DA Henderson

RESURGENCE OF INFECTIOUS DISEASES

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The topic--Resurgence of Infectious Diseases--would seem to be somewhat out of place in the context of the broader policy issues and developments presented by the other speakers. However, the implications of resurgent, new and emerging infections and our response to them introduces a range of current challenges and raises broader questions of policy which we have as yet, only begun to explore.

Let me explain. To those concerned with health, perhaps the single most sobering event of the past decade, perhaps of the past half century, has been the emergence and global spread of the human immunodeficiency virus. The virus and the disease were first identified just a decade ago. This was at a time when the medical community and biomedical scientists as a whole felt confident--some would say complacent--that, for all intents and purposes, infectious diseases, if not consigned to history represented nuisances rather than problems--at least for the industrialized world. Most major infectious diseases could be readily treated or had all but vanished, principally because of better housing, medications and sanitation, in part because of vaccines and in part because of antibiotics. With a substantial biomedical research base, ever exploring new frontiers such as cancer and heart disease, there seemed little point and little

desire to invest resources and to devote time to the vanishing microbes. Both the basic research and professional competence with respect to infectious agents withered. The level of confidence (some have said arrogance) is epitomized by the statement in 1983 of the U.S. Secretary of Health on announcing the isolation of HIV--that a vaccine would be available for use within two years. Now, ten years later--and after an unprecedented mobilization of the best of basic and applied science and the expenditure of billions of dollars--we have antiviral compounds of marginal benefit at best, possible vaccines which are little more than a hope and a fatal infection spreading inexorably across the world. It has been a humbling experience for the medical community.

In the meantime, other previously unknown or unrecognized infections as well as a few once controlled have become manifest--in our own country, Lyme disease, antibiotic resistance to tuberculosis, and Hanta virus infection; dengue hemorrhagic fever, once localized in S.E. Asia, is now prevalent throughout the Caribbean and spreading into Central and South America; new infections have emerged in Africa and some have spread to Europe--Haven fever, Marburg and Ebola virus disease; and within the past 6 months, a new type of cholera has appeared in Asia, possibly the harbinger of the next global pandemic.

Four years ago, the first of a series of conferences was convened

which asked some very basic questions--surprisingly for the first time. What implications do these observations with respect to new infections have? Are there implications with respect to science policy? Inevitably, we were forced to confront some very basic and troubling questions--what, for example, would have been the scenario if an HIV-like disease had been able to be transmitted by coughing by aerosol dissemination.

Indeed, there is nothing to say such could not occur. Microorganisms are in continuing genetic flux and the viruses, in their basic replication cycle, become inextricably a part of cellular DNA. The only encouraging contrary note is the observation that mankind has not yet had to confront and survive a microorganism which was potentially fatal to societal survival. But then, never before have populations been so large, so frequently densely crowded in unsanitary urban slums where transmission is facilitated, nor has it ever been so easy to travel rapidly over long distances and to transmit infections to other continents. Josh Lederberg, Nobel laureate and formerly President of Rockefeller University, in his summary of that meeting said (and I paraphrase): It is clear that man's only competitors for dominion of the planet are the viruses. He added "the ultimate outcome is not fore-ordained."

It was decided at the end of the meeting to request a committee of the National Academy of Sciences to undertake a longer term,

more thorough evaluation of the issues, problems and possible responses. That Committee reported its findings late last year--in substance--agreeing that new and potentially catastrophic problems had to be anticipated for the indefinite future. A response to this challenge demanded a heightened level of surveillance, a far greater capacity in rapid diagnosis and definition of disease and an ability to develop and produce vaccines. This is by far, the most likely prospective defense which could be developed given the difficulties, so far experienced in developing antiviral compounds for treatment of disease. Other, more definitive strategies are now under study.

The HIV pandemic and our research response, meanwhile has generated an unprecedented interest and activity in the immune system given the pathogenesis of HIV infection. As a by-product of a better understanding of the immune process, new opportunities, new horizons in vaccine development have emerged. A recent tabulation shows more than 60 vaccines now at various stages in the research and development process. For the United States, I now foresee perhaps 20 or more vaccines being routinely employed within the decade for disease prevention for all in the population.

