Eradication of Rheumatic Fever
An Unfulfilled Hope

By Milton Markowitz, M.D.

SUMMARY
Rheumatic heart disease is considered one of the few forms of chronic heart disease which can be effectively prevented today. Yet the incidence of rheumatic fever is still appreciable and the complacency of many physicians and public health officials in regard to the rheumatic fever problem is unwarranted. It is timely, therefore, to reexamine the question of whether this disease can indeed be eradicated by presently available methods.

One of the major factors limiting the prevention of initial attacks with antibiotics is that about two thirds of the patients who develop rheumatic fever do so following either asymptomatic or mild streptococcal infections. Furthermore, the low socio-economic group, in whom the risk of rheumatic fever is the greatest, is the least likely to receive adequate care even for overt respiratory infections. Although the number of recurrent attacks has been reduced, approximately 10% of rheumatic patients still develop recurrences either because they are not on prophylaxis at all or they take their medication irregularly.

It is clear, therefore, that the availability of effective preventive agents is not synonymous with effective prevention. While the conditions which account for this fact can be modified so that the incidence of rheumatic fever can be reduced, the disease will not be eradicated until a more biologic means to prevent streptococcal infections becomes available.

Additional Indexing Words:
Rheumatic fever, incidence
Rheumatic fever prophylaxis, compliance
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Dr. T. DUCKETT JONES was one of the first clinician-scientists in this country to devote almost all of his life to the study of rheumatic fever. The renowned Clinical Criteria, which he formulated in 1944,

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brought about a degree of diagnostic uniformity and provided a vitally needed standard for national and international cooperative rheumatic fever studies. The Criteria have also been extremely valuable for medical education, and consequently most physicians trained during the past 25 years are familiar with the varied manifestations of this disease.

Dr. Jones and his colleagues carried out meticulous long-term studies on a large group of patients at the House of the Good Samaritan in Boston. His careful observations as well as his keen critical insight have
provided the best data available on the natural history of the disease in this country during the pre-antibiotic era.1 These data were published two decades ago, and today, it is highly likely that Dr. Jones would have welcomed an appraisal of the current rheumatic fever problem. He would have been greatly interested to know whether his British colleague, Dr. Glover, was correct in 1930 when he noted: “the incidence of acute rheumatism seems to show that it, like tuberculosis, is slowly but surely being conquered. . . . We seem to be seeing the same process of epidemiologic obsolescence in acute rheumatism that Creighton saw in smallpox.”2

In this lecture, I propose to discuss the extent to which Dr. Glover’s prediction of 40 years ago has been fulfilled and to note to what degree the changes which have occurred may be related to preventive measures. The reasons for our failure to eradicate rheumatic fever will also be reviewed and the question of whether this disease can indeed be eliminated by presently available methods will be explored. The personal studies referred to in this paper were carried out with Dr. Leon Gordis, and his invaluable contribution is gratefully acknowledged.

What is the Incidence of Rheumatic Fever?

It is well known that rheumatic fever remains a common and serious disease in many developing countries. However, many people today question whether this condition is any longer a significant problem in the United States. For example, when the subject of incidence of rheumatic fever is discussed with practicing physicians who provide medical care for middle class children, they frequently declare that they rarely see the disease. One might be tempted to conclude that in recent years rheumatic fever has disappeared from their practices, but in truth, rheumatic fever has always been uncommon among patients seen in private practice. Indeed, almost 50 years ago, Poynton commented that “the rarity of these cases of acute rheumatism in children in private practice as compared with hospital practice would form an interesting subject for inquiry.”3 The virtual absence of rheumatic fever in some quarters does not tell us very much about the incidence of the disease.

Mortality statistics are a source of data which may also be misleading in regard to incidence. The number of deaths from acute rheumatic fever has been falling steadily over the past 20 years. However, it is not at all clear whether the declining death rate is due to a change in severity or in incidence of the disease. While both factors are probably involved, there is good evidence to indicate that acute rheumatic fever is milder than formerly, and this may be a significant reason for the declining death rate during the acute stage. In any event, it is not possible to attribute the decline in acute mortality to advances in modern therapy, since deaths from acute rheumatic fever began to fall in 1910, and the rate of decline has been minimally accelerated during the past two decades (fig. 1).

