
SYMPOSIUM ON RHEUMATIC FEVER

Nature of Rheumatic Fever

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RHEUMATIC fever is now recognized as a systemic disease characterized by inflammatory lesions that may be widely distributed throughout the connective tissues in various parts of the body. Despite the generalized nature of the rheumatic process, it would be a disease of relatively little significance if it were not for involvement of the heart. This follows from the well-known fact that the lesions in most areas, such as the joints, appear to heal completely without detectable residual damage in contrast to those affecting the endocardium, which frequently lead to crippling malformations of the valves. Except for the currently uncommon cases in which overwhelming pancarditis or myocarditis threatens life during the acute phase of the disease, the menace of rheumatic fever can be defined almost solely in terms of this delayed and permanent effect on the valves of the heart. The seriousness of this end result of the disease justifies, and to a large extent stimulates, the continued attempts to clarify the mechanisms involved in the pathogenesis of acute rheumatic fever.

Not much insight is gained into the nature of rheumatic fever by classifying it as one of the "collagen diseases" or diseases of the connective tissue. The similarity of the basic mechanisms responsible for the various diseases included in this group has not been established; even if it is assumed that related processes are involved in each case, the fact remains that we are even more in the dark concerning the pathogenesis of the other diseases of connective tissue than we are in the case of rheumatic fever. Here, at least, we have clear evidence for a single incit-

ing factor: infection with group A hemolytic streptococci. The relationship between the streptococcal infection and rheumatic fever is the point of attack of most current studies directed toward the problem of the fundamental nature of rheumatic fever, and, needless to say, there remain many gaps in our knowledge concerning this relationship. Even some of the broad aspects of the role of streptococci have not been settled; it is necessary, for example, to consider the problem of whether the presence of living streptococci is a primary requisite for rheumatic activity.

The concept that rheumatic fever can persist in the absence of viable streptococci arose from clinical observation and has been widely held by workers in this field. It was noted that during the interval between the acute streptococcal sore throat and the onset of rheumatic fever the organisms frequently disappeared from the upper respiratory tract or at least diminished in numbers to such an extent that they were no longer recoverable on culture. In fact, it was often necessary to establish the occurrence of a preceding streptococcal infection by employing serologic tests for antibodies. Although it was recognized that living streptococci might well be harbored within the tonsils or other areas inaccessible to the culture swab, other considerations led to the conclusion that persistent rheumatic activity did not depend on the presence of the organisms. Thus, the pathologic picture of the lesions of acute rheumatic fever did not appear comparable to those that result from direct bacterial infection. It was therefore assumed that something more subtle than the usual relationship between microorganism and infected tissue was concerned in the role of streptococci in rheumatic fever.

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This point of view received a challenge in 3 separate reports of postmortem bacteriologic findings published by Green,¹ Collis,² and by Thomson and Innes³ in 1939 and 1940. Each of these papers was concerned with the recovery of hemolytic streptococci, some of which were identified serologically as the same type as that causing the original infection, from the heart valves of patients dying with rheumatic fever. Green reported positive cultures in 8 of 9 cases, Collis in 22 of 42 valves from 17 cases, and Thomson and Innes in 5 out of 10 cases. The technics employed were similar in each study, and postmortem blood cultures were quite generally negative in these cases. Collis was acutely aware of the pitfalls involved in attempting to base definite conclusions on this type of autopsy bacteriology, carried out under conditions in which the organisms may have been quite widely disseminated during the manipulations, and he recommended that similar studies be undertaken with special precautions to obtain material as soon as possible after death and with the use of aseptic technics patterned after those employed in surgery. In view of the importance of the information, it is regrettable that several different clinics did not find it possible to follow this recommendation, but concentration on the problem was apparently interrupted by World War II. The introduction of penicillin has now made repetition of these studies all but futile. The only known attempt to confirm these bacteriologic findings with more adequate technics prior to the availability of penicillin was carried out on a relatively limited scale and remains unpublished (Watson and Hirst, cited in reference 4), but the findings did not support the view that living streptococci are usually to be found in active endocardial lesions. In general, the participation of viable streptococci in the genesis of rheumatic lesions has been considered unproved, and most workers have continued to act on the working hypothesis that the streptococcal infection operates through some kind of indirect action.

