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THE EMPEROR'S NEW CLOTHES REVISITED, OR REFLECTIONS ON THE PATHOGENESIS OF DENGUE HEMORRHAGIC FEVER*

LEON ROSEN
Pacific Research Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Honolulu, Hawaii 96806

As most of you know, one of the duties of the President of the American Society of Tropical Medicine and Hygiene specified by the by-laws is the presentation of an address at the annual meeting. I do not know what type of address those responsible for this provision had in mind, but a review of previous presidential addresses reveals a wide variety both of philosophical and scientific topics. Since I do not feel competent to address you on a philosophical subject, I have chosen to review a scientific topic which has been of interest to me during the past few years. In making this choice, I know that the subject matter will be of relatively little interest to those of you in other fields and for this I apologize. I shall illustrate later, however, that the topic I have chosen is especially appropriate for the site of our gathering this year and for the bicentennial which our joint meeting commemorates.

Those of you unfamiliar with recent work and discussions on dengue may be puzzled by the first part of the title of this address. I should like to explain that it was chosen to call attention to what I believe is the transparency of arguments used in support of a widely disseminated hypothesis on the pathogenesis of dengue hemorrhagic fever—but that it was not intended that the analogy be carried so far as to imply that those who have proposed this hypothesis are the counterparts of the two rogues in Hans Christian Andersen's story.[1]

There has been considerable speculation as to why dengue, long considered an annoying but benign disease, has in the last 20 years become a leading cause of hospitalization and death among children in a number of Southeast Asian countries.[2] The life-threatening forms of dengue usually are associated with hemorrhage, hypovolemic shock, or both, and generally are described by the term "dengue hemorrhagic fever." There is some question as to whether or not dengue hemorrhagic fever is a "new" disease, but irrespective of whether or not it is new, it is clear that it now is more prevalent than at any time in the known past. The possible reasons for this increased prevalence are the principal subject of my discussion. However, in this geographic setting, I cannot resist a short historical diversion.

There is, as will be noted later, disagreement as to exactly what signs, symptoms, and laboratory findings should be present to classify a patient as having dengue hemorrhagic fever. However, if for the present one accepts the concept that dengue infection associated with hemorrhage and death can be called dengue hemorrhagic fever, I believe we can say that the first case was recognized and described here in Philadelphia almost 200 years ago! It generally is accepted that the first unequivocal description of a dengue outbreak was that of an epidemic which occurred in this city in the summer and autumn of the year 1780.[3] It is of interest to note on this occasion that the outbreak was described by Dr. Benjamin Rush, a physician, who as you have heard, was one of the signers of the Declaration of Independence. Most of you probably have not read Dr. Rush's original description of this outbreak[4] and I should therefore like to call your attention to his exact words in the following passage—"In some cases, the discharge of a few spoonsful of blood from the nose accompanied a solution of the fever on the third or fourth day; while in others, a profuse hemorrhage from the nose, mouth, and bowels, on the tenth and eleventh days, preceded a fatal issue of the disease." Those of you familiar with the hemorrhagic manifestations of dengue will recognize the typical time relationship between the onset of illness and the onset of hemorrhage. Parenthetically, I might add that Dr. Rush did not publish his description until 1789, some 9 years after the outbreak, which perhaps is some

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consolation to those of us who are behind in our writing.

My interest in dengue hemorrhagic fever began in 1964 when the first of a series of dengue outbreaks occurred on the South Pacific island of Tahiti.[5,6] The disease had been absent from the entire South Pacific for approximately 20 years and, because of the recent occurrence of dengue hemorrhagic fever outbreaks in Southeast Asia, there was apprehension in 1964 that similar forms of dengue might appear on Pacific islands. This concern was heightened when it was found that the Tahiti outbreak was caused by dengue type 3, a serotype first discovered during investigation of a dengue hemorrhagic fever outbreak in the Philippine Islands. The dengue type 3 outbreak on Tahiti proved relatively benign, although some hemorrhagic phenomena were observed. It was followed 7 years later by an outbreak on the same island of dengue type 2, during which more severe hemorrhagic disease and some deaths were observed.[7] By this time, the sequential infection hypothesis with respect to the pathogenesis of dengue hemorrhagic fever had been proposed[8] and widely discussed.[9-12] This hypothesis holds that severe dengue hemorrhagic fever, and especially dengue shock syndrome, is produced by an immunopathologic mechanism elicited by a second, heterotypic, dengue infection occurring during a certain critical period of time following an initial dengue infection. Observations made on Tahiti during the dengue 2 outbreak provided no reason to question this hypothesis.

