Global Assessment of Rheumatic Fever and Rheumatic Heart Disease at the Close of the Century

Influences and Dynamics of Populations and Pathogens: A Failure to Realize Prevention?

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Rheumatic fever and rheumatic heart disease were very common in the United States in the years before and during World War II. Because of the public health significance of acute rheumatic fever and crippling rheumatic heart disease, in 1944 T. Duckett Jones published the initial version of what we know as the Jones criteria, assisting clinicians in accurately making the diagnosis of acute rheumatic fever. The clinical importance of these criteria worldwide is documented by the modification of these important clinical adjuncts by the World Health Organization in 1988 and, more recently, by a special American Heart Association writing group. The first lecture honoring T. Duckett Jones' important contributions and his memory was given at the 35th annual Scientific Sessions of the AHA in Cleveland, Ohio, in 1962. That lecture, entitled "Rheumatism Then and Now," was delivered by Dr Paul Dudley White.

Not only is this the 30th anniversary of the T. Duckett Jones Memorial Lecture but, of special personal significance, this is also the 20th anniversary of the 1972 Jones Lecture, entitled "The Chain That Binds the Heart to the Throat," delivered by my mentor and friend, Dr Lewis W. Wannamaker, then a Career Investigator of the AHA. Among those individuals selected for this honor by the AHA are several others I would like to acknowledge who have had an important personal influence on me. Included are names familiar to clinicians and laboratory investigators with an interest in streptococcal infections and rheumatic fever: Drs Rebecca Lancefield, Milton Markowitz, Gene Stollerman, Angelo Taranta, Richard Krause, Elia Ayoub, Leon Gordis, and Floyd Denny.

While considering the tradition of this lecture, I recalled that Dr White, the first Jones Lecturer, was a founder of the AHA's international program. This very successful effort has proved important by allowing colleagues from around the world to exchange ideas and collaborate in mutually beneficial clinical and research activities. In today's troubled world, is there a more effective way to promote international good will? This is pertinent because several of the countries I will refer to are sites of political conflict.

For these reasons I will attempt a different approach to a global assessment of the status of rheumatic fever and rheumatic heart disease at the close of the 20th century. Whenever a truly global evaluation of cardiovascular disease has been undertaken, the magnitude of the morbidity and mortality resulting from rheumatic heart disease in the industrializing countries of the world today—countries that account for about two thirds of the world’s population—has been extraordinary.

There has been a tendency for many cardiologists (for this malady remains the possession of the cardiologist in most countries) simply to accept the continuing morbidity and mortality without completely and scientifically examining all of the reasons. For example, in the minds of many cardiologists around the world, the incidence of rheumatic fever and the high prevalence of rheumatic heart disease are usually attributed primarily to suboptimal conditions among socially and economically disadvantaged populations and, in many countries, to ineffective and inefficient delivery of primary health care. Some national and international health agencies and ministries of health share this somewhat cavalier attitude about this cardiovascular sequel to group A streptococcal upper respiratory tract infections. Such individuals and organizations often seem to believe that this disease will disappear once the social and economic problems have been more completely addressed. This is neither an adequate explanation nor an appropriate approach. Nor can I agree with those who have suggested that incidence of the disease has decreased simply through use of penicillin or other antimicrobial agents.

There are additional and perhaps even more important factors that have not been adequately recognized or addressed. In this global assessment I will not discuss what has happened; I will examine why. The problem(s) must be more completely defined before realistic and cost-effective public health solutions can be implemented in countries where the costs of promoting and delivering health care are often unattainable.

The difficulties in precisely defining the epidemiology of rheumatic fever and rheumatic heart disease in this
FIG 1. Comparison of the percentage of cardiovascular disease caused by rheumatic fever and congenital heart disease in schoolchildren in Ethiopia in the late 1980s with similar percentages in rural and urban populations in the United States at the close of World War II. The area of lightest shading for Ethiopian children represents other diseases such as pericarditis and fibrosis.

rapidly changing world at the close of the 20th century are easy to understand. Epidemiology is still a developing science in many countries. Many of the assessments and reports of rheumatic fever/rheumatic heart disease, as well as those of other cardiovascular diseases like hypertension and coronary artery disease, are hospital-generated and therefore tend to be incomplete.