The whole question of the role of living streptococci has now been reopened by the studies of the group at the Streptococcal Disease Laboratory of the Francis E. Warren

Air Force Base. In pursuing their investigations on the prevention of rheumatic fever by treatment of streptococcal infections, these workers found that even when penicillin therapy was delayed for as long as 9 days after the onset of clinical pharyngitis, the incidence of rheumatic fever was sharply reduced in comparison with untreated or sulfadiazine-treated controls.⁴ These results were interpreted quite logically as indicating that living streptococci may be required for the development and perpetuation of rheumatic fever. However, it seems to the present writer that the findings are susceptible to alternative interpretations. For example, it is conceivable that a quantitative "dosage factor" may be involved and that even delayed elimination of streptococci in certain cases will have the effect of holding the stimulus to a level below that which will result in the overt manifestation of rheumatic fever. There is relatively little information on the manner in which the body disposes of killed streptococci, and the amount of streptococcal products accumulated may depend to some extent on the duration of infection.

In any event, there are clinical observations that are difficult to reconcile with the concept that the living streptococcus is an essential component of the active rheumatic process. Most clinicians concerned with the follow-up care of a rheumatic population have observed instances of streptococcal disease in which even prompt and vigorous penicillin therapy did not prevent recurrence of rheumatic fever, and there is no good evidence that the severity or duration of the attack has been greatly affected. The chronic cases of rheumatic fever with unequivocal persistence of disease activity over a period of many months are also not easily explained on the basis of persistence of streptococci unless the organisms can remain latent in some fashion such as that described by Denny and Thomas in the case of rabbits infected intravenously with streptococci.⁵

One might suppose that the widespread use of penicillin therapy would have quickly settled the issue of the role of viable streptococci, and, indeed, the failure of this medication to affect the course of the disease has served to support the thesis that living organisms are not impor-

tant. However, it must be conceded that penicillin has not been employed in a way that would satisfy a critical proponent of the contrary thesis. It is now well established that the bactericidal effect of penicillin is exerted only on streptococci that are in the active phase of growth and that once growth and metabolism have stopped, the organisms may remain viable in the presence of concentrations of penicillin much above those that are lethal for growing cells. In view of this fact, a test of the effect of penicillin on the course of rheumatic fever would require more massive doses and more prolonged administration than are ordinarily used, and in addition should probably include the concomitant use of cortisone in an attempt to reactivate metabolically inert streptococci. Further studies are obviously needed to solve this basic problem.

Clarification of the role of living streptococci is important not only because of the implications with regard to the clinical management of rheumatic fever. This information is also needed in determining the direction to be taken by future studies on the mechanism by which streptococci induce the disease. It has been pointed out that the protective effect of delayed penicillin therapy in the study discussed above throws doubt on hypotheses that explain the pathogenesis of rheumatic fever either on the basis of a direct toxic action of some streptococcal substance or on the formation of auto-antibodies.⁴ On the other hand, the results tend to support the thesis that a hypersensitivity reaction to some streptococcal antigen is involved. This, in turn, is in harmony with the most widely held view regarding the pathogenesis of the disease, since the majority of workers in the field are operating on the assumption that hypersensitivity, or at least some form of antigen-antibody interaction, is involved in the basic pathologic process.

Despite the general adherence to this point of view and its attractiveness as an hypothesis, proof of the role of hypersensitivity depends upon fragments of indirect evidence that cannot be considered conclusive. There is no information concerning the nature of the antigen-antibody system involved except for the strong implication that the antigen is probably of

streptococcal origin. The type of evidence on which the hypersensitivity theory is based include the following: (1) the similarity of the latent interval that separates the streptococcal infection and the onset of rheumatic fever to the time required to attain maximal antibody response after an antigenic stimulus; (2) the resemblance of certain manifestations of rheumatic fever to those of serum sickness; (3) the suggestive similarity of the lesions of rheumatic fever to those obtained in studies of experimental hypersensitivity in animals; and (4) the fact that rheumatic subjects on the average show a greater antibody response to various streptococcal antigens than do patients with uncomplicated streptococcal infections in the same epidemic.