If mortality data for acute rheumatic fever do not reflect trends in attack rates accurately enough, what is the true picture of rheumatic fever incidence today? In general, national incidence data have always been inaccurate, chiefly because of the incompleteness in reporting, regional differences in availability and quality of diagnostic services, and the failure to distinguish between primary and recurrent attacks. In view of the difficulties of gathering valid data on a national basis, attempts have been made to study the attack rate in different urban areas. Several years ago, Gordis and associates4 studied the incidence of rheumatic fever in Baltimore. They reviewed the records of all patients discharged from Baltimore hospitals between 1960 and 1964 with the diagnosis of acute rheumatic fever. In addition to the record review, a survey of approximately 700 practicing physicians was carried out to obtain an estimate of the proportion of patients with acute rheumatic fever who were treated at home. From the data obtained, the annual primary attack rate in Baltimore was estimated at 21 per 100,000 individuals, age 5 to 19 years. This attack rate
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is almost certainly a minimal figure, since it does not include patients with mild or subclinical rheumatic fever who were not seen by physicians. Although the number of such cases is not known, it is not insignificant since both pediatric and adult cardiac clinics still continue to see patients with rheumatic heart disease who have no overt history of rheumatic fever.

How does the present Baltimore incidence compare with the attack rate of several decades ago? Unfortunately, precisely comparable data for the pre-antibiotic era are not available. However, in 1935 and 1936, an extensive national health survey was conducted which included Baltimore and several other cities in the same region. Within this region, the annual incidence of initial attacks of rheumatic fever during the study period was 28.5 per 100,000 population aged 5 to 19 years.

Although the manner in which the data were collected differed in the two studies, this is as near as one can come to comparing the incidence before and after the introduction of antibiotics. If such a comparison is valid, it appears that there has been less than a 30% decline in the incidence of first attacks. It is not possible to know to what extent this decline has been due to the availability of antibiotics; it can be argued, however, that the fall in the primary attack rate is not nearly as striking as might have been anticipated following the introduction of simple and effective agents for treating streptococcal infections and the demonstration that adequate therapy of such infections could prevent rheumatic fever.7

The Failure to Prevent First Attacks

Why have our efforts to prevent first attacks of rheumatic fever fallen short of our expectations? Is it because we have reached the limits of prevention by presently available technics or are we using these technics inadequately? In an effort to answer these questions, the histories of 261 patients with first attacks of acute rheumatic fever were reviewed to determine whether the attacks could indeed have been prevented.8 The results of this study are shown schematically in figure 2.

Thirty-four percent of the patients had no history of a clinically apparent antecedent respiratory infection. There was, therefore, no reason for them to have been seen by a physician. It is well known that acute

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**Figure 1**
Crude United States death rates from acute rheumatic fever, 1910-1960.4

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**Figure 2**
rheumatic fever may follow an asymptomatic streptococcal infection. Thirty-two percent of the patients did not consult a physician despite the presence of a symptomatic respiratory infection. Many children with symptoms will not bother to tell their parents and when they do, many parents are unwilling or unable to seek medical care. Finally, 34% of the patients developed rheumatic fever despite the fact they had been seen by a physician for a preceding respiratory infection. Most of these patients did not have the benefit of a pharyngeal culture (fig. 2).

Comparable results have been reported in several other studies. These data provide some insight into why rheumatic fever persists today. Clearly, rheumatic attacks in patients with no history of a preceding respiratory infection are not currently preventable even with optimum medical practice and availability of health services. Thus, for a third of the children who develop rheumatic fever, we have reached the biologic limits of prevention and such attacks will continue to occur until better methods become available.

In contrast to the group of patients without symptoms, there would appear to be some potential for improving our preventive efforts for patients with overt respiratory infections who do not seek medical care as well as for those who see physicians but receive inadequate care. However, the task of reaching these patients and the physicians who care for them is greatly complicated because the population at greatest risk for rheumatic fever lives in the slums and is least likely to seek or to obtain adequate medical care. The concept that the incidence of rheumatic fever is related to social conditions was recognized long ago and was reemphasized by Glover in 1930. The Baltimore studies also demonstrate this relationship. Figure 3 shows a map of the city with each dot representing the place of residence of a rheumatic fever patient with an initial attack identified in the aforementioned hospital record review study. There is an obvious concentration of cases in two areas in the central part of the city. These are the Negro slums and while these areas have high population densities, this is not the reason for the clustering of cases. When attack rates are calculated, it becomes evident that the incidence of initial attacks of rheumatic fever is two to three times higher in the low income area than in the rest of the city.