Following its appearance on Tahiti in 1971, dengue type 2 spread to a number of other Pacific islands which had been free of dengue infection for at least 25 years. Most of the ensuing dengue type 2 outbreaks were unremarkable, but one which occurred on the remote island of Niue in 1972 was particularly severe. It was reported that this small island, with a population of some 5,000 persons, had experienced a high incidence of hemorrhagic manifestations with dengue infections and that a number of deaths caused by dengue had occurred, including some among children.[13] Since it was very unlikely that dengue had occurred on Niue in the 25 years preceding the type 2 outbreak, it obviously was improbable that the deaths among children were caused by sequential dengue infections. In view of this unexpected development a retrospective epidemiologic and serologic investigation was carried out on Niue several months after the outbreak. The findings of this inquiry can be summarized as follows.

First, it was shown by use of plaque-reduction neutralization tests that the 1972 outbreak was caused exclusively by dengue type 2 virus. Furthermore, there was no evidence of infection with any other dengue serotype for the preceding 25 years.

Second, it was found that several of the children who died (as well as some who survived) had hypovolemic shock and other clinical manifestations similar to those described in association with severe dengue infections in Southeast Asia. The observations with respect to shock were particularly convincing since the physician who recorded them was unaware at the time that shock had been associated with dengue infection.

Third, no evidence was found that other infectious diseases, such as meningococcal meningitis or leptospirosis, could have caused the deaths among children.

In view of what appeared to be good evidence that dengue shock syndrome on Niue was caused by primary dengue infection, it was natural to search for confirmation elsewhere and to examine critically the data cited in support of the sequential infection hypothesis.

In examining the literature on dengue hemorrhagic fever, it soon becomes obvious that no consensus exists with respect to the definition of this expression. Some authors include any dengue infection with hemorrhagic manifestations or even only a positive tourniquet test. On the other hand, at least one believes that the expression should be limited to patients with such specific findings as hypoproteinemia and thrombocytopenia.[10] In fact, it has been suggested that there are two distinct clinical entities, "normal" dengue on one hand, and "altered dengue" on the other.[10] In this view, even if a patient has a dengue infection with severe hemorrhage, but no hypoproteinemia, then the case should not be classified as dengue hemorrhagic fever. I, personally, cannot find any convincing published data, as distinguished from speculation, which suggest that the various clinical manifestations of dengue are anything but a continuous spectrum from inapparent infection on one hand to death on the other. I do not mean to imply that both the hemorrhage and the shock which occur in dengue infections are necessarily

the result of the same pathogenetic process, but rather, that I am unaware of any criteria by which dengue infections can be separated into two distinct clinical entities, with no significant overlap. Nevertheless, in order to avoid the additional complication of semantic argument, I will limit the remainder of my discussion of data bearing on the sequential infection hypothesis to those dealing only with the dengue shock syndrome—which is acknowledged by all to occupy the severe end of the clinical spectrum of dengue hemorrhagic fever.

The arguments advanced in support of the sequential infection hypothesis can be summarized as follows. First, most patients[8] (one author says all patients[14, 15]) with dengue shock syndrome have secondary type antibody responses. Second, of those persons with clinical dengue seen by physicians, the shock syndrome is seen in a higher percentage of individuals who appear to have secondary type antibody responses as compared with those who appear to have primary infections.[8] Third, the depressed levels of serum complement observed in dengue shock syndrome patients have been interpreted[16] to result from the presence of antigen-antibody complexes, presumably formed only in sequential dengue infection.

I should like to examine each of these arguments in turn. First, it should be obvious to those familiar with the principles of epidemiology that the significance of the first argument cited cannot be evaluated without knowledge of the characteristics of the population at risk. As an example, it has been reported that dengue hemagglutination-inhibition antibody was found in more than 97% of the population less than 5 years of age in Rangoon, Burma.[17] For the sake of illustration, let it be assumed that this antibody resulted from previous infection with any of three types of relatively avirulent dengue virus. Then, let it be assumed that a particularly virulent fourth type of dengue virus is introduced to Rangoon and infects everyone in the city. It can be seen that if all individuals, irrespective of previous antibody status, had an equal risk of developing dengue shock syndrome, more than 97% of all shock cases observed would show secondary type antibody responses. Since the populations at risk cannot be clearly identified in those studies cited in support of the sequential infection hypothesis, the first argument in support of this hypothesis, in my opinion, cannot be considered as convincing.

Those who question this conclusion are invited to examine the original publications[11, 12, 18-24] and attempt to, 1) define the geographic distribution and size of the populations at risk and the number of persons with clinical dengue hospitalized, or otherwise seen by physicians, from those populations; 2) assess the validity of the virologic and serologic methods employed to identify the population at risk of primary infection and the nature of the antibody response in persons with clinical dengue seen by physicians; and 3) evaluate the statistical significance of the numbers involved.