The finding that patients with rheumatic fever have a greater mean antibody response to streptococcal antigens has been amply established by several independent studies. Similar results have been obtained with each of several antibodies, but there is always overlapping between the antibody titers of the rheumatic and nonrheumatic groups so that the differences are not absolute and have little diagnostic value. Nevertheless, this indication of an altered immune response must be considered of possible significance in the pathogenesis of rheumatic fever, and it has led to the concept that exaggerated immunologic reactivity may be an essential component of the rheumatic diathesis. A number of different investigators have attempted to test this concept by comparing the response of normal and rheumatic individuals to the injection of various non-streptococcal antigens. Unfortunately, the results obtained have not been in complete agreement. Creger, Choy, and Rantz⁶ found some evidence for hyperreactivity on the part of rheumatic subjects injected with such antigens as heterologous human erythrocytes, but the numbers of patients involved were too small to allow definite conclusions. Miller, Kibrick, and Massell⁷ observed a small increase in the mean titer of typhoid agglutinins in rheumatic patients as compared with controls after the injection of typhoid vaccine. The most definitely positive results in studies of this type were reported by Wagner and Rejholec⁸ who em-

ployed a *Brucella abortus* vaccine. They found a statistically significant difference in the titer of agglutinins, but an even more definite difference in the occurrence of incomplete antibodies as measured by the Coombs technic.

In contrast to these studies, completely negative results were obtained by other workers using a variety of antigens, including pneumococcal polysaccharide,⁹ influenza virus vaccine,⁷ and diphtheria toxoid.^{10, 11} No differences between rheumatic subjects and controls were found with still other antigens in extensive unpublished work carried out at Fort Warren (cited in reference 12). The experiments in which diphtheria toxoid was employed as antigen are of special interest for 2 reasons. In the first place, nonprecipitating antibodies were measured in addition to precipitins and the capacity of the sera to neutralize toxin *in vivo*. Since no difference was detectable in the formation of nonprecipitating antibodies by rheumatic and nonrheumatic subjects, it is evident that the results obtained by Wagner and Rejholec with incomplete antibodies to brucella do not represent a general phenomenon for this type of antibody. The second point of interest in the diphtheria toxoid studies is that only Schick-negative subjects were used, and consequently the booster type of antibody response was elicited. In theory, this should be more comparable to the situation in rheumatic fever, since the patient has almost certainly had one or more previous experiences with streptococcal antigens and the antigenic stimulus of a streptococcal infection preceding rheumatic fever would simulate that of a booster injection.

In summary, most of these efforts to obtain experimental evidence of hyperreactivity have revealed little or no difference between rheumatic patients and controls in the response to a variety of antigens. Certainly nothing comparable to the naturally occurring increased response to streptococcal antigens has been observed, and it is necessary to conclude that the theory of general immunologic hyperreactivity of rheumatic subjects has not been supported. There are, of course, other possible explanations for the enhanced streptococcal antibody response in rheumatic fever. For ex-

ample, it may be a reflection of a conditioning process resulting from greater previous experience of the susceptible individual with streptococcal infection. Alternatively, it may reflect a quantitatively greater antigenic stimulus that is not necessarily manifested by greater clinical severity of the streptococcal infection that precedes the attack of rheumatic fever. Regardless of the explanation for the pattern of immune response in rheumatic fever, the demonstration of hyperreactivity contributes to the continued emphasis on the probable role of antigen-antibody mechanisms in the disease.

Much of the work on the relationship of streptococci to rheumatic fever has as its goal the identification of the specific streptococcal component or components that are of primary importance, either as antigens or as biologically active substances with some direct action on the tissues. The difficulty with this approach has been the lack of criteria that would allow one to determine whether a given substance is implicated or should be eliminated as of no consequence. Up to the present time no experimental model has been devised that makes it possible to carry out an unequivocal test of the rheumatogenic potentiality of various substances in a laboratory animal. Individual investigators have interpreted and weighted the available evidence in many ways with the result that widely varying emphasis governs the attack employed in different laboratories. This diversification of approach is highly desirable in that the uncertainties concerning the mode of action of the streptococcus demand that a variety of points of view be brought to bear on the problem.

The investigator must look for clues to the mechanism of the disease in the clinical pattern and natural history of rheumatic fever. Thus, the subacute and chronic cases, in which the whole range of clinical manifestations of the disease may persist despite the progressive elapse of time from the inciting streptococcal infection, must be taken into consideration in the formation of hypotheses regarding the role of streptococci. Admittedly, if living streptococci are indeed associated with perpetuation of the disease, this pattern of the rheumatic