From a policy perspective, does such an investment in vaccines make sense? Most certainly, it does by any cost-benefit calculation. As in a recent World Bank analysis document,

prevention of disease by immunization is, far and away, the single most cost-beneficial procedure in our entire medical armamentarium and, certainly, one of the simplest of procedures. Indeed, it represents one of the few new medical procedures which actually promises to save money. But in medical systems which have universally been organized, structured and compensated to deal with sickness care--not health care--acceptance of the principle that prevention should command priority remains even now a somewhat alien concept. And immunization, both its research and application, is and has been dealt with as an afterthought and not as an intrinsic essential component of the health care system. If you have doubts about this, only consider the expenditures devoted to organ transplantation and cancer therapy research--and weight the benefits which have derived.

With the addition of ever more effective antigens, new questions arise. How can they be combined to permit application of many at the same time; can we not apply them by mouth rather than by injection; can we achieve effective protection with only one rather than several applications? Even with the growing but still modest research resources available, it is becoming apparent that many can be given by mouth; a great many can be combined and can be given at a single application. Some may be given to the mother to protect the newborn in the early natal period and some, through biotechnology, are experimenting with antigenic gene fragments incorporated in plants.

It is now apparent that the prospects for immunization are awesome, especially for the third world, indeed as our research and development base is appropriately expanded, we will be more adequately prepared to counter the challenges of new or emerging microbial agents.

The critical question now is whether the private pharmaceutical sector can be induced to exploit this challenge. It is, by no means clear that it can or will. Both governments and patients alike are today more responsive to expending large sums on drugs and procedures to deal with known existing illness than to prevent illness which would have otherwise occurred in never-to-be-known individuals in the population. Having spent nearly a decade in endeavoring to persuade governments as to the wisdom of investing in the eradication of smallpox, I can say with some feeling that European and American governments found little difficulty in mobilizing tens of millions in countering small epidemics when the disease was imported; in fact, for this disease, they were even prepared to assign all manner of quarantine officers to inspect vaccination certificates and to expend resources in vaccinating their own populations. In support of a global effort to eradicate a disease, that was quite another story--at the end of the first five years of the program, we had received at WHO little more than a total of $100,000 in cash from all governments combined.

This point has relevance if indeed effective multi-component vaccine prevention programs are to be developed. Manufacturers see little profit in developing and producing a vaccine which, in the ideal, would be given once and protect for life and a vaccine product for which generically there is consumer and government resistance to paying prices sufficient to recoup R & D costs and to realize a reasonable return on investment. An anti-hypertensive or anti-arthritic agent which would have to be taken daily for life is far more attractive commercially.

There are many examples of tangible and immediate problems we now face in vaccine development. Six vaccines are now being employed in the global immunization program. Not one of them is wholly satisfactory, variously for reasons of antigenicity or safety or heat stability. This is well recognized. An agenda of approaches to resolution of the problems is likewise generally agreed. Yet each of those vaccines is basically unchanged from what it was 25 years ago. Such studies as are now being done are almost entirely funded by government--and parsimoniously at that. A second illustrative problem--the U.S. Army, as part of its defense research system effort, developed and tested an effective vaccine to protect against a fatal hemorrhagic disease of the pampas of south central South America--Junin hemorrhagic fever. The vaccine proved highly efficacious. The Argentine government sought to obtain a supply for routine use; the Army was prepared to transfer the technology. However, no laboratory was prepared

or able to respond in any way. A third example--earlier this year, our government sought to procure, through contract, a reasonably substantial supply of one of the more uncommon bacterial vaccines. None of the commercial vaccine producers was even willing to submit a bid. I could go on at some length but the point is clear. Vaccines represent unique products with vastly different characteristics and intensive commercial interests for pharmaceuticals.

Only very recently have we begun to appreciate this. But, at the same time, vaccines, generically--and I repeat--represent the most cost-beneficial interventions of our entire medical armamentarium. They are of tremendous importance to the industrialized world and many fold more critical to the developing world.

How to foster the development and application of vaccines especially for the third world was the subject of a National Academy of Sciences study released only last month. I can't begin to summarize the quandaries explored or the full range of options considered. In sum, however, they conclude that to realize the potential of many, perhaps most vaccines, a public sector National Vaccine Authority will need to be created to mobilize and coordinate the public-private sector effort which is required. For the Academy, this was in finding, both bold and surprising. In the U.S., we will be addressing these

recommendations over the coming year through a Federal interagency committee.

In summary, while we are undergoing a convulsive change in our health care system, we are beginning--but only beginning-to see prevention-and one of its most important components, immunization--in a very different light with a very different order of priority. At the same time, it is becoming apparent that there will be a need to address this challenge in a very different manner than we have the curative problems. And the urgency of so doing is only heightened by the appearance of new and emergent infections.