Original

EMERGING MICROBIAL THREATS*

by

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I am delighted that the IOM has agreed to undertake the challenge of this study of microbial threats to health. It is, as you know, a logical extension of the symposium two years ago on new and emerging viruses. Josh and Steve Morse were generative forces in that symposium and many of you here today participated. I personally pretend no unique insights with regard to these special challenges which we now know have been, are and will be with us so long as both man and microbes coexist.

However, I did come away from that symposium with a substantially altered point of view -- both concerned by our lack of capacity to detect and respond to new or emerging microbial challenges but, at the same time, puzzled as to the reasons for our collective long-standing complacency. I am happy to share those thoughts with you.

Certainly, the HIV virus and the emerging pandemic is the proximate cause for great concern. AIDS has challenged the best of our molecular biologists,

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* Presented to the Institute of Medicine Committee on Microbial Threats to Health at the National Academy of Sciences on February 25, 1991.

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epidemiologists, behavioral scientists and, indeed, the capacities and structure of our health care system. We have learned a lot and we have made progress but, on the whole, we have not come off all that well. We have no vaccine, as yet. The few drugs we have developed may postpone serious illness but it is uncertain they prolong life and preventive measures have, so far, proved disappointing. At the same time, we are not at all successfully coping with a massive re-emergence of dengue fever throughout the Caribbean and some parts of Latin America. The emergence of Lyme disease as a troublesome and not inconsequential problem and the first epidemics of cholera in this hemisphere in the 20th century. These, of course, represent but a few of an array of problem diseases only recently recognized or which have extended their dominion far beyond previous bounds. Among the new and problematic infections are the Arena viruses -- Machupo, Junin and Lassa fever; Marburg, Ebola and monkeypox virus diseases; the Hautian viruses and canine parvovirus infection. And, all the while, we await the return once again of a 1918 swine flu variant -- with which, indeed, we are even today, not well prepared to cope. Moreover, and a point which is seldom mentioned, we have seen the decline over the past two decades of a not insubstantial proportion of our vaccine manufacturing capability, both in the U.S. and Europe, and thus we have a diminished capacity in the art and science for producing the best possible weapons against infectious diseases -- i.e., vaccines.

The concerns are there; our interest has not been. Not all that many years ago, the view was widely expressed and widely held that we had effectively conquered

the infectious diseases -- at least those of importance to the industrialized world. It was time to turn our full attention to the chronic diseases, few, if any, of which were believed to be caused by infectious agents, although even this latter presumption is now increasingly questioned. I remember the 1960s particularly well because of the insistent counsel and advice I received from mentors to leave the infectious disease field in favor of tackling the truly important chronic disease problems. Obviously, I did not take that advice but it was a marginal call.

Change has occurred but it is recent. It is apparent now from what we know about molecular biology, the replication of microbial agents and their mutational capacities, that we are destined indefinitely to cope with an ever-changing array of microbial challenges. This stems, in part, from the fact that "the essence of a virus is its fundamental entanglement with the genetic machinery of its host (a happy turn of plans for which I am indebted to Josh) and, of course, the rapidity of microbial multiplication such that even infrequent mutations occur at short temporal intervals. At the same time, we are travelling more rapidly and in greater numbers than ever before and living in environments, both urban and rural, which are markedly different from the past.

Josh brought home the consequences when he said "Our only real competition for domination of the planet remains the viruses" and added "The survival of humanity is not preordained." There are those who would suggest that this has little more credence than did Chicken Licken's alarm that the sky is falling. The

occurrence of the AIDS pandemic has been sobering counter evidence. Serious as that problem is, one has only to speculate what impact such an epidemic would have had, had it been able to spread with greater facility.

Three other events of this century were, for me, equally sobering in illustrating the awesome potential of microbial agents: The 1918 Swine influenza pandemic, the myxomatosis epidemics among Australian rabbits; and the canine Parvo virus epidemic of 1978. Each of these is known to all of you.

The origin of the Swine flu strain remains obscure but what is apparent is that after its appearance, it spread rapidly across the world sparing only a few and isolated populations. And this at a time when international travel was but a small fraction of what it is today. In the U.S., during two 10-week periods in the autumn of 1918 and spring of 1919, 550,000 died (10 times the number who died in the war). Worldwide 20 to 30 million are estimated to have died. Views have been expressed that the displacement of populations and turmoil of WWI might somehow explain such an epidemic. Moreover, as it has been argued, presumed secondary pneumonial, and staphylococcal pneumonias, for example, could be readily treated with antibiotics were such an epidemic to reoccur. Undoubtedly, population displacement during WWI played some role but we must bear in mind that the pandemic was global in scope and wreaked havoc equally in the United States as well as in Europe. More sobering to me was to review case histories and to realize that most died of a fulminant hemorrhagic pneumonia within a matter of 48 to 72 hours after onset and

without evidence of secondary bacterial infection. Based on what I know of our capacity today to detect such a strain at an early date and our capacity to rapidly produce a vaccine in adequate quantities, I have no confidence whatsoever that a better scenario could be written in the 1990s.

