in their rheumatogenic capacity. The type 4 epidemic of Kuttner[18] appeared to have no rheumatogenic capacity. These infections apparently were typical clinical examples of streptococcal disease, although it is somewhat unusual that only eleven of the thirty-two patients showed a diagnostic increase in the antistreptolysin titer. Whether the failure

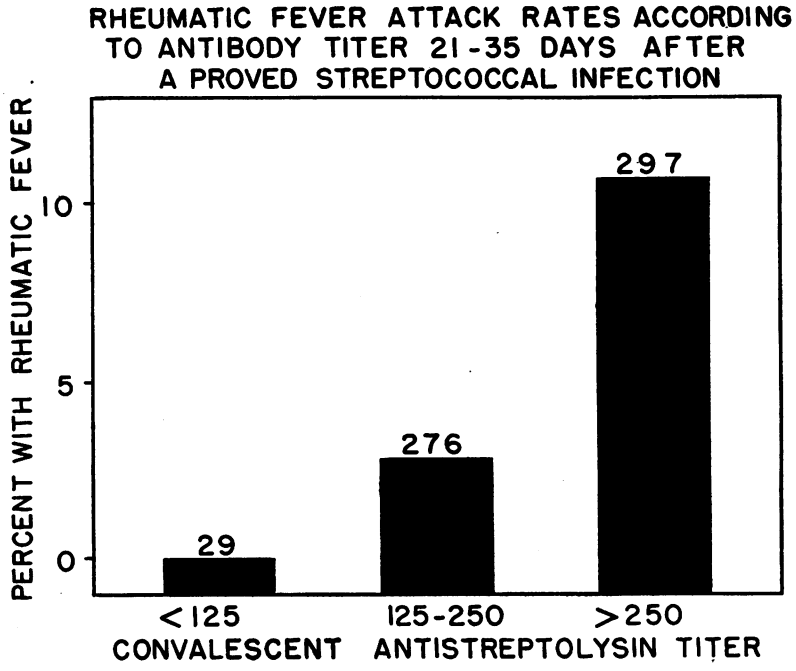

Fig. 2

of this type of streptococcus to induce rheumatic fever was related to its failure to produce an antibody response cannot be determined. It may be of interest to record that rheumatic fever has been observed to follow type 4 infections in Wyoming. Coburn[19, 20] made an interesting observation during a study of 20 strains of streptococci isolated from infections which were followed by rheumatic fever and 20 strains isolated from patients who did not experience such a sequela. Most of the strains from the latter group failed to produce streptolysin O in vitro.

Although the data in Table VII may be interpreted as showing variations in the rheumatogenic capacity of various strains of streptococci, it is difficult to be certain of this since there may be multiple factors altering the attack rates in such populations. For example, the chances of recurrence are related to the number of years of freedom from an attack of rheumatic fever.[21] Furthermore, if a streptococcal infection were defined as occurring only in those patients whose sera showed an antibody response, the attack rates might be comparable. It is apparent that further data are required in such population groups.

TABLE VIII.—RHEUMATIC FEVER DEVELOPING WITHIN 34 DAYS OF ONSET OF EXUDATIVE TONSILLITIS OR PHARYNGITIS

Treatment	*Exudative Tonsillitis*	*Rheumatic Fever*
None	996	23
Penicillin	978	1

For some years it has been recognized that patients developing rheumatic fever are especially likely to have high titers of antibody to various streptococcal antigens.[22,23] The correlation of the magnitude of the antibody response (antistreptolysin) with the attack rate for acute rheumatic fever is shown in Figure 2. All patients in this study harbored group A streptococci and were shown to develop a diagnostic increase in the antistreptolysin titer following the infection. In the group of 602 patients the attack rate increased as the height of the convalescent titer increased.

