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

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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.

T he 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 pathogenic 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 streptococcus.5 6 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 categories of hypotheses 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 postulated as a streptococcal pathogenesis for rheumatic fever.1 These authors present evidence supporting a role for the group A streptococcus as the triggering agent for development of rheumatic fever. Almost individually each hypothesis has been supported by data that fail to account for the vast number of rheumatic fever cases. 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.”7 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
Despite clinical observations such as that by Pickles\textsuperscript{13} in the early 1940s, and numerous molecular based studies of the molecular mechanisms. The fact that penicillin has always resulted in lesions, but none of the models 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 and damage to all four heart valves in a random fashion? This observation must be answered before there can be unqualified acceptance for the antigenic mimicry hypothesis?

To omit the role of human host genetic or acquired variability in rheumatic fever susceptibility would be unwise. The concept of differing human susceptibility and human host factors was not addressed by Li and colleagues.\textsuperscript{1} That is, there is variation in how humans respond to 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 and damage to all four heart valves in a random fashion? This observation must be answered before there can be unqualified acceptance for the antigenic mimicry hypothesis?

One of the five might have valvar involvement (carditis), another only arthritis (joints), a third chorea (central nervous system involvement), a fourth erythema marginatum (skin), and the fifth individual not develop any sequelae? What other interpretation is logical?

Even based upon the currently available incomplete data, I believe that there is little question about the pathogenetic role of the group A streptococcus in rheumatic fever! But until an encompassing prospective effort among epidemiologists, clinicians, microbiologists, immunologists, and other basic scientists can be initiated to provide more convincing data, speculation about the pathogenetic mechanism(s) will persist. As clinicians and scientists, until the exact mechanisms are known we must keep an open mind. Thus, even though investigative efforts like that reported by Li and colleagues\textsuperscript{1} might be subjected to criticism, we are obligated to consider them.

**CONCLUSION**

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.\textsuperscript{17,18} 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**