THE AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE
Vol. 21, No. 3

Printed in U.S.A.

CAN THE WAR TO CONTAIN INFECTIOUS DISEASES BE LOST?*

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The President of this Society has two honors, first to represent the membership during his year in office and second to prepare and deliver a Presidential Address. The first type of activity is largely dictated by the desires of the membership and this year these were exemplified by our concerns that the World Bank recognize the importance of health problems in their economic development programs, our consideration along with other major scientific societies that there be a sound and adequate national policy on international health issues, and finally the development by the officers and committees of a program for the annual meeting that would encompass the interests of our diverse membership.

The second activity is a personal choice of the President, namely, his choice of a subject for the Presidential Address, and he must choose between a specific aspect of his own career and research or the selection of a broader topic that he hopes will concern the entire membership. I have chosen a broad theme, namely that we face serious problems in our continuing effort to control the infectious diseases that prevail in both tropical and temperate regions. I fear that society and the scientific community have become complacent with the advances made in research and their relative freedom from epidemics. I contend that while we have won many battles in our research effort the longer range and bigger war to contain certain infectious diseases can still be lost. I believe there are a variety of technical, economic, social and political factors that will influence the outcome of this contest. We as scientists tend to forget that the majority of these factors can be quite independent of the status of our scientific knowledge or competence. I will attempt to illustrate my concerns, and you will find my views are somewhat less optimistic than those Dr. Hinman expressed in 1966 in his Presidential Address "How much control of communicable diseases?"[1] Or those expressed in 1969 by Dr. Sencer in the Craig Lecture "Health protection in a shrinking world."[2] Indeed, some of the more pessimistic views expressed by Dr. Snyder in the Thirty-Sixth Craig Lecture on "Population and disease control"[3] are reflected in my concerns.

I will start this discussion by relating an event in 1965. In that year, the Surgeon General of the United States Public Health Service asked a representative group of scientists and public health administrators to review the position and activities of the United States with reference to the internationally quarantinable diseases. I was privileged to be a member of this committee, under the chairmanship of Dr. John M. Weir. The unpublished report to the Surgeon General in 1966 focused on the "Big Six," the internationally quarantinable diseases, and attempted to ask the serious questions: are programs based on rational scientific knowledge and progress? and, is program perpetuation based on a tradition rather than evidence of efficacy? Such reviews are to be recommended, and I would like to take a few minutes to highlight the findings as they are reflected in the current posture of our government and changes in regulatory actions subsequently endorsed by the World Health Organization[4] that affect us all.

Louse-borne typhus fever, louse-borne relapsing fever, cholera and smallpox were no longer believed to represent major threats to the United States. This evaluation reflected a confidence in our capacity to contain rapidly any introduction of these diseases and a belief that an introduction was unlikely and that they would be unable to spread in a modern American community. The other two of the "Big Six," yellow fever and plague, also were looked upon with less than alarm as they no longer appeared to represent an epidemic threat in North America. We knew the widespread endemic status of plague in the western states and that it had to be kept out of urban rat populations and we knew how to do it. We knew the continued endemic state of jungle yellow fever in South America and Africa, but had high

* Presidential Address given before the 20th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Statler-Hilton Hotel, Boston, Massachusetts, 2 December 1971.

confidence in the effectiveness of the yellow fever vaccine and the *Aedes aegypti* eradication programs then under way.

One outcome of these deliberations was that when you return to the United States from most international travel, you no longer have to possess a valid vaccination certificate for smallpox, cholera or yellow fever. Rather, you may be urged to receive such immunization before travel to an endemic or epidemic area to protect your own health or because some other country requires it. In 1965, 70,000 persons were vaccinated against smallpox on arrival at our borders. This has been stopped as we know that vaccination on arrival in New York, Miami, Los Angeles, San Francisco, etc. will not interrupt an incubation period and save our country. These steps have represented enlightened progress based on research and a relatively effective international disease reporting system. The actions in no way reflect a decreased desirability for the international traveller to protect himself from infection by immunization to a number of diseases before he travels.