Methods established for the control of acute rheumatic fever have been based on the fact that there is a causal relationship between the acute streptococcal infection and the subsequent attack of rheumatism. Thus, the continuous exhibition of the sulfonamide drugs decreases the attack rate of streptococcal infections and rheumatic fever.[11] Such procedures are limited to selected population groups and include primarily individuals who have had a previous attack of rheumatic fever. Because of the relation between the magnitude of the attack rate and the height of the antibody response, it has been assumed that methods of therapy of the acute streptococcal infection which result in an inhibition of antibody formation might also reduce the attack rate of rheumatic fever. Three drugs, penicillin, aureomycin and terramycin are known to inhibit antibody production when administered to patients with streptococcal infections.[24] A summary of the results obtained when penicillin is administered to patients with streptococcal illnesses is shown in Table VIII. Early treatment resulted in a twenty-fold reduction in the incidence of rheumatic fever. The one patient who developed this sequela following therapy had had rheumatic fever and chorea one year previously and did not receive treatment with penicillin until the fifth day after the onset of tonsillitis. The results obtained with aureomycin therapy have been similar to those obtained with penicillin. These results

confirm the observations of Massell, Dow and Jones[25] who studied the effect of antibiotic therapy of streptococcal infections on the recurrence rate in rheumatic subjects.

Discussion

In summary, the study of the epidemiology of rheumatic fever has indicated that there are environmental, bacterial and host factors which play a role in the development of rheumatic fever. It would appear from the limited data presented, however, that many of these factors are important only because they are related to the preceding streptococcal infection which initiates the attack of rheumatic fever. Thus it seems likely that latitude, altitude, crowding, economic factors and age all affect the incidence of rheumatic fever only because they are related to the incidence of streptococcal infections in general. A better understanding of the mechanism of action of these factors on the incidence of streptococcal infections may lead to better methods for control of rheumatic fever.

The data indicate that host and bacterial factors are most important once a streptococcal infection is established. From the attack rates following streptococcal infections in the general population there is little evidence that the various serological types of streptococci vary in their rheumatogenic capacity, nor is there definitive evidence that the type of disease produced is an important factor in the attack rate of rheumatic fever.

Studies of rheumatic populations have shown marked variations in the attack rate for rheumatic fever following streptococcal disease. At the present time these data are difficult to interpret and considerable more information is required to determine the role of the streptococcus and the role of the host. It would appear, however, that both bacterial and host factors may be important in the altered attack rates observed.

In this group of rheumatics recent contact with the streptococcus also may play a role. It has been postulated that multiple streptococcal infections increase the attack rates for rheumatic fever,[26] and for this reason alone the previous rheumatic may be more susceptible than normal subjects to rheumatic fever. Data are now being obtained concerning attack rates following one and two observed streptococcal infections to assess the role of multiple infections. The fact that the attack rate for recurrent rheumatic fever falls as the interval of freedom from an attack

increases, indicates that repeated attacks of streptococcal infections may increase the attack rate.

Another explanation for the increased susceptibility of the rheumatic patient to subsequent attacks following a streptococcal infection is that such a population has a high degree of a "host factor." The data presented indicate that individuals who develop rheumatic fever respond in an altered fashion immunologically. This altered response again may be due to bacterial or host factors. Studies have been underway during the past three years to determine the relative importance of these two factors. Since there is evidence that there is a predisposition to increased antibody production,[27, 28] subjects with streptococcal infections are being tested with multiple antigens to determine the role of the infection and the role of host factors in the determination of the type of antibody response. It has been the working hypothesis that such immunological hyperreactivity may be responsible in a large part for the development of rheumatic fever, and also may be the inherited characteristic that accounts for the high attack rates in certain families.

To date, all successful methods for the prevention of rheumatic fever have been based on the knowledge of the relationship of group A streptococcal infections to the disease. Thus the prophylactic administration of antibacterial agents prevents most streptococcal infections and thereby prevents an attack of rheumatic fever. Such methods of control have been limited in their use almost completely to one population group, the previous rheumatic. The use of penicillin or aureomycin in the treatment of acute streptococcal infections as a preventive measure is likewise limited since approximately 40 to 50 per cent of individuals infected fail to develop sufficient clinical symptoms to require medical attention. It would appear that only by the control of all streptococcal infections can rheumatic fever be eradicated.

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