Acquired valvular heart disease remains an extraordinarily important problem in the world today. At the bottom of Fig 1 are recent data that reflect the results of more than 1200 pediatric echocardiograms obtained and examined by Abegaz in Ethiopia, where roughly twice as many children have valvular (ie, "rheumatic") heart disease as congenital heart disease. The data are particularly striking when compared with the top two pie diagrams in the figure. These latter data were compiled in the United States at the close of World War II (not with echocardiography) by Robinson et al7 in schoolchildren in San Francisco and by Jackson in rural Iowa. This similarity in the prevalence of categories of cardiovascular disease in schoolchildren between a developing country at the close of the 20th century and in the United States only four decades ago graphically illustrates the current importance and relevance of the disease in the world today.

The recent data from Africa are no different from rheumatic fever data from many other countries. The incidence of rheumatic fever in Kuwait in the mid-1980s approached that in the United States at the end of World War II.9 The prevalence of rheumatic heart disease among both lower- and middle-class schoolchildren in Brazil was close to 10%.10 In 1991, at a provincial hospital in Vietnam, I was told that the prevalence of rheumatic heart disease was estimated to be 66 per 1000 schoolchildren, almost 7% (T.D. Trinh, personal communication, 1991).

With these examples, I have modified and added to concepts originally proposed by Strasser and DiSciascio and Taranta to illustrate my own epidemiologic perspective on the history of rheumatic fever during the several centuries preceding the close of the 20th century (Fig 2). The incidence of rheumatic fever increased, probably during the industrial revolution. In Western Europe and North America it clearly began to decrease before the introduction of antibiotics. However, in many countries, this decrease has not occurred, or it has varied considerably from one locale to another. After consideration of these differences, it is very likely that social or economic changes do not fully explain the observations.

In fact, those with an interest in the epidemiology and pathogenesis of rheumatic fever and rheumatic heart disease were forced to seriously reevaluate the conventional explanations during the mid-1980s in, of all places, the United States. Three or four decades ago, the incidence of rheumatic fever in many parts of the United States ranged from 20 to 50 per 100 000 per year or even higher, but by the late 1970s, incidence was less than 1 per 100 000 per year— the disease was rare.

FIG 2. A schematic historical perspective of the changes in the incidence of rheumatic fever in industrializing and industrialized countries showing the relation between the changes in standard of living and delivery of primary health care, and also the introduction of antibiotics into clinical medicine.
FIG 3. A comparison of the temporal association between the recovery of mucoid phenotypes of group A streptococci from the upper respiratory tracts of children with uncomplicated pharyngitis with the number of cases of acute rheumatic fever seen at the Primary Children's Hospital in Salt Lake City, Utah, from 1984 to 1990. As more mucoid strains were isolated, so did the number of cases of rheumatic fever increase (Daly J, Hill H, Veasy L.G. 1992. Unpublished data).

Then an unexpected change occurred. Rheumatic fever, which not infrequently was associated with severe clinical manifestations, appeared to resurge. The largest report, by Veasy and colleagues,16 indicated that a striking increase occurred in Utah in the mid-1980s. Between 1985 and 1992, more than 250 cases of acute rheumatic fever were diagnosed in Utah (L.G. Veasy, personal communication, 1992). The peak was reached in 1985 and 1986, with some decrease in subsequent years, but recently there seems to have been another relative increase; more than 15 cases were seen at the Primary Children's Hospital in Salt Lake City between January and November 1992 (L.G. Veasy, personal communication, 1992).

An unexpected finding in many of these localized outbreaks in the United States has been that they have not occurred in inner-city, disadvantaged populations. In fact, these cases often have occurred in middle-class families with ready access to medical care.16 This pattern is strikingly different from what might have been expected. In some cities acute rheumatic fever was not prevalent among inner-city residents; it was suburban or even rural.

To determine whether this resurgence of rheumatic fever was even more widespread and did not simply represent epidemiologic artifact, in 1988 Dr Rae Ellen Kavey and I carried out a telephone survey of pediatric cardiologists at large pediatric medical facilities in a number of states. Each respondent was asked to tabulate the number of patients with rheumatic fever admitted to their medical facility between 1985 and 1988 and to compare that with the number of patients with rheumatic fever admitted during the previous 10 years. Cities in 24 states gave evidence of an increase in number of cases admitted between 1985 and 1988 (when compared with the expected number based on the previous decade) of as much as 5 to 12 times that expected.17 A peak was reached in 1986-1987.18 Most of these outbreaks were not associated with poverty, either in civilian or several affected military recruit populations. What was the explanation?