I should now like to turn to analysis of the second argument cited, that is, that a higher percentage of patients with secondary dengue infections seen by a physician have shock syndrome as compared with those with primary dengue seen by a physician. There are several potential flaws in the data cited to support this argument, including the possible effects of, 1) differences in patient age, 2) different dengue serotypes and strains, and 3) errors in classification of the nature of the antibody response—that is, whether it indeed was primary or secondary. In my opinion, however, the most important potential flaw in the argument is the possibility that persons with primary dengue infections do not have a lower incidence of shock syndrome as compared with those with secondary infections but, rather, a higher incidence of undifferentiated febrile disease. The only way to differentiate between these alternative explanations would be to calculate the incidence of the different clinical manifestations on the basis of the population at risk. As noted above in considering the first argument, such population data are not available. Thus, the second argument in support of the sequential infection hypothesis, in my opinion, cannot be accepted as convincing.

With regard to the observation of reduced levels of serum complement in dengue shock cases, it is first pertinent to note that no observations were made on control patients with shock that clearly was non-immunologic in nature.[25-28] One, thus, cannot exclude the possibility that the low levels of serum complement were related to the severity of disease or shock rather than to the possible presence of antigen-antibody complexes. This criticism is supported by two recent sets of observations. Complement determinations carried out on hospitalized dengue patients in 1975 in Fiji during a dengue type 1 outbreak showed that low

serum complement levels were related to the severity of clinical manifestations, and not to whether the patient was undergoing his first or a subsequent dengue infection.[29] Patients with severe primary dengue disease were observed to have depressed serum complement levels. None of the Fiji patients had dengue shock syndrome, but low levels of serum complement have been documented[30] in primary dengue shock syndrome cases to which I will refer later. Thus, the observation of depressed serum complement levels in dengue shock syndrome cannot now be accepted as an argument in support of the sequential infection hypothesis.

If dengue shock syndrome is the result of immunopathology associated with sequential dengue infection then, obviously, the syndrome should not occur in persons undergoing their first dengue infection. One group of authors who favor the sequential infection hypothesis report that dengue shock syndrome does occur in primary dengue infections, but only in children less than one year of age.[10, 19] This observation is reconciled with the sequential infection hypothesis by the further hypothesis[10] that these very young children are somehow sensitized as a result of having recently been born of dengue immune mothers.

Although the observations on Niue were epidemiologically and clinically convincing to me it could be argued that, because of the absence of laboratory studies during the outbreak, the particular individuals with shock syndrome were not shown to be infected with dengue virus at the time of their illness by virus isolation or the demonstration of a significant rise in antibody titer. To counter this objection a search was begun for a piece of evidence that might be called the "smoking gun," that is, a documented case of dengue shock syndrome in an individual older than 1 year of age unequivocally undergoing a first dengue infection. Such a case was found in Jakarta, Indonesia in 1973. The patient was a 3-year-old child who had typical dengue shock syndrome with fever, abdominal pain, profound shock, epistaxis, hematemesis, and melena. The child had no plaque reduction neutralizing antibody against any of the four dengue serotypes on disease day 2 and a titer of 1:320 against dengue type 2 on disease day 19. No dengue type 1, 3, or 4 plaque reduction neutralizing antibody was present on disease day 19.[31]

Subsequently, additional cases were documented by our laboratory from the island of Tonga[32] and from Manila,[33] and by others[30] in Bangkok. It was in the Bangkok cases that reduced serum complement levels were first demonstrated in children older than 1 year of age with primary dengue shock syndrome. Thus, it now seems established beyond a reasonable doubt that dengue shock syndrome can occur in persons older than 1 year of age undergoing their first dengue infection, and consequently, sensitization by previous dengue infection is not essential to the pathogenesis of this syndrome. Hemorrhage, thrombocytopenia, and shock occur in other viral infections,[9, 34] and even in other flavivirus infections, such as yellow fever.[35, 36] There is no evidence that previous infection with a related virus plays a role in the pathogenesis of hemorrhage or shock in these infections.

While it still might be hypothesized that sequential dengue infections are more likely to give rise to dengue shock syndrome than primary infections, as already pointed out, there are as yet, in my opinion, no valid data to support such a contention.

Some of you no doubt wonder why anyone would wish to speak at length about the pathogenesis of dengue hemorrhagic fever. One reason is that the sequential infection hypothesis has very important practical implications with respect to the possible use of vaccines to prevent dengue infection. If sensitization does indeed occur, it obviously would be unwise to vaccinate unless protection could be conferred simultaneously against all four serotypes. The administration of a monovalent dengue vaccine would be contraindicated and the application of vaccine prophylaxis would have to await the development of effective vaccines against all four serotypes. There also would be an ethical problem with respect to vaccine development since human volunteer studies would be necessary and some volunteers would have to receive a monovalent preparation at some stage of the vaccine trials. Finally, even after a vaccine had been developed, one might question the desirability of its use in an individual previously infected naturally with one or more dengue serotypes.