You are undoubtedly asking yourself, so what's new, what is the concern? We clearly have won the battle and are well on the way to winning the war as the next step is to eradicate these diseases from the face of the earth. Let us take a realistic look at the probability of eradication of the "Big Six."

We are not going to eradicate yellow fever in the foreseeable future. In fact, my concern is that in spite of our extensive knowledge and our ability to prevent yellow fever we still observe epidemics in Africa[5] and I expect we may see another epidemic of classical *Aedes aegypti*-borne urban yellow fever in the Americas in our lifetime. I do not believe that this is an unreasonable expectation based on the following observations.

Several recent Pan American Health Organization Study Groups[6,7] have reviewed the current status of *Aedes aegypti* and *A. aegypti*-borne diseases in the Western Hemisphere. Three findings emerge:

1. Yellow fever still is widely extent in South America as is evidenced by the continued identification of human cases (Fig. 1). These observations indicate that the jungle cycle continues in primates and mosquitoes and a significant proportion of persons in rural populations are not vaccinated and have contact with the jungle cycle. Indeed, there is evidence that a lower proportion of urban than rural populations are immunized, so that human populations in urban centers are largely susceptible.

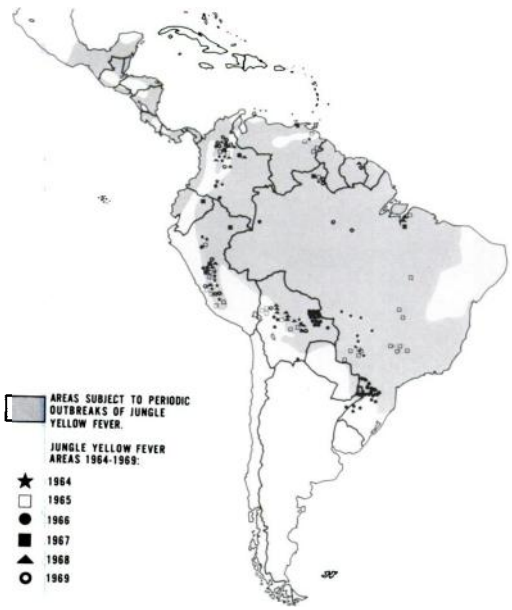

FIGURE 1. Jungle yellow fever in the Americas.*

* Source: Reeves, W. C. Recrudescence of arthropod-borne virus diseases in the Americas. In *Symposium on Vector Control and the Recrudescence of Vector-borne Diseases*. Proceedings, Washington, D. C., Pan American Health Organization, 1972. In press.

2. Efforts to eradicate *A. aegypti* from the Western Hemisphere have not succeeded. Reinfestations have occurred in areas that were formerly declared clean. Nations, including the United States, have stopped their eradication efforts for political, economical or technical reasons.

3. An extensive area of the Carribean, and some parts of South America must be assumed to be receptive to urban transmission of yellow fever. This belief is based on the resurgent and recurrent series of dengue fever epidemics that have occurred from 1963 to the present time. The area affected in 1968–1969 is illustrated in Figure 2. We must assume that the densities of *A. aegypti* that prevail and allow the epidemic spread of dengue viruses also could support the epidemic spread of yellow fever.

One may ask, how is it possible as we enter 1972 that we must concern ourselves with what

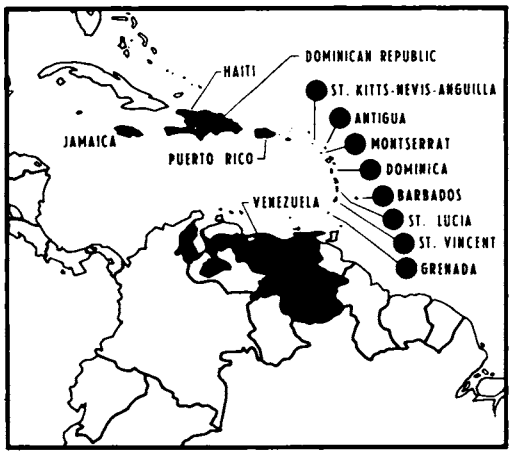

FIGURE 2. Occurrence of dengue in the Caribbean, 1968 to 1969.*

* Source: Reeves, W. C. Recrudescence of arthropod-borne virus diseases in the Americas. In *Symposium on Vector Control and the Recrudescence of Vector-borne Diseases*. Proceedings, Washington, D.C., Pan American Health Organization, 1972. In press.

