Epidemiological Approaches to Understanding the Pathogenesis of Rheumatic Fever

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The rheumatic fever syndrome has been clinically recognized for several centuries. Its cause was unknown, despite clinical suggestions of an association with haemolytic streptococcal infection. How and why 'acute articular rheumatism' affected the heart remained an intriguing mystery.

It was the meticulous studies of bacteriologist Rebecca Lancefield in the 1930's that resulted in a laboratory method for differentiation of haemolytic streptococci. This technique ultimately led to the epidemiological conclusion that only the group A streptococcus can lead to this non-suppurative sequel of a bacterial infection. This observation stimulated serious attempts to solve the pathogenetic puzzle of this disease which represented a significant public health problem. As recently as the Second World War, rheumatic fever caused major problems in military forces; the disease was also common in the civilian populations of the United States and Western Europe in the 1950's and early 1960's. (Less was known about the incidence of rheumatic fever in the rest of the world at that time, for it was thought that this was primarily a disease of temperate climates and not of tropical zones.) Clinicians, epidemiologists, immunologists, pathologists, and bacteriologists all sought to explain the 'enigma.'

These intensive efforts began over four decades ago. Yet today the problem remains. Why is this so, and what can be done to solve it?

As one reviews past efforts to understand and to control rheumatic fever, it appears that two widely acclaimed observations may also have had an unintentionally negative effect. The first was the careful epidemiological study at the Warren Air Force Base, showing that adequate antibiotic therapy of streptococcal sore throat could prevent rheumatic fever. The other was the Danish observation documenting a fall in incidence of rheumatic fever temporally related to a rise in the standard of living. In retrospect, especially from a public health point of view, these two observations provided hope that penicillin and better living conditions would promptly lead to the marked reduction in, or even the disappearance of, rheumatic fever around the world.

This reduction did occur to some extent, especially during the last two decades in the industrialized countries of North America, Western Europe, and in Japan. How much of this fall in incidence was due to primary and secondary penicillin prophylaxis or to improvements in crowded living conditions has never been completely determined, but the decrease did occur concomitantly. However, a 'negative' result of this decrease in rheumatic fever has been that, to some extent, it has discouraged both basic and applied studies of the pathogenetic mechanisms leading to the disease. Furthermore, this projection undoubtedly has influenced governments and public health authorities (especially in some developing countries) to assign somewhat lower priorities for public health programmes for control of rheumatic fever. Decisions appear to have been made to wait for improvement in efficiency of health delivery systems and in living standards, rather than undertake active campaigns.

We now find ourselves facing a peculiar situation: rheumatic fever and rheumatic heart disease—called by some the most preventable of cardiovascular diseases—remain responsible for significant morbidity and mortality in these developing countries of the world, countries which make up about two thirds of the world's population. Predictions suggest that many of these countries which suffer severe economic constraints will not be likely to be able to raise their standards of living sufficiently in the foreseeable future to significantly alter the incidence of this disease. The adverse economic impact of rheumatic fever and
chronic rheumatic heart disease has been described.\textsuperscript{4,5} It has become obvious to clinicians, to basic scientists, to epidemiologists, and also to public health authorities that renewed emphasis should be directed to defining the basic pathogenetic mechanisms responsible for development of rheumatic fever. Control measures can be more efficiently designed after the pathogenetic mechanism(s) is understood. For example, an effective streptococcal vaccine, one control measure frequently mentioned, is unlikely until the aetiologial role of the specific responsible streptococcal antigen is completely understood.

The need for carefully collected epidemiological data is essential to attaining this goal. Important advances have been made in the study of the molecular biology of the group A streptococcus. However, epidemiological observations make important contributions to understanding the basic science. This is especially true in view of the fact that there is no satisfactory natural or experimental animal model of rheumatic fever. In his Duckett Jones lecture, 'The Influences of Infection on the Geography of Heart Disease' Krause summarized this concept very well: 'We must recognize the issues pertaining to the epidemiology, pathogenesis and prevention of rheumatic fever, considering the prevailing geography in each country. When we do that there will emerge new medical opportunities for eliminating this disease, area by area'.\textsuperscript{6}

Several examples of how careful epidemiological contributions can assist in explaining the pathogenesis of rheumatic fever can be cited:

First, additional information is needed about the group A streptococcus itself. It has been suggested by Stollerman, Bisno, and colleagues that not all strains of group A streptococci lead to rheumatic fever; they believe that there may be unique streptococcal strains with 'rheumatogenic' potential.\textsuperscript{7,8} However, no factor has yet been isolated to identify which streptococcal strains could have 'rheumatogenic potential' so that they can be submitted to the bacteriologist for molecular dissection. Collection of strains of group A streptococci from epidemics and also from individual cases of rheumatic fever are needed. Furthermore, both rheumatic fever-associated and routine strains of the same serological type must be collected and examined at the laboratory bench. It appears, for example, that M type 5 is frequently associated with rheumatic fever, making this one serotype that deserves special emphasis.