A number of fascinating observations have arisen from this resurgence in the United States that should influence the understanding and current assessment of the epidemiology of rheumatic fever worldwide as we approach the next century. Several reports from the United States allow this evaluation by examining the associated and likely causative group A streptococcal organisms.

Studies carried out in our laboratory at the University of Minnesota since the mid-1980s provide reasonable documentation that the recent and probably continuing outbreaks of rheumatic fever in the United States have occurred concomitantly with the appearance of different strains of group A streptococci.19,20 Previously uncommon serotypes of group A streptococci (eg, M-18) have been commonly recovered, and the phenotypic appearance of these strains has been quite different. Mucoid-appearing strains, which have been infrequently recovered during the past several decades, have been isolated from around the United States. In at least three cities there was a temporal association between the isolation of such mucoid strains of group A streptococci from throat cultures of patients with pharyngitis and the incidence of rheumatic fever. With the invaluable assistance of Drs Judy Daly, Harry Hill, and George Veasy at the Primary Children’s Hospital in Salt Lake City, Utah, we could temporally correlate this relation (Fig 3). At the same time that mucoid group A strains were being recovered from throat cultures of outpatients with uncomplicated pharyngitis, new cases of rheumatic fever were being diagnosed. The peaks occurred simultaneously. We collected similar data from Rochester, NY (with the assistance of Drs Edward Clark and Marilyn Menegus at Strong Memorial Hospital), and Columbus, Ohio (data provided by Drs Mario Marcon, Hugh Allen, and Bud Hosier).

This relation could be challenged as a coincidence, an artifact, or a quirk. But, in fact, other simultaneous epidemiologic observations strongly suggest a relation between the resurgence of rheumatic fever in the mid-to late 1980s in the United States and the appearance of more virulent group A strains. In 1989 Stevens and colleagues21 reported 20 cases of a streptococcal toxic shock–like syndrome, also associated with apparently more virulent group A streptococci. The mortality, even
with appropriate medical care, was 30%. Many other cases have been reported, not only from the United States but also from Scandinavia and other parts of Europe.\(^2\) Fig 4 is a schematic representation of the epidemiologic curves of the apparent temporal relation between rheumatic fever and the streptococcal toxic shock–like syndrome or streptococcal sepsis occurring in the United States at the close of the 1980s. These two different manifestations of group A streptococcal infections essentially overlapped: two vastly different manifestations or sequelae of group A infection occurred at virtually the same time.

Just as a temporal relation has been observed between the appearance and spread of mucoid phenotypes of group A streptococci in communities and the appearance of rheumatic fever, similar attempts have been made to more firmly establish a relation of virulent streptococci with severe systemic group A streptococcal infections. The available evidence suggests that this increase in severe streptococcal sepsis is probably also associated with more virulent organisms.\(^2\)

For example, Dwight Johnson, Dennis Stevens, and I compared the distribution of serotypes of group A streptococci associated with rheumatic fever, streptococcal sepsis and/or toxic shock–like syndrome with almost 1000 strains associated with uncomplicated pharyngitis from 31 states. An important difference between our evaluation and other published reports\(^2\) is that we included a large, concomitantly collected control group of group A isolates from patients with only uncomplicated pharyngitis. We did not examine only submitted isolates from the suppurative and nonsuppurative sequelae of these infections. This is an important distinction. We were able to document a propensity for certain group A serotypes to be associated with specific categories of group A streptococcal–related disease. For example, M types 3 and 18 were frequently associated with rheumatic fever, whereas M types 4 and 12 were more frequently associated with uncomplicated pharyngitis. The M-1 streptococcus was associated with toxic shock and severe sepsis; the differences were statistically significant.\(^2\)

Unique and important to validation of this hypothesis of the epidemiology of group A streptococcal infections and their sequelae is what appears to be a geographic shift in the isolation of the more virulent M-1 isolates. To document this, a virulence ratio (the ratio of M-1 streptococci associated with severe sepsis and toxic shock compared with the percentage of M-1 isolates from uncomplicated cases of pharyngitis) of M-1 group A streptococci isolated from the eastern and western parts of the United States in 1989 and 1990. The ratio decreased in the east and increased in the west, suggesting a movement of virulent M-1 strains across the country during this period of time. Adapted from Johnson et al.\(^2\)