**Attack Rate of Recurrences Reduced**

The incidence of recurrent attacks is also higher in children in the low socioeconomic group. For example, in the Baltimore study, recurrences were four times more common in the black than in the white population. The annual recurrence rate for the entire 5 to 19-year-old population was 3 per 100,000. How does this rate compare to the incidence of recurrences before prophylaxis was available? Referring again to the National Health Survey in 1935, the data showed a recurrence rate of 12 per 100,000. There has been, therefore, a significant decline in recurrences over the past 30 years. This decline can probably be

**Figure 3**

Map of City of Baltimore with each dot representing residence of patient hospitalized with initial attack of rheumatic fever, 1960-1964.
attributed to the availability of anti-streptococcal prophylaxis. Nevertheless, one eighth of Baltimore hospitalizations for rheumatic fever between 1960 and 1964 were for recurrent attacks. The major reasons why these attacks continue to occur are either because rheumatic individuals discontinue prophylaxis entirely or because they take their medication very irregularly. Therefore, if recurrent attacks are to be entirely eliminated, it is necessary to identify delinquent patients and to devise methods for improving patient cooperation.

Several years ago, Dr. Gordis and I began a series of investigations of children and adolescents enrolled in an oral penicillin prophylaxis program. These studies were designed to answer three questions: (1) How faithful were patients in following the recommended drug regimen? (2) What was the risk of streptococcal infections at various levels of compliance? (3) Could compliance be improved by changes in the way medical care was provided for these patients?

In order to study the question of patient fidelity, a simple urine test for detecting penicillin was developed to provide an accurate objective method of determining compliance. A filter paper strip dipped into urine containing penicillin will inhibit the growth of penicillin-sensitive organisms. This inhibition also occurs even when the filter paper is kept at room temperature for several days. Based on this observation, a mail-in kit was devised which enabled school nurses to collect specimens from rheumatic fever children. The children were instructed to take 200,000 units of penicillin G before breakfast, and weekly specimens were collected in the mornings at school on a randomized schedule. The patients were not told the reason for the urine collections. By this method, 1800 specimens were obtained from 136 rheumatic children over a period of 5 mo. Based on results from 10 to 20 urine specimens obtained from each patient during the study, the children were classified in the following manner: good compliers if more than 75% of the specimens were positive, poor compliers if fewer than 25% were positive and intermediate if they fell in between. The results of this study showed that only 32% were good compliers, whereas 36% were noncompliers. Thus, over the 5-mo study period, more than a third of the patients who were attending a rheumatic fever clinic were taking penicillin only one quarter of the time or less.

In theory, if poor compliers were identified, recurrences could be prevented in most if not all of them by administering monthly injections of long-acting penicillin in place of oral medications. In order to select patients at the greatest risk, it would be helpful to know the frequency of streptococcal infections at different levels of compliance. To answer this question, the incidence of these infections was studied in 83 rheumatic children in whom the penicillin urine test and streptococcal antibodies were determined at regular intervals.

The results of this study are shown in figure 4. Twenty of the 83 children had a significant rise in antibodies, indicating that a streptococcal infection had occurred during the study period. Fifteen of the 20 streptococcal infections occurred among 46 children who by the urine test were shown to have taken their penicillin less than a third of the time. The other five streptococcal infections were distributed among the remaining 37 children.
These data suggest that children who take oral penicillin more than a third of the time seem to be fairly well protected against streptococcal infections and, therefore, against recurrences of rheumatic fever. Conversely, individuals taking their medication less than a third of the time appear to be sufficiently vulnerable to warrant a different approach to prophylaxis. Unfortunately, the number of patients in the poor compliance category is so large that a long-term program involving monthly injections of penicillin for this group would present another set of problems. It seemed worthwhile, therefore, to see if patients' cooperation could be improved by changing the kind of medical care provided to these children. Traditionally, patients enrolled in specialty clinics at teaching centers are frequently seen by different physicians at each visit. In addition, it is customary for these physicians to provide care chiefly for those medical problems related to the categorical condition under observation. It seemed possible that if more comprehensive medical care were offered and if a continuous physician-patient relationship were established, compliance with the physician's recommendations would improve.