we thought would be a disappearing disease before this time? The problem is complex. Our research knowledge is sufficient that we know how to prevent the disease in human populations but the fact is that economic limitations and political priorities have become an influencing factor. For all practical purposes we have been told, "Sorry, you cannot have your objectives of eradication of a vector and the associated epidemic potential, instead, economy dictates that we must live with this problem." A factor that adds to the problem is that the vector and a number of persons and organizations in a constantly extending circle have exhibited resistance to the available insecticides. Thus, laws are passed and social views evolve that restrict insecticide development and use and the vector develops resistance to the available products so that efforts are ineffective or economically prohibitive. It seems clear that we will continue to live with yellow fever and that we can only hope to contain it. If an epidemic develops, it will probably be stamped out by vaccination and large-scale application of some type of insecticide. The program will be expensive and will be associated with large losses in tourism and trade.

You might say, "Well, yellow fever is the exception among the diseases listed," and it may be. However, let us not be complacent. In the past ten years cholera has extended and has been active in much of Asia, Europe, and Africa. The populations in the Americas and Australasia are the only continental groups to escape, and the epidemic has been called pandemic or worldwide.[8] You ask, "How can the Surgeon General stop a vaccination requirement in the face of a pandemic?" The answer is simple; vaccination and quarantine are ineffective measures to stop the spread of cholera, and high levels of sanitation and early alertness to an introduction are the most economical and effective protections we have. The El Tor Vibrio has demonstrated the competence of cholera to resurge and the receptiveness of much of the world to reintroduction. This is a great change from our view ten years ago when we believed that advances in sanitation and vaccination had pushed cholera to its last stronghold in a limited area of Asia. We have no assurance or magic way to prevent resurgences in the future and our best hope is to minimize their impact by development and maintenance of an environment unreceptive for transmission. Thus, our posture in 1972 will be that projected by John Snow in his report, "On the mode of communication of cholera" written in 1854,[9] namely, maintain a pure water supply and clean environment and cholera will disappear.

We see little hope for eradication of plague, as it is an enzootic infection established in wildlife over much of the world. We depend on prevention or early detection of infection in urban rodent populations. Such spread has the potential to lead to an epidemic in man. The most sobering developments with reference to plague are the finding of resistance to warfarin in both *Rattus norvegicus* and *Rattus rattus*,[10] and the recognition of ambulatory carriers of pneumonic plague in Southeast Asia.[11] If such a resistance or carrier state becomes common and widespread, it will markedly affect our control efforts. We constantly hear of an increased prevalence of rats in sectors of our urban centers called ghettos. For all practical purpose, public action already has taken DDT and some related insecticides out of our arsenal for flea control. Thus, we again have the situation where new research developments for control are needed and intelligence and surveillance must be kept high or we could be back in a war to control epidemic plague in an urban center.

The brightest picture in the war over the "Big Six" is with reference to smallpox and the two

louse-borne diseases, typhus and relapsing fever. Smallpox appears to have been forced back to its last strongholds by the jet gun, an effective vaccine and a dedicated corps of eradicators. We look forward to the pronouncement by WHO of "Smallpox-is-eradicated-Day." I doubt if the public will dance in the streets on that day as they take such achievements for granted; only failures attract wide attention. In the case of smallpox, the goal of eradication seems attainable if one is not the complete sceptic. The complete sceptic points to the continued occurrence of measles and poliomyelitis in the United States in pockets of population that have escaped or resisted our nationwide and expensive efforts to reach them for immunization. Up to now, the politicians, economists, and populace have not lost patience with the cost or effort of the programs and we assume this attitude will prevail for smallpox.

