Pathogenesis of acute rheumatic fever and rheumatic heart disease: evasive after half a century of clinical, epidemiological, and laboratory investigation

E L Kaplan

Rheumatic fever and rheumatic heart disease continue to be a problem for medical and public health communities—the fact that penicillin has failed to eradicate this disease process is irrefutable proof of the need for more laboratory, epidemiological, and clinical research.

The report by Li and colleagues in this issue of Heart once again reminds both basic scientists and clinicians of the unsolved mystery of the pathogenetic mechanism(s) responsible for the development of rheumatic fever and rheumatic heart disease. These authors present observations implying a role for this virus in what they term “chronic, acquired valvar disease”. While their report evokes questions about study design, methodology, and the relative paucity of firmly supporting data, nevertheless the concept must provoke thought. Li and colleagues’ attempt to demonstrate a pathogenetic role for herpes simplex I as an agent in the development of rheumatic valvar heart disease falls short of establishing a relation. Additionally, the authors fail to adequately describe and take into account the sizeable body of evidence supporting the role for the group A β haemolytic streptococcus (Streptococcus pyogenes). Rheumatic fever and rheumatic heart disease remain a significant cause of cardiovascular morbidity and mortality in countries around the globe even into the 21st century; it is a medical and public health problem which needs a solution.

This hypothesis is not the first time that a virus has been postulated to be pathogenetically related to rheumatic fever and its sequel, rheumatic heart disease. For example, among the many previous attempts to attribute rheumatic heart disease to viral infection were the reports in the 1960s by the late George Burch and colleagues who described valvar lesions associated with coxsackie B virus infection in cynomolgus monkeys. They published intriguing photographs of mitral valve lesions in monkeys that were considered to be essentially identical to the early valvar lesions of acute rheumatic fever.2,4 Twenty years later, Wedum—and later Peter Rowe—was enthusiastic about a viral contribution to rheumatic fever when she hypothesised a pathogenetic role for the measles virus in rheumatic heart disease, either alone or as a co-factor with group A streptococci.7,8 Numerous other more recent examples could be cited. Yet, similar to the present report, all still remain hypotheses.

**PATHOGENESIS OF RHEUMATIC FEVER**

Extensive reviews have been written about the pathogenesis of rheumatic fever and existing data have been exhaustively reviewed. The data supporting a role for the group A streptococcus as the triggering agent for development of rheumatic fever cannot be ignored.7 However, in concluding that currently available data are not sufficiently convincing about a role for viruses in the pathogenesis of rheumatic fever, one must be careful not to be intolerant of new concepts. It is clear that viruses may cause heart disease; viruses have been implicated in other forms of cardiovascular disease such as myocarditis and even atherosclerotic lesions to name only two.8,9 Autoimmune mechanisms have been postulated to account for cardiac damage.10,11 But there is little to directly associate these viruses with rheumatic fever.

Historically there have been three major hypotheses of which have been promoted during the past five decades to explain a streptococcal pathogenesis for rheumatic fever. These include: (1) direct infection (for example, by the group A streptococcus); (2) effects of a streptococcal toxin (streptolysin O has been among the most commonly discussed); and (3) most feasibly, the concept of antigenic mimicry in association with an abnormal immune response.

During the past half century, it is the concept of antigenic mimicry and/or an abnormal immune response to group A streptococcal extracellular or somatic antigens which has been most interesting. The issue was concisely summarised in a recent review by Cunningham who commented: “The disease is autoimmune in nature and most likely results in part from the production of autoreactive antibodies.” Yet, although many candidate group A streptococcal antigenic moieties have been investigated, none has been unequivocally demonstrated to be the inciting “culprit” or to fully explain the disease process.

**AUTOIMMUNE HYPOTHESIS**

Among the most widely promoted concepts in support of an autoimmune hypothesis involving the group A streptococcus has been the observation offered in the mid 1960s by Stollerman. Perceptively, he noted an intriguing epidemiological correlation between outbreaks of group A streptococcal infection and rheumatic fever in children. The hypothesis that group A streptococcal infection is a necessary but not sufficient factor to cause rheumatic fever was subsequently postulated by several investigators. Since then, numerous reviews have been written about the autoimmune hypothesis of rheumatic fever, and this hypothesis remains one of the most important hypotheses to explain the pathogenesis of rheumatic fever.

