The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease

T. Duckett Jones Memorial Lecture

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I AM DEEPLY HONORED to have been invited to give the 1984 T. Duckett Jones Memorial Lecture. This year marks 40 years since Dr. Jones first published his paper entitled "The Diagnosis of Rheumatic Fever." Jones had the foresight to recognize the importance of standardized diagnostic criteria from three points of view. He wrote: "(1) Otherwise, [without standardized criteria] the incidence of rheumatic fever may be interpreted as varying greatly whether the data are collected by surveys, the development of a rheumatic fever register, making the disease reportable, or the study of hospital records. (2) The interpretation of study programs of prevention and care is obviously dependent on such diagnostic criteria." Jones' third point dealt with the importance of standardized diagnostic criteria if valid information regarding ultimate prognosis were to be obtained and provided to patients and their families. It is noteworthy that the primary benefits he described were not so much the improved clinical management of individual patients with rheumatic fever, but rather facilitation of the collection of meaningful incidence data and evaluation of the effectiveness of prevention programs. In this article I would like to discuss the dramatically changing incidence of rheumatic fever and its relation to our preventive efforts. The studies I will present were possible only because of the broad acceptance and utilization of the diagnostic criteria promulgated by Dr. Jones 40 years ago.

Throughout history people have been intrigued by the apparent appearance and disappearance of human disease, believed by many to be actions of the gods in direct response to human behavior. Over the years there have been attempts to develop a scientific ration-
FIGURE 1. Comprehensive care and changes in rheumatic fever incidence, 1960–64 to 1968–70 (Baltimore, black population, ages 5 to 14 years).

comprehensive care solely on the basis of these findings. A further analysis was therefore carried out with the following rationale: If the comprehensive care programs were indeed responsible for the observed decline in rheumatic fever by providing quality ambulatory care to children, they could have had such an impact only in children who had clinically overt pharyngitis. If so, we would expect the decline observed in rheumatic fever to have been limited to those cases that had been preceded by clinical pharyngitis and to see relatively little change in the incidence of cases preceded by subclinical pharyngitis, since such children would have had no reason to seek medical care and consequently the comprehensive care programs would not be expected to have any impact in this group. As seen in figure 2, when analyzed in this fashion the entire decline in rheumatic fever was found in cases that had been preceded by clinically overt acute pharyngitis. Thus the data up to 1970 were highly consistent with the hypothesis that in Baltimore, the decline in rheumatic fever, which was limited to blacks, was primarily a result of the comprehensive care programs in the inner city.

More recently, we carried out a third study in Baltimore utilizing the same methods as the two previous investigations. As seen in figure 3, from 1968–70 to 1977–81, incidence rates of rheumatic fever dropped dramatically in both whites and blacks to extremely low rates. Perhaps the most dramatic view of these changes is seen in figure 4, which shows spot maps for rheumatic fever cases for the first and last 5 year periods of this study, 1960–64 on the left and 1977–81 on the right. Only five cases were seen in Baltimore from 1977 to 1981, and all were clinically mild.

National data for the United States. These findings are consistent with data reported from other communities, such as those of Land and Bisno from Memphis, Tennessee.4 Available evidence suggests that this is also the pattern in other cities in the United States in most populations. National data for hospital discharges with a diagnosis of rheumatic fever from the National Hospital Discharge Survey conducted by the National Center for Health Statistics, and kindly provided by Dr. Edward Bacon of the Center, confirm this decline (table 1). The decline is also seen when the rates are

FIGURE 2. Changes in the annual incidence of first attacks of rheumatic fever in relation to preceding clinical respiratory infection.

FIGURE 3. Average annual incidence of first attacks of rheumatic fever ages 5 to 19, by race, Baltimore, 1960–81.

examined by age and race (table 2). Thus we have a marked decline in rheumatic fever, indeed a virtual disappearance of the disease in both blacks and whites in Baltimore, and this appears consistent with most available data from elsewhere in the United States.

“New” and “disappearing” diseases. What can account for the extraordinary phenomenon we are observing in acute rheumatic fever in the United States? To address this issue I would like to discuss briefly other diseases that have either appeared or at least increased in incidence or disappeared or declined in incidence in the course of the 20th century. Among the “new” diseases, or those that have at least increased markedly in incidence during the last few decades, are: lung cancer, clear cell carcinoma of the vagina, phocomelia, toxic shock syndrome, legionnaires disease, Kawasaki disease, Reye syndrome, Lyme arthritis, and AIDS. Each has attracted considerable interest, including perhaps most notably the rapid increase in AIDS.