The canine parvovirus epidemic, described by Parrish, provides another dimension to the story. Over a period of little more than a year during the late 1970s, millions of dogs died of one epidemic disease characterized by severe diarrhea and a leukemia-like illness caused by canine parvovirus 2. This swept the canine world and eventually was detected in coyotes and wolves. It was found to be a direct derivative of a feline strain being grown to prevent distemper in cats but its DNA structure differed by less than 1%. The point to me is that numerous or major mutational changes may not be required to alter the properties of a virus -- just so they happen to be the right ones.

The potential lethality of a virus in a virgin susceptible host population is well-illustrated by myxomatosis which, as you know, was deliberately released in Australia in 1950 in an effort to control the rabbit population. It was a strain native to South American rabbits but caused comparatively mild disease characterized by a few small tumors and occasional deaths. However, for European rabbits, such as were introduced into Australia, it was highly fatal -- causing death, in more than 95%. Over successive generations, genetic selectivity diminished this rate. Even so, after 13 years and at least that many generations, more than half the strains isolated killed

more than 70% of rabbits. Parenthetically, it is worth noting that there is evidence that the effect of another orthopox virus, variola, on many North American Indians tribes was comparable -- literally decimating them. And thus, the comparative ease of settlement of North America!

Given this history and the obvious implications to the future, it would seem only logical for the U.S., indeed the world's scientific community, to be especially vigilant. However, as I am sure you are aware, there is at present no plan which addresses the issue of new or emerging microbes and indeed few resources today devoted to infectious disease epidemiology and disease surveillance; to basic and clinical research throughout the vast reaches of the developing world or to the science and technology of vaccine development and production, the most likely and perhaps only practical defense we would have to counter a serious microbial threat.

I should like to take the liberty of offering a few ideas to help launch discussion because, unless there is a mechanism and capacity to detect and define potential threats, all else is meaningless. The basic questions are: How might we detect such new or emerging agents at an early date so as to be able to devise appropriate preventive and therapeutic modalities? What do we look for? What types of surveillance and reporting systems can one devise?

Interestingly, some of the questions have been asked and responded to at least once before. One such time was 1950, soon after onset of the Korean War. It was

perceived then that a biological warfare attack on civilian populations in this country was a realistic possibility. A number of different microbial agents were candidates and several of them could be readily dispensed in crowded centers by a lone saboteur bearing no more than an innocuous appearing briefcase. To stop such an act was seen to be all but impossible. However, early detection was vital so that measures could be taken to prevent spread, to treat and/or to decontaminate. A special unit was created at the Centers for Disease Control which would be on 24-hour call to investigate immediately any unusual disease outbreaks. Thus, the Epidemic Intelligence Service came into being. Young medical officers were trained in field epidemiology and assigned to CDC, state health departments and universities. Requests for help were responded to immediately on receipt of a request. The availability of resources which could be quickly mobilized increased the reporting of outbreaks. And, in due course, the states themselves strengthened their own capacity and capability to investigate outbreaks.

To detect new or emerging viruses, the challenge we face bears some similarities to the challenge of 1950. We are uncertain as to what we should keep under surveillance or even what we should look for. However, the challenge differs in that the new or emerging viruses may not occur as outbreaks, as would be expected with biological warfare. Rather, new or emerging viruses may be manifested by scattered single cases -- such as presumably happened with AIDS and as now occurs with monkeypox. Second, it seems to me most probable that new infectious entities of significance are most likely to first occur either in densely populated areas where

crowding and poor sanitation are prevalent or where man, monkeys and other wild mammals live closely together in tropical rain forest areas. In sharp contrast to the 1950 challenge in the U.S., such areas are minimally endowed with curative care facilities which might identify the unusual illnesses. Moreover, they are all but bereft of sophisticated, let alone competent, microbiological expertise and equipment.

Thus, the 1950 approach in the U.S. of creating a national Epidemic Intelligence Service, while providing a partial answer to detection of new entities, would not alone provide much assurance in developing countries that newly emerging viruses would be detected in a timely manner. What, therefore, might be proposed?

A surveillance system to detect new and emerging virus diseases must inevitably consist of three components. The first are clinical units, which are capable of detecting unusual cases or constellations of cases. In a tropical area this is an especially difficult task given the background level of diverse conditions which present themselves.

The second component -- having detected an unusual case or group of cases, there must be a defined channel for reporting the occurrence and a receptive, knowledgeable unit to receive it.

Finally, there must be some sort of capacity and responsibility at national, regional and international levels which is available to respond to unusual events or

requests for assistance. Indeed, the existence and responsiveness of such units itself serves to strengthen reporting from a network of clinical units because they learn that special assistance is available to help.

To identify the needs off a sensitive surveillance system which would detect new disease entities within a reasonable time frame, I felt it helpful to consider different basic epidemiological characteristics of a new disease which need to be anticipated. One manifestation of a new entity might be in epidemic form involving perhaps a hundred to several thousand clinical cases over a limited time frame and geographic area. If there were a number of associate deaths with rash and/or hemorrhagic manifestations, recent experience with new viruses -- Ebola and Marburg -- would suggest that, even in remote areas, they would soon come to notice, and assistance in dealing with them would probably be sought. The likelihood of such outbreaks being properly investigated depends on national governments utilizing appropriate expertise, but to do so they need assurance that competent assistance would be available to them and could respond in a timely fashion.