The autoimmune hypothesis is based on the observation that the immune system reacts to group A streptococcal antigens, leading to the development of autoantibodies that may cross-react with cardiac tissue. This hypothesis is supported by several lines of evidence, including the presence of anti-streptococcal antibodies in the sera of patients with rheumatic fever, the detection of anti-cardiac antibodies in the sera of affected individuals, and the demonstration of a cross-reaction between streptococcal and cardiac antigens in vitro.

However, despite the compelling evidence supporting the autoimmune hypothesis, there are several limitations to this explanation. First, the precise nature of the autoantigens involved in the pathogenesis of rheumatic fever remains unclear. Although several autoantigens, including heat shock proteins and cardiolipin, have been proposed, their role in the disease process is not well understood. Second, the autoimmune response in rheumatic fever appears to be complex, involving both cellular and humoral immunity, and it is not clear how these different components interact to cause the disease.

In addition, the autoimmune hypothesis does not explain the sharp geographic and temporal variations in the incidence of rheumatic fever, which are not well understood. Furthermore, the hypothesis does not account for the apparent decline in the incidence of rheumatic fever in recent years, despite a steady increase in the prevalence of group A streptococcal infection. Finally, the autoimmune hypothesis does not explain the similarity of rheumatic fever across different populations, which is inconsistent with the concept of an autoimmune response to a specific antigen.

Given these limitations, it is clear that the autoimmune hypothesis is not the sole explanation for the pathogenesis of rheumatic fever. Other factors, including viral and environmental triggers, may also play important roles in the development of this disease. Nevertheless, the autoimmune hypothesis remains an important cornerstone of our understanding of the pathogenesis of rheumatic fever, and further research is needed to better elucidate the complex interplay between autoimmunity and infection in the development of this disease.
strepococcal upper respiratory tract infections associated with a relatively limited number of M-protein types which were followed by outbreaks of rheumatic fever. In attempting to focus on an inciting factor, he used the term “rheumatogenicity” or “rheumatogenic M-types” to try to limit the number of streptococcal strains that might have the capacity to initiate the postulated immune response during the latent period between infection and onset of clinical disease. Reports such as the one by Kuttner and Krumweide more than 60 years ago, and other examples of an increased frequency with which a relatively limited number of specific M-types (for example, M-5, M-6, M-18) have been isolated during rheumatic fever outbreaks in communities, have provided support for a concept of enhanced rheumatogenicity and—by inference—suggesting antigenic mimicry. Yet, no investigation to date has incontrovertibly identified a/the “rheumatogenic factor”. This lack of evidence has resulted in scepticism (perhaps healthy) about differences in rheumatogenicity among the more than 130 now recognised different M protein types of group A streptococci and has led some investigators to search for other inciting agents.

Multiple attempts to strengthen the available data explaining a streptococcal pathogenesis by identifying a specific animal model for the study of rheumatic fever and rheumatic heart disease have not been entirely successful. Numerous models created by injecting various somatic and extracellular antigens have been injected into multiple animal species and almost always have resulted in lesions, but none of the models have the combined clinical or pathologic features of rheumatic fever/rheumatic heart disease. The only recognised natural host (and reservoir) for group A streptococci is the human, and an appropriate animal model has not been identified in half a century. Thus, laboratory efforts to define a comprehensive concept of streptococcal rheumatogenicity have been severely hampered.

MITRAL VALVE INVOLVEMENT

An equally unsettling example when thinking about group A streptococci and antigenic mimicry is the fact that clinical studies have emphasised the overwhelming predisposition for involvement of the mitral valve. Embryologists remind us that all four valves develop from the same embryonic cell rest. If true antigenic mimicry involving heart valve tissue is responsible, would one not expect random involvement of a fourth valve? Investigators to search for other inciting agents.

The inability to solve this pathogenetic riddle about rheumatic fever represents more than simply the intellectual challenge. Available data confirm this cardiovascular disease to be a continuing problem for medical and public health communities even in industrialising countries. It is very difficult to control any disease process until the pathogenetic mechanisms are understood. The fact that penicillin has clearly failed to eradicate this disease process is irrefutable proof to many of the need for more laboratory, epidemiological, and clinical research. Continuing investigation is imperative to either separate cardiac sequelae of these two vastly different microorganisms (group A streptococci and herpes simplex 1) or to determine if the cardiac or valvar damage represents a similar form of end organ damage from two very different infectious agents. The challenge is obvious.

REFERENCES