In order to test this hypothesis, a controlled study was undertaken to determine whether comprehensive care could indeed have a favorable influence on the regularity of prophylaxis.\(^{16}\) To obtain base-line data, compliance was determined in a group of 77 children over a 12-mo period. At the end of this period, the patients were stratified for age, sex, and compliance and then randomly allocated to one of two groups—a control group and a comprehensive care group. The control group continued to receive the same type of care as previously in the rheumatic fever clinic. The comprehensive care group was assigned to two physicians who provided complete care for all medical problems during and after clinic hours, including nights and weekends. The study was carried out over a period of 15 mo during the course of which urine tests for penicillin were performed at regular intervals. In addition, careful records were kept of all patient-physician contacts as a measure of medical care input (fig. 5).

The changes in compliance during the study period are shown in figure 5. The percentage of noncompliance increased in both groups, and there was no difference between the group cared for by the traditional specialty clinic and the one receiving comprehensive care. Therefore, the data indicate that altering the clinic structure to provide broader care, greater continuity of care, and a closer physician-family relationship had no apparent effect on compliance in a group of rheumatic fever patients. Compliance is of vital importance in rheumatic prophylaxis programs as well as in many other chronic illnesses, and there is a need for more research in this area of patient behavior.\(^{17}\) It is possible that other health personnel, such as public health nurses or community health aides, would be more effective than physicians in influencing patient cooperation. However, this study emphasizes the necessity to evaluate the effectiveness of health care programs before changes are instituted.

**Future Directions**

The studies which have been presented indicate the nature of some of the rheumatic fever prevention problems and shed some light on the questions raised at the beginning of this discussion. The question of the extent of rheumatic fever in this country can only be
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answered if a means were established by which incidence data were collected regularly from sample urban and rural areas. Such a systematic monitoring system would be extremely useful, and if the Baltimore experience is representative, it would probably reveal that rheumatic fever is still more common than is generally appreciated. Unfortunately, we have reached the point when interest in rheumatic fever in this country is diminishing more rapidly than the incidence of the disease. This complacency has developed from a false sense of security and achievement based on the belief that even without additional effort, penicillin will lead us into the promised land of rheumatic fever obsolescence. The unfortunate by-product of this attitude is that lack of interest and support on the part of many agencies endangers efforts to find new preventive methods and to improve existing prophylactic programs.

We have not made maximal use of available preventive methods, because we have not utilized the knowledge provided by epidemiology and sociology in planning the implementation and application of preventive measures. Perhaps our major failing has been that we have not been sufficiently concerned with the fact that individuals at greatest risk for rheumatic fever live in poor or marginal circumstances. Consequently, our efforts have not always been appropriate or realistic for the population at the highest risk. For example, health education programs which counsel mothers to watch out for sore throats have very little meaning for ghetto patients without ready access to good medical care. The influence of throat culture campaigns on the incidence of rheumatic fever will not be very great unless such cultures are taken by the physicians who treat children living in the inner city. In planning rheumatic fever programs, it is necessary to devise and implement specific measures aimed at the high risk population. An example of one such approach might be the establishment of throat culture stations staffed by paramedical personnel in schools located in underprivileged areas. Close scrutiny of how respiratory infections are treated in our emergency rooms might be still another approach.

Many of the problems associated with rheumatic fever prevention are intimately related to the availability and quality of medical care, especially for low income groups. If there were significant improvement in social conditions and in methods by which health care is provided, what effect might these changes have on the incidence of rheumatic fever? One can only guess at the answer, but it is worth noting that in a country such as Sweden the incidence of rheumatic fever is a small fraction of our attack rate. On the other hand, even if ideal prevention programs could be implemented, it is still unlikely that rheumatic fever would be entirely eliminated. At best, our present methods are cumbersome. In addition, there will always remain the problem of the asymptomatic streptococcal infection which accounts for a significant proportion of all rheumatic attacks. It would seem, therefore, that the ultimate eradication of rheumatic fever depends on the development of a more biologic means to prevent streptococcal infections. Furthermore, the capability of preventing streptococcal disease would eliminate morbidity from these common infections and would also prevent acute glomerulonephritis. A streptococcal vaccine offers this hope. Work on a vaccine is in progress and limited trials are already underway. Concern has been expressed over the possible danger of injecting streptococcal antigens into humans. This concern is probably justified in view of our lack of understanding of the pathogenic mechanisms which link the streptococcus and rheumatic fever. Until such knowledge becomes available and until we are safely able to control streptococcal infections, it is unlikely that rheumatic fever will disappear completely. In the meantime, we must abandon the unwarranted attitude that this disease will go away even if nothing is done. Such an attitude will only delay the day when rheumatic fever will indeed be obsolete.
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