The two louse-borne diseases still exist but seem to have retreated into a few remote areas of the world and to a constantly aging and disappearing cohort of chronic carriers in most of the formerly epidemic regions. We trust that cleanliness and freedom from lice will continue to prevail in our populations although those of us from the "square generation" and particularly those who are entomologists, look upon the hairdos and garb of our children and some of our associates not only as a protest, but also as a potential victory for the louse.

I would like to summarize the ongoing war with what I have called the "Big Six" so I can turn to some other problems that concern me. We have an encyclopedic knowledge of the causative agents, their epidemiology, and control procedures for these diseases. The generations that comprise the membership of this organization generally adopted the concept and holy grail of disease eradication. We have not achieved our goals as we enter 1972 and the other sectors of the community who make decisions with reference to allocation of economic resources, to priorities of health programs and to legislation concerning our environment have increasingly made it obvious that their concerns and interests do not necessarily coincide with ours. The battles for knowledge by research on the classical infectious diseases were won brilliantly but are at a comparatively low ebb of funding and interest today. The health department has provided an effective level of health organization, diagnostic services and sanitation in our communities and this has been our home defense. We have increasingly depended on a defense in depth away from our borders that included intelligence on the current status of disease in other countries, a constantly increasing capacity world-wide to control infectious diseases, and the well-informed and immunized traveler. There is a constant need to remind ourselves that any weakening in these defenses will probably be found by one or more of the "Big Six" as they constantly probe at our borders. A close perusal of the weekly Morbidity and Mortality Reports from the Center for Disease Control and the counterpart reports from PAHO and WHO are must readings for anyone who is concerned or who wishes to become sensitive to this problem.

I want to turn now to several other diseases in order to reemphasize my concerns with our capacity for infectious disease control. I made passing reference to dengue fever and its present activity in the Carribean and northern South America; the purpose was to illustrate the possible receptiveness of the region to yellow fever. However, I believe that most of this audience recognizes that dengue fevers continue to be a major health problem in many parts of the world. Dr. Hammon's Presidential Address in 1969,[12] "Observations on dengue fever, benign protector and killer: A Dr. Jekyll and Mr. Hyde" along with many papers in our journal leave no question that dengue is not a benign disease, as the hemorrhagic fever and shock syndrome associated with this infection can result in high mortality. The Americas have been fortunate up to now to escape this associated effect of dengue infections, but I am told that Tahiti, which is currently suffering its third epidemic of dengue since 1964, is now experiencing an associated fatal hemorrhagic disease. Again, you may ask, "So what's new, we already knew most of this?" I believe the what's new part is that extensive areas of the Americas, Pacific and Asia are repetitively experiencing epidemic dengue and that although we say it is a controllable disease, it isn't being controlled or kept out of receptive areas. Increasingly, we are told that *Aedes aegypti* populations have developed resistance to an array of insecticides. In Tahiti, one must assume that both *A. aegypti* and *Aedes polynesiensis* are serving as vectors. The latter is the primary vector of filariasis and

efforts to control it that were started in the 1940's must be assumed to have failed or to have been relatively ineffective. If you have been in Tahiti, as I have in recent years, you know that they have failed. An interesting project is under way that would attempt to control *A. polynesiensis* by the introduction of a potentially competitive species, *Aedes albopictus*.[13,14] *Aedes albopictus* also is an incompetent vector for filariasis, but some persons have objected to the experiment on the basis that *A. albopictus* is a "dangerous mosquito." I must assume dangerous is with reference to being a vector of dengue viruses, and my answer is that if the present vector population has succeeded in infecting over half the population of Tahiti with dengue and if filariasis continues to be transmitted, *A. albopictus* probably isn't the tiger of the *Stegomyia–Scutellaris* complex of *Aedes* vectors. A successful program to control filariasis in the South Pacific would remove an important disease burden from the population.

I referred earlier to the accepted effectiveness of vaccination for yellow fever and an obvious question is, can we immunize a population to dengue and forget vector control? I will not attempt to resolve the issue of dengue vaccine except to say it is certainly within our technical competence to develop a vaccine to the four dengue viruses. The problem that must be resolved, if we wish to immunize populations, is if indeed the hemorrhagic fever and shock syndrome complications represent an immunological disease.