What can account for the relatively rapid appearance of a disease? Certainly better diagnosis and recognition or differences in artifacts of coding can also play a role. Increased physician awareness of infectious agents and changes in the prevalence of the agents or in the biological characteristics of the agents that relate to virulence may also be critical. For diseases having other causes, new agents introduced into the environment or new exposures to them may account for the increase. Finally, removal of certain protective mechanisms may play a role. For example, it has been suggested that Hodgkin’s disease has a higher incidence in upper socioeconomic individuals because such individuals are protected from certain early childhood infections such as Epstein-Barr virus, a model similar to that seen in polio.5

Below are listed some diseases that seem to have disappeared or at least declined in incidence during the 20th century:

As a result of planned eradication campaigns:
- Infectious diseases
  - Smallpox
  - Polio
- Nutritional rickets

As a result of changes in medical practice:
- Retrorenal fibroplasia
- Not completely understood:
  - Stomach cancer
  - Uterine cancer
  - Peptic ulcer
  - Celiac disease
  - Stroke
  - Myocardial infarction
  - Endocardial fibroelastosis

Some of these diseases seem to have declined primarily as a result of planned and well-organized eradication campaigns. These include infectious diseases such as smallpox and poliomyelitis and diseases such as nutritional rickets, which have declined in incidence as a result of specific dietary supplementation. Second, we have diseases that have almost disappeared as a result of changes in medical practice. Perhaps the most dramatic example is retrorenal fibroplasia.

Other diseases have disappeared without any specific eradication campaign. For example, stomach cancer has declined markedly in the United States, as has uterine cancer, with no explanation immediately at hand to account for these changes. Other diseases such as peptic ulcer and celiac disease have also declined and the causes for the declines remain unknown. Isolated endocardial fibroelastosis, without aortic disease, appears to be much less frequent than in previous years. Finally, and perhaps most noteworthy are the
declines in mortality from stroke and coronary heart disease.

What can account for dramatic decreases in incidence and mortality of disease? Changing diagnostic approaches and changes in coding can play a role and produce artifactual changes. For diseases caused by infectious agents, it is at least theoretically possible that the virulence of the agent may diminish or the prevalence of human exposure to the agent may decline. If caused by exposures to other etiologic agents in the environment, such may change over time as existing hazards are recognized and controlled. Finally, changes in lifestyle or changes in the quality and accessibility of medical care may play a role in declines observed in the incidence of disease.

Possible explanations for the virtual disappearance of rheumatic fever. With this background, how can we explain the changes observed in the incidence of rheumatic fever? Reasonably valid population-based incidence data for rheumatic fever did not become available until the 20th century. Hence, although rheumatic fever has been present for centuries and according to some, may have been present in antiquity, it is difficult to state whether at some point in time there was a sudden appearance of the disease or a sudden rise in the incidence of the disease. What is clear, however, is that the 20th century has witnessed a sharp decline in rheumatic fever, at least in the United States and in other economically developed countries.

Could the decline in rheumatic fever be due to changes in the streptococcus itself? Let us examine the possibilities. The first would be that the incidence of streptococcal infections has declined. Although some experts believe that there has, in fact, been a decline in the incidence of streptococcal infections, it is difficult to document such a change. In fact, Hall and Breese have reported from Rochester, New York, that the number of throat cultures positive for group A streptococci did not decline during a time period when a decline in rheumatic fever was observed (unpublished observations). Unfortunately, there is no ongoing systematic data collection system in the United States that could provide the information needed to address this issue.

If the incidence of streptococcal infections has in fact declined, the decline could be part of a cyclical pattern of increases and decreases in incidence of streptococcal infections and that we may just be on the down side of the curve at this point in time. If indeed there is such a cyclic phenomenon, we might anticipate another rise in streptococcal incidence in the future and with it a possible rise in rheumatic fever incidence.

