The search for host determinants of susceptibility to rheumatic fever: the missing link

T. Duckett Jones Memorial Lecture

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Thirty years ago, in his presentation "The Natural History of Rheumatic Fever," Dr. T. Duckett Jones said, "It has become the order of the day to consider that both the morbidity and the mortality in rheumatic fever have decreased to such an extent as to relegate the problem to a position of unimportance." He added, "One may wonder, and reach almost any desired conclusion, about what modifying role, if any, the biological characteristics of the streptococci may have played in the reputedly changing pattern. Others may prefer to ponder about the host factors, such as the effect of improved nutrition, improved housing, or other environmental advances. We know of no convincing study which removes these matters from conjecture."

Rheumatic fever is a challenge to physicians and scientists. Attempts to meet this challenge have brought forth new ideas regarding the clinical manifestations, epidemiology, pathogenesis, and control of this disease. Yet, despite the recognized decline in the incidence of rheumatic heart disease in the western world, it remains a serious health problem to children and young adults in developing countries. Why? Although there is no simple answer to this question, it is clear that research in rheumatic heart disease must continue. As expressed by T. Duckett Jones, "The exact incidence of the disease, or the decrease in incidence or severity, seems of less importance than the need to gain further knowledge of how and why human beings develop rheumatic fever."

In this presentation I will summarize our knowledge in one area of the pathogenesis of rheumatic fever. I will also dwell on the search for host determinants of susceptibility to the disease. It is possible that during this dissertation, more questions will be raised than answers provided. My hope is that what I have to say shall serve as an impetus for some bright young investigator to pursue these questions and to add to the knowledge developed over the last two decades.

Pathogenetic components of rheumatic fever

Almost a century ago, Sir Arthur Newsholme concluded from his epidemiologic observations that rheumatic fever was caused by a pathogenic microbe that infected individuals under certain environmental conditions and became manifest only in predisposed persons (figure 1.) The pathogenic microbe has been identified as the group A Streptococcus. Several studies have brought to light the nature of the environmental conditions and have emphasized the influence of crowding, nutrition, and the availability of medical care on the incidence of the disease.\(^3\)\(^5\) However, the third major link in this configuration, the nature of the "predisposed person" or susceptible host, still remains one of the more challenging pieces of the puzzle. I will attempt to provide some insight into the area of host susceptibility by addressing the following questions:

1. What is the evidence for hereditary influence?
2. Are there genetic markers that could be associated with rheumatic fever?
3. What is the pathogenetic mechanism for susceptibility?

Evidence of hereditary influence in susceptibility to rheumatic fever

That heredity plays a role in susceptibility to rheumatic fever was suggested by Newsholme\(^2\) and supported by other physicians of his time, including Walter Cheadle, whose own wife and son had rheumatic fever.\(^4\) The assumption that heredity influences susceptibility to rheumatic fever stems from many observations delineating the incidence of this disease in fami-
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**FIGURE 1.** Factors involved in the pathogenesis of rheumatic fever.

Families, such as the survey by the British Medical Council in 1927, which provided data on the prevalence of rheumatic fever in 721 putative "rheumatic families." A striking example of such a family tree is shown in figure 2, presenting a family reported by Pickles, a country physician who was able to personally examine and care for all but four of its descendants. These findings, together with subsequent observations reported by Read et al. and by Wilson and Schweitzer, have suggested that the hereditary mechanism for rheumatic fever involves a single recessive gene and that "susceptible persons acquire rheumatic fever much more readily than others." Despite these observations, agreement on the role of heredity is not universal. To quote Angelo Taranta, "Not only are genes shared by blood relatives, but also income, housing, and level of medical care, all of which influence the incidence of untreated streptococcal infections, and therefore of rheumatic fever." To control these confounding variables, Taranta and his co-workers studied the incidence of rheumatic fever in monozygotic and dizygotic twins. Their data revealed that monozygotic twins have a higher concordance rate for rheumatic fever than dizygotic twins, but this concordance was not greater than that for poliomyelitis or tuberculosis. More impressive, however, are data that show the high concordance in these twins for the individual manifestation of rheumatic fever.