Again, dengue illustrates the character of one of our opponents, as the vector and agent pose problems in management, and we seem to be in the unenviable position that we have a wealth of research knowledge that continues to build while we have little or no immediate hope of preventing dengue epidemics.

I wish to extend my examples from the arbovirus field by brief reference to two other current problems. In recent years, Venezuelan equine encephalomyelitis (VEE) has emerged as probably the most important arbovirus of both veterinary and health concern to the Western Hemisphere. In the past ten years the virus has ebbed and surged in its endemic and epidemic cycles through most of South, Middle and Central America.[15,16] Figure 3 illustrates this distribution. In 1971, the virus invaded the United States in

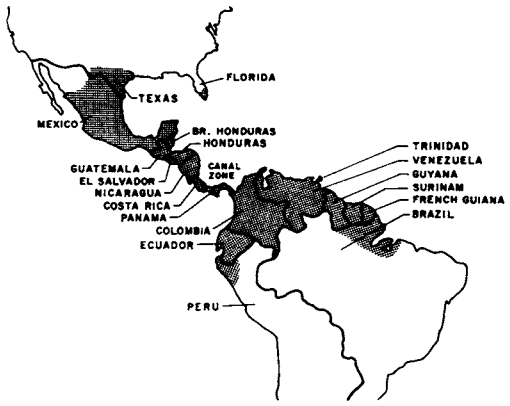

FIGURE 3. Geographic distribution of Venezuelan equine encephalomyelitis virus activity, 1961 to 1971.

June and an epizootic spread occurred in Texas this past summer. The amazing thing was that a number of persons, who are in this audience today predicted this event and it is possible, even probable, that we had the technical knowledge to prevent the spread by vaccination and vector control before it reached the United States. However, for a variety of political and economical reasons and inertia little was done and the introduction took place. A major emergency program that utilized the scientific and technical competency of a large sector of our federal and state veterinary and health resources appears to have contained the disease, although it was still active in October of this year in Texas and areas of Mexico. The frightening aspect of this problem is that if the United States Army had not happened to have stockpiled millions of doses of vaccine, the disease probably would not have been contained in Texas by quarantine and mosquito control measures. I recommend the News and Comments section of the 30 July 1971 issue of Science, "VEE vaccine: Fortuitous spin-off from BW research,"[17] as must reading to you. I comment in this depth on this problem because to the best of my knowledge VEE vaccine is the only such vaccine that is stockpiled in such amount.

To summarize the VEE problem the latest figures are that 3,268,658 horses across the southernmost states and untold hundreds of thousands of horses in Mexico were vaccinated. Over 8,000,000 acres were sprayed with insecticide for vector control in Texas and Louisiana. The final cost studies are still being done but over

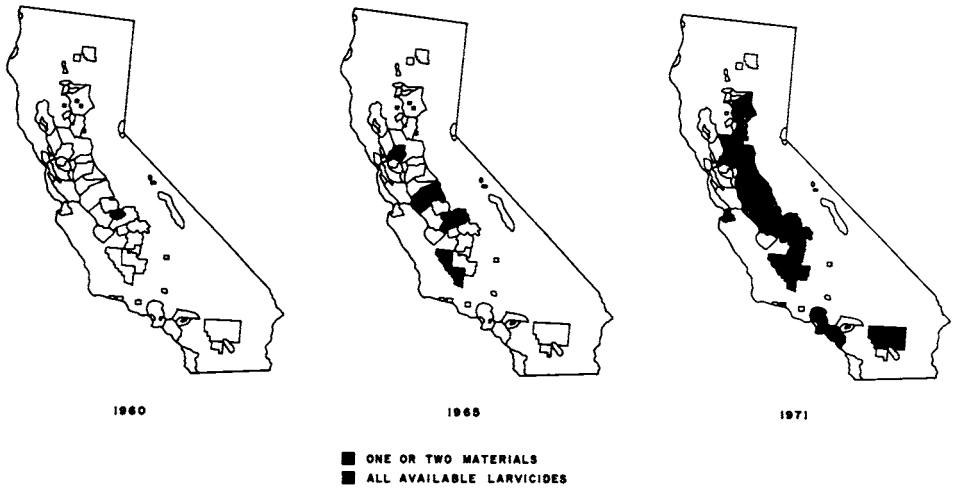

FIGURE 4. Documented organophosphorous resistance in California—*Culex tarsalis*—1960 to 1971.†

† Source: Womeldorff, D. J., et al., 1972. Insecticide susceptibility of mosquitoes in California: Illustrated distribution of organophosphorous resistance in larval *Aedes nigromaculis* and *Culex tarsalis*. *Proc. Calif. Mosq. Control Assoc., 40:* in press.