Could there have been a change in the prevalence of rheumatogenic types in our communities or in the incidence of infections produced by rheumatogenic types? Although there is strong evidence that there are nephritogenic types, the case for rheumatogenic types is not clear. Support for this contention comes from several types of evidence: (1) The temporal and geographic variations observed in rheumatic fever incidence are consistent with the existence of rheumatogenic and nonrheumatogenic types. (2) Early data from Kuttner and Krumweide suggested differences in rheumatic fever attack rates depending on the serologic type of streptococcus in the outbreak. (3) Data from Potter et al. suggest that in Trinidad the serologic types of streptococci causing rheumatic fever differ from those causing nephritis even in the same families. (4) Seasonal differences reported in occurrence of rheumatic fever and of glomerulonephritis are also consistent with different rheumatogenic potential of different serotypes. (5) Rheumatic fever and nephritis rarely occur simultaneously.

Could there have been a change in the virulence of the streptococcus over time? This is certainly a possibility, although as McCarty has suggested, given the fact that no single serologic type has been demonstrated to be rheumatogenic, any changes in virulence would have had to occur in several serologic types of streptococci simultaneously. Nevertheless, we do see some evidence consistent with changes in the virulence of the streptococcus. Scarlet fever has become a much milder disease over the last few decades and its incidence has perhaps declined. Data from Baltimore suggest that the incidence of poststreptococcal acute glomerulonephritis may also have declined, although not as markedly as that of rheumatic fever (figure 5). Further evidence consistent with a possible change in virulence of the organism is the changing pattern of antibiotic sensitivity of the streptococcus. High rates of resistance of streptococci to tetracycline, and to a lesser extent to erythromycin and lincomycin, have been reported.

There is some ambiguity associated with the term "virulence." Virulence may refer to the capacity of the streptococcus to adhere to human epithelium, to its ability to evoke an antibody response, to its ability to produce clinical pharyngitis or other infection, or to its rheumatogenic or nephritogenic potential. Streptococcal virulence has been associated with the M protein of the cell surface, which has antiphagocytic properties and may also enhance the adherence of the streptococcus to epithelial cells by forming a complex with lipoteichoic acid. To date, there is no evidence that the
percentage of streptococcal strains isolated that are M-typeable has decreased and, in fact, data from Rochester suggest that the percentage of streptococcal isolates that are M-typeable may have increased in recent years. Data are needed on changes in the adherence ability of streptococcal strains isolated over time.

If a change in the virulence of the streptococcus has indeed taken place, what could have produced it? It has been suggested that the relatively high proportion of people in the population who have serum penicillin levels at any time may serve to interrupt the chain of transmission, which is often also associated with enhanced virulence. If this were the case, one would expect a decrease in the percentage of isolated strains that were M-typeable. It is also possible that nowadays the streptococcus more frequently encounters people with specific antibodies that prevent this transmission. Unfortunately, population-based data on the prevalence rates of anti-M antibodies are not available.

Another possibility for explaining the decline in rheumatic fever is the disappearance of a cofactor that may operate together with the streptococcus to produce rheumatic fever. Viruses have been known to affect host resistance and responses to bacterial infections. It is well recognized that during influenza epidemics there is an increased risk for both systemic and pulmonary infections caused by many organisms, including Hemophilus influenzae, Staphylococcus aureus, Neisseria meningitidis, Escherichia coli, and Streptococcus pneumoniae. Newborns with upper respiratory viral infections were reported long ago by Eichenwald to be particularly susceptible to infections by staphylococci, streptococci, and H. influenzae. Bacterial adherence had been found to be enhanced by experimentally and naturally acquired viral infections. Antecedent viral infection potentiates the growth of several organisms in the lung, including group B streptococci. Viral infections have also been shown to inhibit normal antibacterial defenses, and all measures of macrophage function seem to be affected. Thus the possibility that viruses may act as a cofactor in promoting the establishment of streptococcal infections or in some other fashion is not unreasonable. Although studies in the past of possible associations of viral and streptococcal infections were not rewarding, the markedly improved technology for viral studies available only in recent years has not yet been adequately applied to exploring this possibility.

It is also possible that some other environmental agent could be serving as a cofactor. Fainstein and Musher found that smokers had increased adherence of pneumococci compared with nonsmokers. Although they did not observe such differences for streptococci, their findings exemplify the possibility that environmental factors may, in principle, affect bacterial adherence and that such a mechanism could be operating with the streptococcus, although the possible agent or agents that may be involved is not known.