**Genetic markers associated with rheumatic fever**

If the sum of these observations intimates a genetic susceptibility to rheumatic fever, should we not be able to find a genetic marker for this disease? Over the past 10 years, several studies have examined the possible association of rheumatic fever with histocompatibility antigens. Increased as well as decreased incidences of some of these antigens were found, but none of the data reached statistical significance. In 1979, Patarroyo et al. reported that an alloantigen designated as 883 was present in about two-thirds of patients with rheumatic fever as compared with control subjects. Indirect evidence derived from these data suggests that the undefined alloantigen 883 may be associated with the DR locus. This finding was of interest to us because of the heightened responsiveness of T cells from individuals with HLA-DR4 to collagen and the high prevalence of the HLA-DR4 in collagen-vascular diseases, particularly in patients with adult arthritis or juvenile rheumatoid arthritis. These observations prompted us to pursue studies to determine whether an association exists between known HLA-DR4 haplotypes and rheumatic fever. Our preliminary findings (Barrett DJ, Maclaren N, Ayoub EM: unpublished data) revealed the following: In examining the overall distribution of HLA antigens in rheumatic fever, we found a higher incidence of the HLA-DR4 haplotype in our rheumatic population. However, because the association between the DR4 antigen and other rheumatic diseases is found only in white patients, we reexamined our data. Although the frequency of this antigen was not increased in black patients, we found a strikingly and significantly higher incidence of HLA-DR4 antigen in our white patients with rheumatic fever.

**FIGURE 2.** Pedigree of family with rheumatic fever. Members with a history of rheumatic fever or signs of mitral stenosis are indicated by black circles. (Reproduced by permission of the publisher from Lancet 2: 241, 1943.)
fever as compared with nonrheumatic control subjects (figure 3).

Relationship of genetic markers to pathogenesis of rheumatic fever

Immune hyperresponsiveness to nonstreptococcal antigens. What is the significance of this association? When we examine its potential role in the pathogenetic mechanism that has been postulated for rheumatic fever, a relationship may become apparent. Speculating on the pathogenesis of rheumatic fever, Swift19 stated in 1928, "The pathogenesis of rheumatic fever can be explained by the existence in certain individuals of a condition of hypersensitiveness (allergies—hyperergy) to streptococci." Ever since, investigators have been attempting to define this condition of "hypersensitiveness." Of the many studies that attempted to show a state of immunologic hyperresponsiveness to a variety of nonstreptococcal and streptococcal antigens, the most notable was reported by Rejholek in 1957.16 In this prospective study, 998 children were immunized with Brucella vaccine and their immunologic responses to the Brucella antigen were measured. Follow-up of these children over a period of 1 year yielded 12 cases of rheumatic fever from among 212 children who acquired streptococcal pharyngitis. All 12 cases of rheumatic fever developed from within the group that had shown a high antibody response to the Brucella vaccine.

Immune hyperresponsiveness to streptococcal antigens. The above observation appears to support the concept of a hyperimmune status in the rheumatic individual. However, in view of the fact that brucellar infections bear no known etiologic relationship to rheumatic fever, one wonders if such a hypersensitive state also exists for the group A Streptococcus and its antigens. Several studies to resolve this issue suggested initially that patients with rheumatic fever manifest a hyperresponsiveness to some of the streptococcal extracellular products, such as the streptolysin O and streptokinase. A study of antibody response to various streptococcal extracellular products by Dr. Wannamaker and myself did not support these contentions.17 Although the mean antibody titers to the streptococcal deoxyribonuclease B (DNase B) were higher in patients with acute rheumatic fever, the antistreptolysin O and antinicotinamide adenine dinucleotidase (NADase) titers were lower in patients with rheumatic fever than in patients with nephritis.