$20,000,000 is probably a conservative estimate for the expenditure in federal emergency funds in this one program. It is fortuitous that a vaccine was in stock, that the mosquitoes were still susceptible to available insecticides and that someone made a decision to spend over $20,000,000 primarily to protect the health of horses and secondarily the health of people in the affected areas. I would point out that the total annual budget for mosquito control in the 453 agencies organized for this purpose in the entire United States came to only a little over $35,000,000 in 1971.[18] We were concerned in California that if VEE virus was introduced, the two mosquitoes most likely to serve as epidemic vectors of VEE viruses in the Central Valley of the state had developed resistance to all licensed insecticides over extensive areas of their distribution.[19] This development is illustrated in Figures 4 and 5. What this meant was that our primary weapon, an attack on the adult and immature stages of the encephalitis vectors with ultra low volume applications of insecticides, had been taken away from us. I am sure that some of you are saying

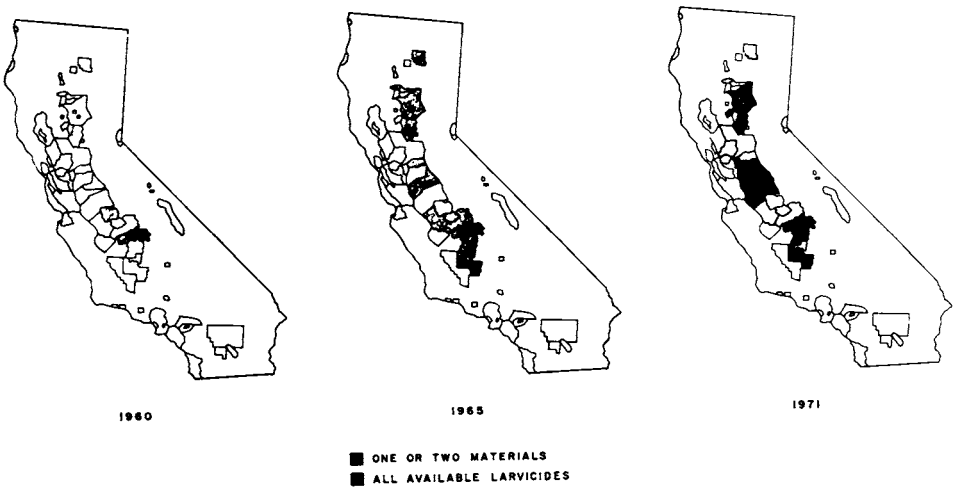

FIGURE 5. Documented organophosphorous resistance in California—*Aedes nigromaculis*—1960 to 1971.†

† Source: Womeldorff, D. J., et al., 1972. Insecticide susceptibility of mosquitoes in California: Illustrated distribution of organophosphorous resistance in larval *Aedes nigromaculis* and *Culex tarsalis*. *Proc. Calif. Mosq. Control Assoc., 40:* in press.

that industry and the research establishment would come up with a new magic compound and they might. However, I would also point out the hard fact that the major industrial resources are backing away from the responsibility for development of new insecticides as they face legislation, constantly increasing costs for testing, clearing and licensing, increased liability risks, and a social stigma concerning their motives and responsibilities.

In summary, in California, and I am sure in regions where they may not be aware of it, we enter 1972 with severe limitations in our ability to control the vectors of encephalitis viruses that can produce epidemics. No major breakthroughs are on the horizon unless one considers a return to the use of oils for mosquito control as a new development.