To what extent can we attribute the decline in rheumatic fever to medical care and primary prevention efforts? It seems an inescapable conclusion that at least part of the observed decline in rheumatic fever must be due to the prompt and appropriate antistreptococcal treatment given by physicians throughout the country. However, although the data in Baltimore for 1968-70 suggest such an explanation, it is difficult to reconcile the more recent decline in rheumatic fever that has occurred in both blacks and whites in Baltimore, with changes in medical care and in the way health services are delivered. In assessing any decline in disease incidence, however, there are potential hazards in assuming that the changes observed are in fact due to medical advances and to the care provided. Rene Dubos wrote, "When the tide is receding from the beach, it is easy to have the illusion that one can empty the ocean by removing water with a pail." Some years ago, Dr. Edward Kass pointed out that major scientific advances that have enhanced our medical care for diseases such as tuberculosis have not been clearly related to the major declines in incidence and mortality of such diseases (figure 6). When we examine a similar presentation of the data for rheumatic fever as shown in figure 7, we see that the decline in rheumatic fever mortality clearly began before antistreptococcal agents became available.

Could the decline in rheumatic fever be due to some change or changes in the host? Given the relatively short period of time during which the incidence of the disease has declined, the changes cannot be accounted for by genetic alterations in human populations. It is
conceivable, however, that improved life-style factors such as nutrition may have affected the host and made him more resistant to streptococcal infections.

It is important to note that host factors have long been recognized as playing a role in the risk of rheumatic fever. The higher risk of rheumatic fever in children has generally been attributed to their greater exposure to streptococcal infections. However, it has been reported that streptococci adhere more vigorously to cells from young compared with middle-aged subjects.17 This suggests the possibility that endocrine factors, for example, may affect infectivity and rheumatogenicity. Examples from other diseases support the notion that such host factors above and beyond any genetically determined susceptibility may play a role. For example, it is well recognized that pregnancy places a woman at increased risk of acquiring poliomyelitis. Particularly in the prevaccine era, it was also recognized that tonsillectomy increased the risk for bulbar poliomyelitis.

It is interesting to reflect on the reasons we have so much difficulty today in explaining the marked decline in the incidence of rheumatic fever. One aspect of this problem specifically merits discussion because it may have implications for our approaches to the etiologies of other diseases in the future. After Lancefield published her landmark work on the streptococcus, investigators interested in rheumatic fever quite appropriately focused their attention on confirming the relationship between the streptococcus and rheumatic fever and on elucidating the pathogenetic pathways involved. As the streptococcus was pursued, the possible etiologic role of factors other than the streptococcus in rheumatic fever received relatively little attention. That such factors — genetic, environmental, or a combination thereof — are in fact probably playing

FIGURE 6. Decline in death rates of diphtheria, whooping cough, Scarlet fever, and respiratory tuberculosis in England and Wales. (Reprinted, with permission, from Kass.17)

such a role is suggested by the data from the studies that yielded estimated rheumatic fever attack rates of 3% in the military and of 0.3% in civilian populations of children. Thus 97 of every 100 recruits who acquired a streptococcal infection did not develop rheumatic fever and 997 of every 1000 children who acquired streptococcal infections did not develop rheumatic fever. Why not? What factors could account for the small percentage of individuals with streptococcal sore throats who subsequently developed rheumatic fever, even in days when rheumatic fever was more common in the United States?

In this context, it is worthwhile to look at the approaches taken by epidemiologists to study the etiology of chronic diseases today, particularly when it is desired to explore the possible role of a number of etiologic agents. The approach often used initially is the case-control study (figure 8). In this design, patients with the disease ("cases") are compared with control subjects without the disease and the proportions of cases and controls with specific characteristics or exposures are compared. In the case of rheumatic fever, in which the streptococcus had been clearly implicated, case-control studies addressing genetic and environmental factors other than the streptococcus would have been very valuable. Thus a study of viral factors in rheumatic fever in association with streptococcal infections could be carried out by comparing cases of rheumatic fever with appropriately selected controls and determining what proportion of cases and of controls had specific prior viral infections of interest. Because the case-control design permits the investigation of a number of possible etiologic factors at the same time, it would be possible to develop a predictive model of which patients with streptococcal infections are at high risk for rheumatic fever. Until now, prediction of development of rheumatic fever has primarily been addressed by focusing on the characteristics of the streptococcus. Although this is a reasonable approach, it should not exclude consideration of host and other environmental characteristics. In his 1982 T. Duckett Jones Lecture, Dr. Elia Ayoub addressed host genetic factors in the genesis of rheumatic fever. I would suggest that other host and environmental characteristics should also be considered.