This understanding of a very dynamic epidemiology of virulent group A streptococcal infections leading to both suppurative and nonsuppurative sequelae has been further strengthened by studies in collaboration with Dr Patrick Cleary and others.\(^2\) By using restriction endonuclease digestion of DNA from group A streptococcal isolates—in this instance, M type 1 group A streptococci—we were able to identify a specific DNA “fingerprint” that was frequently recovered from people with severe systemic group A streptococcal infections. The fingerprint was different from that of the M-1 streptococci isolated from the upper respiratory tracts of children with only uncomplicated pharyngitis. In Fig 6 the percentage of the virulent strains can be observed to be smaller among M-1 strains isolated from 1980 to 1988, compared with the strains isolated during 1988 and 1989 when more severe clinical infections occurred.\(^2\) These data are compatible with a clonal origin of the virulent responsible organism. Thus, at least from this admittedly relatively small number of strains, it would appear that even strain-specific virulence can arise within the homologous serotype and may result in an increase in both the incidence and the clinical
severity of disease. The previously mentioned geographic changes, along with the presence of a more virulent clone(s), quite adequately explain what has occurred in the United States since the mid-1980s.

These observations of an association between group A streptococcal infections and their sequelae with emerging virulent organisms are further supported by other data. Strains isolated from patients with streptococcal toxic shock-like syndrome also appear more likely to produce streptococcal pyrogenic exotoxin A, a very potent extracellular toxin that has been reported to induce release of tumor necrosis factor from granulocytes and lead to pulmonary, hepatic, renal, and other complications. Group A streptococcal strains producing pyrogenic exotoxin A were seen more frequently 30 or 40 years ago, then seemed to have “disappeared”; but recently they have reappeared. Once again, the virulent properties of the organism can be temporally and clinically linked to the presence of an infectious disease.

If a hypothesis is formulated with such virulence data, schematically it might look like Fig 7. There is a normal “background” of group A streptococcal infections in a given population during a period of years. That there is waxing and waning of group A streptococcal infections from year to year is known to all primary care physicians. The data presented thus far suggest that, for reasons not yet completely understood, a single serotype can become prevalent in a given population. Then, for microbiological reasons that are also as yet unexplained, a virulent clone of that specific serotype may “emerge” (for example, M type 1 associated with sepsis or M type 18 associated with rheumatic fever). The result is a cyclical phenomenon of group A streptococcal infections and their sequelae, like that documented recently in the United States, and to some extent in other parts of the world. Most importantly, it is the emergence of these virulence-associated organisms and their rapid spread through a susceptible population that can explain the global epidemiology of group A streptococci at the close of the 20th century. This may also explain why antibiotics have not and probably never will completely control the incidence of these infections. This is not necessarily a new or unique epidemiologic observation about either streptococcal infections or other infectious diseases. In fact, if the literature is examined, the cyclical nature of scarlet fever in Brighton, England, at the end of the 19th century is an excellent example of this.

To provide supporting evidence to explain the global status of group A streptococcal infections and their sequelae, I have used recently gathered supporting data from the United States because adequate epidemiologic data from much of the developing world are simply not available. For example, I am unaware of even a single published report of an epidemic of rheumatic fever in an industrializing country. Clearly, this does not mean that it cannot or has not occurred.

In fact, for any clinician or epidemiologist with an interest in cardiovascular disease there is little doubt that epidemics of group A streptococcal-related infec-

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**Fig 6.** A comparison of the percentage of strains of M-1 streptococci that had a distinct DNA fingerprint when isolated from patients with uncomplicated streptococcal upper respiratory tract infections and those with more severe infections. An increase in virulence-associated strains was found in 1989-1990. Adapted from Cleary et al.24

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**Fig 7.** A schematic representation of the hypothesis of how more virulent clones of group A streptococci arise in a cyclic manner over a period of years. Out of the background (light shading) of normal variation in prevalence and serotype, epidemic serotypes (medium shading) occasionally arise. When this occurs, a more virulent clone (dark shading) may arise and be responsible for more severe or serious infections such as those seen in the United States during the later half of the 1980s and the early part of the 1990s.
tions and their sequelae have occurred in the developing world. Furthermore, there is indirect evidence that these epidemics are likely to be due to more virulent streptococcal strains, just as those we recently have documented to be present in the United States. Two examples from our very recent experience in other countries are compatible with this hypothesis and may help increase our understanding of the epidemiology and status of rheumatic fever/rheumatic heart disease in the world at the close of the 20th century.