I would feel remiss if I did not make at least a passing comment on the fact that malaria as a world-wide problem illustrates and emphasizes all the preceding points. WHO has had to reassess its overall long term objective of global eradication. Unexpected major resurgences of malaria have occurred, with Ceylon as a most dramatic illustration.[20] Vectors have developed resistance to the usual insecticides. Parasites have developed resistance to the available drugs. Populations in areas such as the United States where malaria has been eradicated are constantly reseeded with infection and secondary spread occurs by the needle used to maintain the epidemic of dope addiction. The manufacturers of antimalarial drugs are reluctant to assume responsibility for the side effects of their products or the financial investment for development of new agents.

Finally, before I summarize the points I have made, I would like to make reference to the Presidential Address given last year when Dr. Work reviewed his career in arbovirus research.[21] His unique experiences encompassed associations with the military, the Rockefeller Foundation, the United States Public Health Service and the University of California. It is sobering to look at the degree to which these agencies or their financial resources have been withdrawn or threaten to withdraw from the international phase of infectious disease control and tropical medicine research. I view this action by so many agencies as a loss of much of our defense in depth and the loss of an irreplacable research resource. I do not believe we can isolate ourselves from the rest of the world or delegate our responsibilities to others in the long term war to contain infectious diseases. Any decrease in involvement of the United States Government and other agencies in international concerns and action to control infectious diseases can only be looked upon as a victory for the infectious diseases.

At this point I believe that the diseases and associated problems I have discussed lead us to a series of questions that must concern us as scientists and a scientific society. I make no pretense that I know the answers to the questions, that the answers will be simple or that there even is a solution. The questions are related to political action, social attitudes, economic limitations and professional responsibility. They are:

1. When an epidemic occurs that requires the large scale use of an insecticide, vaccine or drug that has not been licensed and it has been declared illegal to use the material, who will make the decision to use it, how quickly, and what action group will arise to oppose the decision?

2. When an epidemic occurs and it is found that the vector or pathogenic agent is resistant to the usual insecticide, antibiotic or vaccine that is available, who will be blamed for not knowing this has happened and having an alternative material developed, evaluated and available?

3. When the supply of a necessary vaccine, antibiotic or insecticide is inadequate to protect all of an exposed population, who is at fault and who will decide who is to get the benefit of the limited supply?

4. With increased difficulties in financing the cost for development and evaluation of biological and chemical agents for the control of infectious diseases, who is to assume the developmental costs and legal responsibility now that industry is increasingly unwilling to risk the investment or responsibility?

5. When another country or international agency asks us for aid to combat an epidemic, what happens and who takes over, when we say, "Sorry, but our economy, foreign policy, supply of materials, knowhow or the social attitude of a significant part of our population will not permit us to assist you?"

6. Who is to be held responsible when decreased priority for infectious disease research or control programs nationally and internationally result in a scaling down of our first line of defense, namely, our research establishment, health agencies, and diagnostic laboratories, and a serious infectious disease epidemic results that is not quickly controlled and emergency funds are not made available for its control?

7. Finally, how long can our society afford to finance vaccination or other widespread control efforts regardless of the recipients' capacity to pay for it or without regard to the dependence of our economy and society on the control effort?

It clearly must be our hope that the elected officials, staffs of government agencies, scientists, industrialists and other informed public groups that are concerned with the problem will join in an effort to seek effective and acceptable answers to these questions. Such action will not happen just because we as scientists or a scientific society hope that it will. Experience indicates that political, social and economic considerations will increasingly dictate the priorities and that the battles for disease control and economic support for research and development of new control methods may be allowed to fluctuate in economic competition and cost-benefit evaluations with other social concerns. Much of society has expressed disenchantment with the agency or community approach and want to go it alone, based on their own social priorities and beliefs. At the best, I anticipate a marked decrease in the effectiveness of our infectious disease control programs, a decreased reliance on a further pushing back of most diseases to their frontiers and an increased dependence on the informed citizen who protects himself. As a final bright note, there should be an increased sale of the Society's publication, "Health Hints for the Tropics,"[22] and the American Public Health Association's publication, "Control of Communicable Diseases in Man."[11]

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