Another reason for my choice of subject matter this afternoon is that this forum offers excellent exposure for the thoughts I wish to convey. In the last 10 years, the sequential infection hy-

pothesis has been repeated so frequently in oral presentations, primary publications, review articles, textbooks,[37, 38] World Health Organization guides,[39] and signed[40] and unsigned[41] editorials that most nonspecialists think it established fact.

You will remember from Hans Christian Andersen's tale that, not only were the colors and patterns of the emperor's new clothes outstandingly beautiful, but they also had the wonderful property of remaining invisible to anyone who was not fit for his job or was particularly stupid. At the risk of being categorized as one of these kinds of persons, I should now like to turn to the concepts which I believe can explain adequately all observations which have been made on dengue hemorrhagic fever. These are not new ideas, but perhaps the explanation of why they have not been generally accepted previously is new.

Simply stated, I think that all observations on dengue hemorrhagic fever can be accounted for by the concepts that different strains of dengue viruses of all four serotypes vary in their pathogenic potential and that life-threatening dengue and shock syndrome are relatively rare consequences of dengue infection. Certainly the idea that strains of the same virus can vary in their pathogenic potential is not a revolutionary concept and, indeed, if dengue viruses did not so vary it would be more surprising. Similarly, the concept that certain clinical manifestations can be rare consequences of a common infection should not be difficult to accept for anyone familiar with the natural history of poliomyelitis and the infrequency of paralytic disease in relationship to the number of inapparent or non-paralytic infections. Obviously, idiosyncrasies of individual hosts also must play a role, in addition to virulence factors residing in the infectious agent, since only a small percentage of persons infected with even the most virulent polioviruses became paralyzed.

If these concepts are so simple and easily understood, it is natural to wonder why they have not already been widely accepted as an explanation for the observed behavior of dengue hemorrhagic fever. My guess is that for some reason quantitative relationships have been overlooked.

For example, two arguments commonly used in opposition to the hypothesis of dengue virus virulence are the undoubted recent increase in the number of severe dengue infections and the observation that foreigners almost always acquire classical dengue in Southeast Asia whereas the life-threatening forms appear among native children. It is asked first, why dengue viruses should suddenly have started to mutate towards greater virulence at this point in time, and second, why foreigners bitten by the same mosquitoes as those which bite natives do not suffer the same consequences as the latter.

In my opinion, the increased incidence of life-threatening dengue in recent years can be explained by the likelihood that the total number of dengue infections has increased enormously. This has occurred because of the dramatic increase since the end of World War II in the size of urban populations in Southeast Asia, the continued dissemination of the introduced urban vector, *Aedes aegypti*, and the more frequent movement of virus serotypes and strains from one Asian urban center to another as a result of more frequent and more rapid travel of the human population. In other words, the iceberg of total dengue infection has become so large that the visible portion, that is, the severe clinical manifestations, now projects farther out of the water.

The rarity of life-threatening dengue among the foreign population in a city such as Bangkok can be explained by the relatively few persons infected with dengue in relationship to the rarity of the severe complications. It also is possible that different susceptibility of various age-groups plays a role.

The apparent absence of dengue hemorrhagic fever and dengue shock syndrome in such dengue-infected areas as the Caribbean can be explained as the result of the circulation of only a few dengue strains which do not happen to be particularly virulent and the failure to recognize the rare severe clinical forms of dengue when they do occur. An example of how such cases could be missed is furnished by what occurred during a dengue outbreak in the Hawaiian Islands in 1903. Two dengue-associated deaths were reported and one listed as a complication, "purpura hemorrhagica."[42] It would have taken a brave soul indeed to conclude at that time that the bleeding was the direct result of dengue infection and not a coincidental occurrence. It is likely that only when many thousands of dengue infections caused by a relatively virulent strain of virus are concentrated in time and place are the severe clinical forms common enough to be recognized readily as

manifestations of dengue infection and labelled as an epidemic of dengue hemorrhagic fever.

The concept of differences in virulence of virus strains also can explain the apparent dissemination of dengue hemorrhagic fever from one geographic area to another and its apparent decrease in incidence—despite the continued occurrence of dengue infections—in such areas as Manila.

Obviously, this is neither the time nor the place to enlarge upon the implications of various hypotheses concerning the pathogenesis of dengue hemorrhagic fever. I apologize for the possible downgrading of an immunologic mechanism of disease—a sin in this day and age almost as bad as an attack on the American flag and apple pie. I do hope, however, that I have stimulated at least a few of you to take a new look at data on dengue hemorrhagic fever. In any case, it behooves all of us to bear in mind a concept of the Greek Stoic philosopher, Epictetus, who said, ". . . it is impossible for anyone to begin to learn what he thinks that he already knows."[43]

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