Beginning in 1986 an intensive study was undertaken of the epidemiology of streptococcal infections, rheumatic fever, and rheumatic heart disease in Guangdong, a populous southern province of China, in collaboration with Dr Zhendong Huang, Dr XuXu Rao, Ms Chiling Zhou, Dr Zhengxiang Lo, and their colleagues in the Epidemiology Department at the Guangdong Provincial Cardiovascular Institute, Guangzhou, People’s Republic of China. In selected schools in urban and rural areas of Guangdong Province, patients with rheumatic fever and rheumatic heart disease were identified and registered. More than 400,000 physical examinations of schoolchildren have been performed to determine the magnitude of the rheumatic fever problem. Additionally, a prospective study of the incidence of group A streptococcal respiratory tract infections in selected schoolchildren was initiated. The preliminary data are compatible with the proposed concept that the virulence of the microorganism may be very important, more so than many have realized in the past.

Fig 8 (left panel) shows the combined data for this sequel of group A streptococcal infections in six different geographic areas in Guangdong Province. There was a general decrease during the 3-year period between 1987 and 1990. However, upon careful examination of these combined data, a slight increase between 1989 and 1990 is apparent.

Fig 8 (right panel) separates the combined data, showing information from each of the six study sites in southern China. All showed a decrease, with the exception of one (and possibly a second) geographically separated locale. Although the microbiological data are not yet available to document this completely, the one site’s increase likely influenced the combined data curve to result in the demonstrated increase. This is consistent with an isolated increase of rheumatic fever, possibly because of the introduction and spread of a more virulent strain.

This epidemiologic observation in one area of China is particularly interesting because apparently there have been population shifts to the south in the country, raising the likelihood that new and/or virulent serotypes or clones of group A streptococci have been introduced into resident populations that have no immunity. Rapid spread would be possible, just as the previously presented data from the United States suggest. There is also a second possible factor, which substantiates the importance of understanding the global epidemiology of group A streptococcal infections. Collaborative studies involving our laboratory and the National Streptococci Reference Laboratory in Bangkok provide supporting data. Group A streptococci are conventionally characterized by several different techniques. Two of the most common are the M typing and the T agglutination pattern. In our previous examination of almost 1000 isolates from US patients with uncomplicated pharyngitis, we were able to identify 93% of group A streptococci using T typing and 80% of throat isolates by M typing. However, when studying strains from the throats of children in Bangkok, using the same extensive panel of 58 different typing sera in our laboratory, we were able to identify only about 16% of the Thai group A throat isolates by M typing (Fig 9). Similarly, when characterizing smaller numbers of group A isolates recently obtained from Malaysia and Mongolia, we were able to identify less than 20% of the strains by M serotyping. (The strains were kindly provided by Drs Farida Jamal and U. Ugee.)

What is the significance of these unexpected differences and what is the impact on our attempt at a global assessment of rheumatic fever and rheumatic heart disease at the close of the 20th century? This remarkable difference in percent typability of recovered clinical isolates documents and reemphasizes that many group A streptococci are not identifiable, even in a streptococcal reference laboratory with a very extensive battery of typing sera. This further suggests that epidemics of unknown or noncharacterized strains might, in fact, be responsible for the occurrence of epidemics of rheumatic fever. Preliminary data suggest that these non-M typable strains do contain M protein (Tran PO, Johnson DR, Kaplan EL. 1992. Unpublished data).

The practical importance is emphasized by the bar graph (Fig 10) showing the recent admission of cases of rheumatic fever to the Khon Kaen University Hospital in Thailand (provided by Dr Monat Panamonta). With
this many cases occurring annually, and with the potential for as many as 80% of the isolates in that part of the world being unidentifiable, there is good reason to believe that there is much to be learned about the pathogenicity of group A streptococcal isolates from parts of the world where rheumatic fever frequently occurs. Relatively little consideration has been given to this concept or the implications.

