Editorial

Susceptibility to Rheumatic Fever

In the past two decades important advances have been made in our understanding of host mechanisms in resisting infections. A comprehensive review by Janeway has recently appeared in which the various components of the body's defense mechanisms, their specific roles in response to bacterial infection, and the clinical syndromes of diminished resistance to infection are described.¹ He originally presented much of this review as the T. Duckett Jones Lecture at the 1967 annual meeting of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association. Although Dr. Jones is best known for his formulation of criteria for the diagnosis of rheumatic fever, he was also keenly interested in bacterial and host factors in the pathogenesis of this disease and for many years studied the immune responses of rheumatic patients at the House of the Good Samaritan in Boston. It is, therefore, appropriate to comment on some of these factors in relation to the development of acute rheumatic fever.

It is still not understood why only a relatively small number of individuals develop rheumatic fever following group A streptococcal infections while most do not. There is no evidence that this is related to varying "rheumatogenic" capacities of any of the more than 50 serological types of group A streptococci or to differences in extracellular enzymes and toxins. Host factors may, therefore, play the critical role in determining why some patients develop rheumatic fever following a streptococcal infection. The high familial incidence of rheumatic fever is well known and suggests a relationship between susceptibility of the host and constitutional factors, either genetic, environmental, or both. A recent study of families with more than one child with rheumatic fever showed that siblings tended to have the same clinical manifestations and cardiac sequelae, suggesting that genetic factors may be important.² However, efforts directed at finding a genetic marker in rheumatic families have resulted in contradictory findings.³,⁴ It has also been suggested that children of rheumatic families may have an increased susceptibility to streptococcal infections.⁵ However, a 5-year study of individuals in rheumatic and non-rheumatic families showed no differences in the incidence of streptococcal infections and of carrier rates among siblings of rheumatic children and a control population.⁶

Individuals in whom rheumatic fever develops after untreated streptococcal infections are usually only those who show a marked rise in antistreptococcal antibodies. It is of interest to note that streptococcal infections of the skin generally evoke only a mild immune response and, while such infections are common in children, they rarely, if ever, precipitate an attack of rheumatic fever.⁷ The immunological hyperreactivity against streptococcal antigens exhibited by patients during an attack of rheumatic fever has never been satisfactorily explained. It had been believed that individuals with repeated streptococcal infections were particularly prone to rheumatic fever and that the host's exaggerated immune response was related to these prior infections. However, the number of past infections was not found to be higher in rheumatic subjects than in a control population in studies which used type-specific antibody determinations to detect previous streptococcal infections.⁸,⁹

A different approach to the study of the relationship of the immune response to susceptibility to rheumatic fever is to examine

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the incidence of this disease in patients with abnormal immune mechanisms. Perhaps the best known and most common antibody deficiency syndrome in children is hereditary sex-linked agammaglobulinemia. Rheumatic fever has not yet been reported in children with agammaglobulinemia even though they are unusually susceptible to bacterial respiratory infections. While this may simply be due to the relatively small number of agammaglobulinemic patients observed to date, it is in striking contrast to the high incidence of rheumatoid-like arthritis and other collagen-vascular diseases in patients with this condition.1 In view of the inability of these children to form antibodies, it is not surprising that a disease which is characterized by an exaggerated immune response does not occur in this group. Patients with acute rheumatic fever characteristically have bone marrow plasmacytosis, high streptococcal antibody titers, and increased immunoglobulin levels. Recent studies have shown that both gamma-1A and gamma-2 globulin levels are increased, but that gamma-1M globulin is rarely elevated.9

Although it has not yet been possible to establish an immunochemical basis for susceptibility to rheumatic fever, evidence is accumulating which suggests that this disease may be the result of an immunopathological process. Kaplan and his associates have shown that group A streptococci cross-react with human heart muscle and that the streptococcal antigen involved resides in the cell wall of the organism.10 Similar reactions between streptococcal cell membranes and human heart muscle have also been demonstrated by Zabriskie and Freimer.11 More recently, Goldstein and co-workers12 have shown that group A streptococci cross-react with glycoproteins of human heart valves and that antibodies, against glycoprotein, could be detected in some children with rheumatic fever.

Nevertheless, despite our increasing knowledge of the biology of the Streptococcus and the immune responses of the host, as well as the discovery of antigens they share in common, the reason why the ubiquitous Streptococcus initiates the disease process in some individuals and not in others still remains a mystery.

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References