The relative lack of rigorously designed and conducted case-control studies in the search for a full understanding of the etiology of rheumatic fever is understandable, since much of Lancefield's work was published at a time when the case-control design had not yet received full recognition and acceptability and was only sporadically used. Not until the 1950s, when the case-control study design played a major role in establishing the relationship between cigarette smoking and lung cancer, was the case-control study fully legitimized. By this time the streptococcus was viewed as the full solution to the etiology of rheumatic fever, and as a result, a diligent search for other variables that might be involved was never carried out. Thus rheumatic fever began its dramatic decline in the United States before adequate attempts had been made to investigate the role of other etiologic agents above and beyond the streptococcus. Consequently, in the absence of a full understanding of the etiology of rheumatic fever today, we are unable to definitively explain its decline.

**Rheumatic fever in the third world.** Although the risk of rheumatic fever has been sharply declining in the United States, the picture is far different in developing countries. Worldwide, rheumatic heart disease remains the most common form of acquired heart disease in children and young adults and an important cause of all heart disease seen in adults. The status of rheumatic fever and rheumatic heart disease in developing countries has been succinctly summarized by Markowitz:

1. Rheumatic fever is the most frequent cause of heart disease in the 5 to 30 year age group.
2. Acute rheumatic fever and rheumatic heart disease are two of the most common causes of death in young people.
3. Rheumatic heart disease causes 25% to 40% of all cardiovascular disease. Estimated prevalence of rheumatic heart disease in India schoolchildren is six to 11 per 1000. Thirty-three to fifty percent of all hospital admissions for heart disease are for rheumatic heart disease.

Even in the United States, however, there are areas and population groups that have not clearly shared in the decline in incidence of rheumatic fever. For example, in the Navajo from 1962 to 1977, the annual attack rate was 12.4 per 100,000 for all ages, with the highest rate of 23.4 per 100,000 in the 10 to 14 year age group. Rates of 96.5 per 100,000 have been reported in Samoans living in Hawaii, with 50% of the patients having carditis. Recently, the Colorado Department of Health reported 14 confirmed cases of rheumatic
fever in the first 6 months of 1984 compared with only two to three cases reported annually in recent years. 25 Two points emerge: First, any hypothesis developed to explain the decline observed in rheumatic fever in most of the United States must also explain its persistence in certain American population subgroups and in the developing world. Second, this persistence both in the United States and abroad should preclude any complacency on our part in regard to rheumatic fever.

Conclusion. In conclusion, although the group A streptococcus is the critical etiologic agent of rheumatic fever, the disease may well be multifactorial in origin. While improved medical care and the use of penicillin and other antibiotics have contributed significantly to the decline of rheumatic fever in the United States, the decline antedated the availability of antibiotics, and in addition the changes in rheumatic fever in the United States cannot be fully accounted for solely by medical care and antibiotic use. The difficulty is that we lack adequate information regarding other possible cofactors. Studies of such factors are not feasible in the United States today in view of the very low incidence of the disease, but such etiologic investigations could be initiated and conducted in developing countries.

From the clinical standpoint, the low risk of rheumatic fever today suggests that perhaps we should reassess present policies regarding our hunt for the streptococcus and our determination to eradicate it. However, any relaxation of our currently recommended approaches to streptococcal infections should be undertaken with great caution, since we do not understand the reasons for the decline and consequently cannot fully anticipate the possible results of any relaxation in policy. In any case, such a relaxation would be highly inappropriate for developing countries in which the risks of rheumatic fever and rheumatic heart disease remain so high.

Finally, there is an urgent need for additional research both on the biology of the streptococcus and the pathogenetic mechanisms involved in the development of rheumatic fever as well as on other factors that may interact with the streptococcus and influence the risk of disease. Such research may not only be valuable in improving the health of populations that are at high risk for rheumatic fever in developing countries, but may also shed light on the pathogenesis of other non-suppurative sequelae of infectious diseases.

References
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