In contrast to these results, studies in our laboratory suggest that an immune hyperresponsiveness may exist to a specific streptococcal cell-wall antigen, the group A carbohydrate. As shown in our initial observation,18 antibody to this streptococcal component persists at high levels and longer than the ASO and the anti-DNase B in patients with rheumatic fever (figure 4). However, the prolonged persistence of high levels of this antibody is limited to patients with rheumatic valvular disease and is not seen in patients with poststreptococcal glomerulonephritis or in patients with

FIGURE 3. Prevalence of HLA-DR haplotypes in white (left) and black (right) patients with rheumatic fever and in nonrheumatic control subjects. Incidence of HLA-DR4 phenotype is significantly increased (p < .01) in whites with rheumatic fever as compared with controls.
rheumatic fever without cardiac involvement, such as isolated Sydenham's chorea. The specificity of this response was further illustrated in a prospective study in which 70 patients with acute rheumatic fever were followed up in our clinic for 7 years.\textsuperscript{19} Analysis of these patients yielded three groups: one group of 28 patients with mitral valvular disease that persisted during the period of observation, a second group of 20 patients with mitral insufficiency but in whom the valvular disease resolved clinically during this period of observation, and a third group of 22 patients without cardiac involvement. Serial determination of the antibody to the group A carbohydrate revealed that approximately 90\% of patients with persistent valvular disease had elevated levels of this antibody at the end of the period of observation (figure 5). In contrast, the majority of the other patients manifested a return to normal levels within 2 to 3 years after the initial attack of acute rheumatic fever.

While these findings show that certain patients with rheumatic fever have an exaggerated immune response to a streptococcal antigen, the group A carbohydrate, the intriguing aspect of these data relates to prior observations on the response of experimental animals to this antigen. Extensive studies by several groups of investigators\textsuperscript{20-23} have shown that the magnitude of the

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**FIGURE 4.** Mean antibody titers to the group A streptococcal carbohydrate in 15 patients with rheumatic valvular disease, 16 patients with isolated Sydenham’s chorea, and 12 patients with poststreptococcal glomerulonephritis. The titers were determined at various intervals after onset of the acute episode. All patients with rheumatic fever had been maintained on penicillin prophylaxis after the acute attack. (Reproduced by permission of the publisher from J Exp Med \textbf{128}: 1081, 1968; copyright 1968 by The Rockefeller University Press.)

![Graph](https://example.com/another_graph.png)

**FIGURE 5.** Incidence of elevated titers of antibody to the group A streptococcal carbohydrate at various intervals after acute attacks in 28 patients with persistent rheumatic mitral insufficiency throughout the period of follow up, 20 patients in whom the mitral insufficiency resolved during follow up, and 22 rheumatic patients without cardiac involvement. (Reproduced by permission of the publisher from Clin Immunol Newsletter \textbf{3}: 107, 1982; copyright 1982 by Elsevier Science Publishing Co., Inc.)
response and the idiothetic heterogeneity of the antibody to the group A carbohydrate that is produced after immunization of laboratory animals are genetically controlled. This observation is of special relevance because the locus that controls the immune response to a variety of antigens in mice, the H-2 or Ir/Is locus, appears to correspond to the DR locus of the major histocompatibility complex on the sixth chromosome in man.24

Thus it would appear that we have nearly come around full circle. On one hand we have presented preliminary evidence for the presence of a genetic marker for susceptibility to rheumatic fever, and on the other hand we have demonstrated the potential for a genetically influenced state of altered immune regulation to the streptococcal group A carbohydrate antigen. How can we invoke a link between these two findings and the pathogenetic mechanism of the disease? A hypothetical link may be suggested by recent data on mechanisms involved in the control of the immune response. Studies by Greene et al.25,26 and by Barrett et al.27 in our laboratory showed that the human lymphocyte response to mitogens and antigens in vitro can be suppressed by a soluble lymphokine from concanavalin A–activated lymphocytes. This suppressive substance appears to exert its effect by binding to a glycoprotein receptor(s) on the mononuclear cell surface membrane. The addition of N-acetylgalcosamine and rhamnose blocks the suppressive effect of this substance(s). The fact that the group A streptococcal carbohydrate is a polymer of the two sugars, N-acetylgalcosamine and rhamnose, makes this finding particularly relevant to our problem. One could therefore speculate that there is a link between the specific chemical structure of this streptococcal antigen and its potential influence on the immune response. This, together with evidence for a genetically acquired influence that may modulate the immune response to this antigen in certain individuals, could form the hypothetical basis for a mechanism that may determine host susceptibility to rheumatic fever. This possibility is currently being pursued in our laboratory in an effort to comply with T. Duckett Jones’ plea to “remove these matters from conjecture”21 and, hopefully, to end the long search for this missing link.

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