Could or should the WHO be in a position to discharge such a role? In principle, the answer should be -- yes. In fact, however, WHO has pathetically few resources of its own which are not specifically committed to such as AIDS or other categorical programs. The viral diseases unit at headquarters, however defined, consists of no more than five persons. Virus disease programs in most WHO regional offices are staffed by one or two persons only. Inevitably, those who staff such units

are prized more for their administrative skills in bringing experts together than for their own professional expertise. To date CDC has primarily filled the role as an emergency international resource.

Another scenario for a new or emerging virus -- less dramatic -- would be the occurrence of large outbreaks with few associated deaths and/or few of the dramatic manifestations of hemorrhage or rash. Small outbreaks with high case-fatality rates and/or hemorrhage and rash would very likely escape detection in most parts of the developing world today. National Epidemic Intelligence Service units, developed on the CDC model, could serve to encourage outbreak reports and would serve a valuable surveillance function.

A more difficult problem is posed by new or emerging viruses which cause only sporadic cases or comparatively few severe cases over a finite time span. Such presumably was the scenario for the emergence of HIV. This poses the most difficult problem of all. Such cases might be identified and characterized at a reasonably early date if seen in a reasonably staffed and equipped clinical center which was knowledgeable of tropical diseases and could identify the unusual and unexpected. Unfortunately, there are few such centers anywhere in the world and, indeed, there are few persons with real expertise in tropical medicine in either the industrialized or developing countries. In our own interests, let alone the interests of populations living in the tropics, it would seem prudent to foster the development of a network of units with expertise in tropical medicine. Here we have much to learn from those in

the agricultural sector. Beginning with initiatives taken by the Ford and Rockefeller Foundations in the early 1960s, a network of international agricultural centers has developed, now funded by many governments and agencies. In all, there are now more than 25 and these, in turn, have stimulated the creation of a complementary network of national centers and extension services which regularly collect vast amounts of useful data. More than 50 U.S. academic institutions now receive core support to permit them to relate to and participate in the international network. For health there is exactly one comparably supported international center and only a handful of U.S. academic centers which receive extremely modest support for a few specific programs in tropical medicine.

For purposes of improving a woefully inadequate surveillance program, I see the need for the development of a network of internationally supported health centers which, in developing countries, I believe should be based in periurban areas of major cities in the tropics. The periurban areas are customarily where migrants and travelers from rural areas are found. A clinical facility in such an area would thus serve to provide a window on events in surrounding rural areas. Preference, I believe, should be given to more densely populated areas and those near the tropical rain forest.

Such centers would have to have several components: (1) a clinical inpatient and outpatient service for infectious diseases; (2) supporting diagnostic laboratories which, as needed, could serve as a locus for research studies; (3) an epidemiological

unit which might serve as a national resource and which would be engaged in a variety of ongoing studies in a population "laboratory" of perhaps two to five million persons (By focusing research efforts within a defined area, rapport could be developed with local leaders and an invaluable data base would gradually accrue); (4) an education-training unit for national, as well as international staff. Finally, I believe such centers would need to be formally identified as part of an international network with designated counterparts in the industrialized countries.

The task of timely detection of emerging microbial problems is itself a formidable challenge. Defining the threat is a second order problem and one for which we are better prepared -- provided there is some entity charged with that responsibility and which is given the resources to do so.

That brings me to my concluding point -- the need for a government locus to assume responsibility for such problems on an international basis. HHS presently has only a limited mandate to do so and has been provided few resources for international activities; the Department of Defense probably does more of relevance in this field than any other Agency but its mission inevitably is more narrowly focussed than that needed and necessary support is waning. Funds for international health programs flow primarily through AID and prerogatives to fund such programs have been jealously guarded. Whatever its success as a development Agency, its research and development program has never been held in high esteem -- to the extent that in 1979 a separate Institute for R&D was proposed to and authorized by Congress, its

funding denied at the last moment only by procedural technicalities. Since 1979, as is widely known, AID's technical competence, especially in health, has eroded further. Last month, AID announced a brand new conceptualization of its mission divided into four parts: (1) a Strategic Management Initiative; (2) a Democracy Initiative; (3) a Business and Development Partnership Initiative; and (4) a Family and Development Initiative. The research agenda of the last of these has as its principal research agenda: "the design and conduct of studies and surveys of the needs of families and of individuals in the context of their family relationships and responsibilities." Its only mention of infectious diseases is subsumed under an item: "to research the impact of certain diseases on family relationships and stability, e.g. AIDS and other sexually transmitted diseases, drug and alcohol abuse, etc."

If in the course of your deliberations, you decide, as I have, that emerging microbial agents do pose a threat which is worthy of attention, responsibility for an appropriate structure and action will need to be assigned somewhere in Government. Consider your recommendations carefully.