process affords little assistance in narrowing down the possible modes of action of streptococci, since all of the various components and potentialities of the organism would be present. On the other hand, if the disease can continue in the absence of living cells, the investigator's attention must turn to a search for ways in which the initiating infection can have such a protracted effect. If one chooses to base a theory on the framework of a streptococcal antigen-antibody reaction, it is possible to invoke the evidence obtained by experimental immunologists that even in the case of soluble antigens at least a small portion may remain in the tissue for long periods of time. Thus, it is conceivable that certain antigens released by streptococcal cells either during growth, as in the case of the several extracellular antigens, or upon disintegration of the organism may remain localized in some tissues long after the infection has been eliminated. The possibility of an additional potential source of retained bacterial products is suggested by the properties of the streptococcal cell wall. This rigid structural portion of the cell, which contains the group-specific polysaccharide as an integral component, is highly resistant to dissolution under physiologic conditions. Although microbial enzymes have been found that will lyse the cell wall, it has not been possible to demonstrate comparable enzymes in human tissues. Unless some unknown mechanism exists for dealing with this material, elimination of residual cell walls following phagocytosis and partial digestion of streptococci may be an inefficient and prolonged process.

The chronic cases of clinically manifest rheumatic fever obviously pose special problems in the understanding of the nature of the disease, but perhaps an even more perplexing question arises from the implications of the finding of Aschoff bodies in the auricular appendages of a large number of patients undergoing commissurotomy for mitral stenosis. For the most part, these patients show no clinical or laboratory evidence of rheumatic activity, and if one accepts the occurrence of Aschoff nodules as unequivocal evidence of disease activity it is necessary to assume that the process continues at a subclinical level almost indefinitely in a substantial proportion of cases. This assumption would be of considerable

significance in the study of the mechanisms concerned in rheumatic fever, and it is important both for the clinician to re-examine his criteria for rheumatic activity and for the pathologist to evaluate carefully the group of lesions classed together as Aschoff bodies. One pathologist has expressed the opinion that the lesions found in the auricular appendages obtained at operation do not have the typical structure of Aschoff bodies and are not characteristically distributed throughout all 3 layers of the heart.¹³ He concluded that the prevalence of these lesions did not justify a redefinition of the active rheumatic process.

In one of the most recent reports on this subject¹⁴ the authors attempted to divide the lesions found on biopsy of the auricular appendage into 2 types: the atypical lesions that were static in appearance and those showing findings consistent with an early or fresh lesion. As criteria for the latter type they selected the following: fragmentation of collagen fibers, alterations in the ground substance, degeneration of myofibers, and the occurrence of exudative inflammatory reaction in or around the lesion. On the basis of these criteria they found evidence of active lesions in only 2 per cent of the cases studied (8 of 400). This figure is not quite so overwhelming as that obtained in conventional studies in which one-third or more of the biopsies are interpreted as showing evidence of Aschoff bodies, and it seems more reasonable to fit these findings into the accepted pattern of the origin of rheumatic activity. These 8 patients showed no clinical evidence of activity, although the generally negative laboratory studies included definitely elevated sedimentation rates in 5 of the 8 cases. Antistreptolysin O titers are stated to have been noncontributory, but it is evident that a more intensive search for indication of a recent experience with streptococci is indicated in cases of this type. While it is too early to draw final conclusions on the implications of the biopsy data, the current status of the problem strongly suggests that it is unnecessary to assume that the rheumatic process can persist indefinitely without the repeated stimulus of streptococcal infection. On the other hand, it will not be surprising if it is demonstrated that some degree of rheumatic activity can occur in the absence of clinical and

laboratory findings, since there is almost certainly a threshold level below which the magnitude of an inflammatory process is too small to cause symptoms or detectable changes in the currently available tests for inflammation.

The preceding discussion emphasizes the defects that exist in our understanding of the chain of events leading from an infection with hemolytic streptococci to the occurrence of rheumatic fever. There is an evident need for continued investigation of various phases of the problem, ranging from studies on the behavior of the organism in host tissues and of the host reaction to its presence to further basic studies on the biology of the streptococcus. The role of the streptococcus has been stressed—some may think overstressed—to the virtual exclusion of other considerations that may bear on the pathogenesis of the disease. However, it is obvious that other factors play a role in the disease, not only because relatively few individuals appear to be susceptible and only a small percentage of streptococcal infections lead to rheumatic fever, but also because practically all diseases are modified to some degree by environmental and host factors. Nevertheless, the inciting action of streptococcal infections in rheumatic fever is the one key available that promises to provide information on the fundamental nature of the disease, and as mentioned above, it is this relationship to a specific bacterial agent that sets rheumatic fever apart from the other diseases of connective tissue. In any event, the problem of the role of the streptococcus must certainly be solved and the solution may at the same time lead to an understanding of the other factors that modify the pathogenetic effect of the organism.

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