One very obvious implication relates to the active research currently under way to develop an effective group A streptococcal vaccine. From a global perspective, our admittedly preliminary data should warn that such efforts must be conceived with calculated caution. In the late 1960s, with a crude (by today’s standards) group A streptococcal vaccine, about 15% of a group of children immunized actually developed rheumatic fever.33 The precise characteristics of group A strains prevalent in areas of the world where rheumatic fever and rheumatic heart disease represent a major cardiovascular problem must be recognized before a vaccine is constituted or subsequent clinical trials are initiated. If efforts are directed to developing a group A streptococcal vaccine based on prevalent serotypes (not to mention virulent clones of serotypes) in only certain parts of the world, if the data just presented from Asian countries are reflective of the prevalent varieties of group A streptococci in those countries, and if up to 85% of those group A isolates are currently nonidentifiable and yet have the capacity for leading to sequelae, then such a vaccine would be constituted to protect against the wrong organisms or for the wrong populations. The medical, economic, and public health consequences are obvious.

This can be emphasized by using the example of another common bacterial infection of children. Fig 11 is a modification of data from a recent report about the epidemiology of Hemophilus influenza type B meningitis in Finland.34 The recent decrease in the incidence of meningitis due to this microorganism is striking, especially when temporally related to the introduction of the apparently effective vaccine. Yet, keeping in mind the almost 80 different recognized serotypes of group A streptococci, as well as the data presented above (even if there were to prove to be an antigenic moiety or
epitope[s] of the M protein which is conserved), with what degree of certainty can one be assured that a group A streptococcal vaccine would be effective? This is a vitally important, yet incompletely answered, question at present. Does this concept and this uncertainty not speak for the necessity for enhanced global surveillance of group A streptococcal infections? These are among the important questions to be addressed by investigators around the world. Until these answers are known, is it not reasonable to urge not only caution, but also renewed basic microbiological and immunologic research, epidemiologic research, and applied research?

In conclusion, rheumatic fever and its sequel, rheumatic heart disease, remain a major unsolved problem in cardiovascular medicine among children and young adults in the world today. In fact, it is responsible for much more cardiovascular disease in children admitted to hospitals in many countries than is, for example, congenital heart disease.

Social and economic factors have traditionally been considered major factors influencing the epidemiology and pathogenesis of these cardiovascular sequelae of group A streptococcal infections, but new data and new laboratory techniques during the recent resurgence of these group A β-hemolytic streptococcal infections and their sequelae provide very strong evidence that specific serotypes (and perhaps even more virulent clones of those serotypes) of organisms are of paramount importance. By implication, it is also very clear that antimicrobial agents alone will not (perhaps cannot) eradicate this threat. Although vaccines theoretically can provide a more effective approach to prevention, significant problems remain to be addressed. A more complete and a more accurate database is required to determine where the disease is really a problem and how it may be effectively addressed.

Thirty years ago Dr Paul Dudley White, discussing “Rheumatism, Then and Now,” concluded the Jones Lecture with the comment that “...the chain of events, biochemical and immunological, between the original streptococcal infection and the beginning of the rheumatic process is still unknown.” It is especially fitting, I think, that on the 30th anniversary of that lecture, presented by the founder of the international program of the AHA, we find that we cannot simply accept the global status quo of rheumatic fever and rheumatic heart disease. More basic, more epidemiologic, and more applied research is required so that in 30 years Dr. White’s concluding sentence can be viewed in the light of an accomplishment, not that of a challenge still to be met.

Acknowledgments

I would like to express my gratitude to the many colleagues who contributed directly or indirectly to the preparation of this lecture. All, both those from the United States and those from abroad, made significant contributions. Unfortunately, because of space limitations, I cannot mention each individually. However, I would especially like to acknowledge the contributions of Dwight Johnson, without whose careful laboratory work and suggestions this information could not have been synthesized. I am also grateful to Drs Dennis Stevens, Patrick Cleary, Patrick Schlievert, George Veasy, Saowani Chumderpadetsuk, Monat Panamonta, Zhendong Huang, and Xu Xu Rao and Ms Chiling Zhou for their essential contributions to this lecture. I would also like to thank my colleagues at the World Health Organization for making it possible for me to have access to important material. Dr Milton Markowitz has been valuable as a sounding board for these concepts. Dr Kathryn Taubert has been most helpful during the preparation of the manuscript for publication.

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