Second, more must be learned about the epidemiology of group A streptococcal infections themselves. It is impossible to fully understand the non-suppurative sequelae of group A infections until uncomplicated streptococcal infections themselves are fully understood. The observation has been made that rheumatic fever follows only infection of the upper respiratory tract (in contrast to acute nephritis which may follow either skin infection or upper respiratory tract infection).\textsuperscript{9} Additional observations are needed to further document and to explain this. The immunological difference between acute streptococcal upper respiratory tract infection and the relatively harmless, but common streptococcal carrier state also is not understood.\textsuperscript{10} Furthermore, the host immune response to group A streptococcal infection is quantitatively (and perhaps qualitatively) different following streptococcal pyoderma when compared with upper respiratory tract infection.\textsuperscript{11} Could these epidemiological observations represent valuable pathogenetic clues?

Third, the question of specific human susceptibility to streptococcal infection and rheumatic fever has continued to perplex scientists and clinicians. Genetic susceptibility has been included in many hypotheses. However, it seems unlikely that this can be the only factor involved since changes in human genetic susceptibility during a very short period of time (ie, three decades) would seem impossible and could not explain the observed decrease in rheumatic fever.

Recently, provocative data have become available suggesting the presence of specific alloantigens on non-T cells which seem to indicate rheumatic susceptibility in 75–90% of individuals with rheumatic heart disease.\textsuperscript{12–14} This intriguing possibility requires additional controlled epidemiological study in many different ethnic groups, geographical locations, and in patients with different stages of acute rheumatic fever and chronic rheumatic heart disease. If substantiated, the ability to define individual 'susceptibility' to rheumatic fever would have obvious public health implications for the vast populations of developing countries, and even for schoolchildren in the industrialized countries of the world.

As a fourth example of the need for intensified epidemiological emphasis in searching for pathogenetic mechanisms responsible for rheumatic fever is the practical clinical entity of what has been referred to as 'malignant' or 'juvenile' mitral stenosis.\textsuperscript{15} It has been reported from some areas of the world that rheumatic mitral stenosis develops rapidly in young children, often occurring between six and ten years of age. Yet, there is insufficient supporting data to provide convincing proof that the disease process actually is different in these children. In fact, the suggestion has been made that these children with rapidly progressing valvular disease are simply individuals who have experienced recurrent attacks of rheumatic fever, causing more severe valvular heart damage to occur at an
accelerated rate. Careful studies of host and of bacterial factors in these patient populations could provide important new and useful insight about both the pathogenesis of rheumatic heart disease and its control.

SUMMARY
Thus, in 1985, over four decades after discovery of the first important clue towards understanding the pathogenesis of rheumatic fever, medical science still has not defined the mechanism(s). Objective evaluation of available data from around the world indicates that penicillin alone will not lead to effective control. Furthermore, in geographical areas where streptococcal infections, rheumatic fever and rheumatic heart disease are most prevalent, it seems unlikely that standards of living will rise quickly enough to impact on the incidence of this disease during the next several decades.

There is renewed worldwide interest in and emphasis on the implementation of rheumatic fever control programmes. The World Health Organization (WHO), in collaboration with the International Society and Federation of Cardiology (ISFC), is promoting a strategy to develop national programmes for the prevention of rheumatic fever and rheumatic heart disease. In 1984–5, designated by the ISFC as the Year of the Rheumatic Child, the WHO Cardiovascular Disease Unit initiated plans to collaborate with 15 developing countries in the development and implementation of rheumatic fever control programmes. Because of the inescapable conclusion that control methods are most efficiently applied when pathogenetic mechanisms are understood, additional epidemiological data should be collected to assist both basic scientists and clinicians in understanding more about this unique disease.

REFERENCES